

Baş Editör / Editor-in-Chief
Bilgin Timuralp

Editör / Editor
Gulmira Kudaiberdieva

Bu Sayının Yayın Danışmanları
Advisory Board of This Issue

Hania A Ammar
Sglimbea Anca
Ahmet Çağrı Aykan
Kadir Babaoğlu
Okan Badıllıoğlu
Auroro Bakall
Cem Barçın
Zehra Buğra
John GF Cleland
Yüksel Çavuşoğlu
Ayhan Çevik
Necmettin Çolak
Recep Demirbağ
Suat Doğanç
Rasim Enar
Ertuğrul Ercan
Alim Erdem
Sevcan Erdem
Enes Elvin Gül
Evin Gülbahçe
Tuncay Hazirolan
Sinan İçsen
Ergün Barış Kaya
Sinan Altan Kocaman
Ergin Koçyıldırım
Baktybek Kojonazarov
Levent Korkmaz
Serdar Kula
İbrahim Halil Kurt
G.B. John Mancini
Emel Okulu
İsmihan Selen Onan
Aytaç Öncül
Emin Evren Özcan
Kanat Özışık
Cengiz Öztürk
Domenico Palombo
Hakan Paydak
Florian Rader
İbrahim Sarı
Ahmet Sert
Radojica Stolic
Asife Şahinarslan
İbrahim Halil Tanboğa
Yasin Türker
Renato De Vecchis
Kıvanç Yalın
Ayşe Yıldırım

Özgün Araştırmalar / Original Investigations

Cardiac CT angiography in an epidemiologic study - the methodology of "The Multicenter AIDS Cohort Study"
Epidemiyolojik bir çalışmada Kardiyak BT anjiyografi- "The Multicenter AIDS Cohort Study"nin yöntemi
Yalçın Hacıoğlu et al.; Torrence CA, Baltimore MD, Pittsburgh PA, Chicago IL-USA

New approach to heart rate in chronic heart failure-Heart rate performance index
Kalp yetersizliğinde kalp hızına yeni bir yaklaşım-Kalp hızı performansının göstergesi
Aydın Akyüz et al.; Tekirdağ-Turkey

Adiponectin, NT-pro-BNP and left ventricular ejection fraction in systolic heart failure
Sistolik kalp yetmezliğinde adiponektin, NT-pro-BNP ve sol ventrikül ejeksiyon fraksiyonu
İstemihan Temgiz et al.; İzmir, Çanakkale, Kocaeli-Turkey

Impaired coronary flow reserve and increased aortic stiffness in metabolic syndrome
Metabolik sendromda bozulmuş koroner akım rezervi ve artmış aort sertliği
Derya Tok et al.; Ankara-Turkey

Editorial Comment: Relations between microvascular function and aortic stiffness in metabolic syndrome
Editöryel Yorum: Metabolik sendromda mikrovasküler fonksiyon ile aort sertliği arasındaki ilişki
Tae Joon Cha, Kyoung Im Cho; Busan-South Korea

Hospital volume, risk-adjusted mortality rate and coronary intervention relationship in Korea, 2003 to 2004
2003 ve 2004 yıllarında Kore'de koroner girişim, hastane kapasitesi ve risk-ayarlı mortalite ilişkisi
Yong Hoon Kim et al.; Chuncheon City-South Korea

Editorial Comment: Hospital volume and mortality relation in PCI-Is there a need for modification of guidelines in Asia?
Editöryel Yorum: PKG'lerde hastane kapasitesi ile mortalite ilişkisi-Asya'da kılavuzların değiştirilmesine gereksinim var mı?
Ayhan Olcay; Istanbul-Turkey

Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and contrast-induced nephropathy
Anjiyotensin dönüştürücü enzim inhibitörleri, anjiyotensin reseptör blokerleri ve kontrast nefropatisi
Nezih Barış et al.; İzmir-Turkey

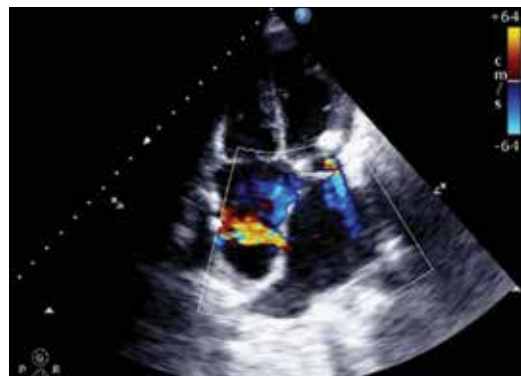
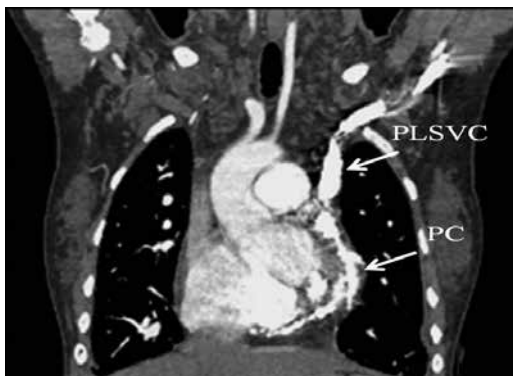
Evaluation of right ventricular functions in nasal polyposis: an observational study
Nazal polipozisde sağ ventrikül fonksiyonlarının değerlendirilmesi: Gözlemsel bir çalışma
Eda Şimşek et al.; Erzurum, Afyon-Turkey

Derlemeler / Reviews

Value of stress echocardiography in mitral stenosis
Mitral darlığında stres ekokardiyografisinin değeri
Kadriye Orta Kılıçkesmez; İstanbul-Turkey

Epicardial adipose tissue: a review of physiology, pathophysiology, and clinical applications
Epikardiyal yağ dokusu: Fizyoloji, patofizyoloji ve klinik uygulamalara ilişkin bir gözden geçirme
Cihan Şengül et al.; İstanbul-Turkey

Sayfa/Page: E16-E17



Baş Editör / Editor-in-Chief
Bilgin Timuralp, Eskişehir, Türkiye

Editör / Editor
Gulmira Kudaiberdieva, Bishkek, Kyrgyzstan

Baş Editör Yardımcıları / Associate Editors

Necmi Ata, Eskişehir, Türkiye
Mehmet Bilge, Ankara, Türkiye
Sanem Nalbantgil, İzmir, Türkiye

Kurtuluş Özdemir, Konya, Türkiye
İnan Soydan, İzmir, Türkiye
Mehdi Zoghi, İzmir, Türkiye

Bölüm Editörleri / Section Editors

Hipertansiyon / Hypertension
Alparslan Birdane, Eskişehir, Türkiye

Metabolik Sendrom / Metabolic Syndrome
Sadi Güleç, Ankara, Türkiye

Pediyatrik Kardiyoloji / Pediatric Cardiology
Ercan Tutar, Ankara, Türkiye

Kalp Yetersizliği / Heart Failure
Yüksel Çavuşoğlu, Eskişehir, Türkiye

İnvaziv Kardiyoloji / Invasive Cardiology
Yılmaz Nişancı, İstanbul, Türkiye

Kardiyovasküler Cerrahi / Cardiovascular Surgery
Ahmet Tulga Ulus, Ankara, Türkiye

Ekokardiyografi / Echocardiography
Berrin Umman, İstanbul, Türkiye

Baş Editör Danışmanı / Editor-in-Chief Consultant
Suna Kırac, Denizli, Türkiye

Biyoistatistik Baş Danışmanı / Senior Consultant in Biostatistics
Kazım Özdamar, Eskişehir, Türkiye

Biyoistatistik Danışmanları / Consultants in Biostatistics

Canan Baydemir, Eskişehir, Türkiye

İlker Ünal, İzmir, Türkiye

Uluslararası Yayın Kurulu / International Editorial Board

Adnan Abacı, Ankara, Türkiye
Kamil Adalet, İstanbul, Türkiye
Ramazan Akdemir, Ankara, Türkiye
Levent Akyürek, Göteborg, Sweden
Tayfun Aybek, Ankara, Türkiye
Mehmet Ateş, İzmir, Türkiye
Saide Aytekin, İstanbul, Türkiye
Vedat Aytekin, İstanbul, Türkiye
Ljuba Bacharova, Bratislava, Slovak Republic
Luiggi P. Badano, Udine, Italy
Gani Bajraktari, Prishtina, Kosovo
Işık Başar, İstanbul, Türkiye
George A. Beller, Charlottesville VA, USA
Ahmet Birand, İstanbul, Türkiye
Dirk L. Brutsaert, Antwerp, Belgium
Gerald D. Buckberg, Los Angeles, CA, USA
Cahid Civelek, St. Louis, MO, USA
Ubeydullah Deligönül, Tyler TX, USA
Ufuk Demirkılıç, Ankara, Türkiye
Ertan Demirtaş, Ankara, Türkiye
Ali Emin Denktaş, Houston, TX, USA
Polychronis Dilaveris, Athens, Greece
Fırat Duru, Zurich, Switzerland
Rasim Enar, İstanbul, Türkiye
Oktay Eray, Antalya, Türkiye
Ertuğrul Ercan, İzmir, Türkiye
Okan Erdoğan, İstanbul, Türkiye

Ali Ergin, Kayseri, Türkiye
Çetin Erol, Ankara, Türkiye
Ali Serdar Fak, İstanbul, Türkiye
Roberto Ferrari, Ferrara, Italy
Armen Y. Gasparyan, West Midlands, UK
Ali Gholamrezaezhad, Tehran, Iran
Hasan Gök, Konya, Türkiye
Bülent Görenek, Eskişehir, Türkiye
Sema Güneri, İzmir, Türkiye
Deniz Güzelsoy, İstanbul, Türkiye
Masayasu Hiraoka, Tokyo, Japan
Coşkun İkizler, Ankara, Türkiye
Barış İlerigelen, İstanbul, Türkiye
Gökhan İpek, İstanbul, Türkiye
Erkan İriz, Ankara, Türkiye
Diwakar Jain, Philadelphia, USA
Charles Jazra, Bavchrieh, Lebanon
Göksel Kahraman, Kocaeli, Türkiye
Mehmet Kaplan, İstanbul, Türkiye
Sezer Karcier, İstanbul, Türkiye
Erdem Kaşıkçıoğlu, İstanbul, Türkiye
Cihangir Kaymaz, İstanbul, Türkiye
Mustafa Kılıç, Denizli, Türkiye
Serdar Kula, Ankara, Türkiye
Serdar Küçüköğlu, İstanbul, Türkiye
Hakan Kültürsay, İzmir, Türkiye
Samuel Levy, Marseille, France

Jason M. Lazar, New York, USA
Peter Macfarlane, Renfrewshire, Scotland
Robert W. Mahley, San Francisco, CA, USA
G.B. John Mancini, Vancouver BC, Canada
Matti Mänttari, Helsinki, Finland
Barry J. Maron, Minnesota, USA
Pascal Meier, London, UK
Franz H. Messerli, New York, USA
Haldun Müderrisoğlu, Ankara, Türkiye
İstemi Nalbantgil, İzmir, Türkiye
Navin C. Nanda, Birmingham, AL, USA
Altan Onat, İstanbul, Türkiye
Hakan Oral, Ann Arbor, MI, USA
M. Remzi Önder, İzmir, Türkiye
Zeki Öngen, İstanbul, Türkiye
Necla Özer, Ankara, Türkiye
Mehmet Bülent Özün, Ankara, Türkiye
Mehmet Özkan, İstanbul, Türkiye
Süheyla Özkutlu, Ankara, Türkiye
Azmi Özlür, İstanbul, Türkiye
Ahmet Fatih Özyazıcıoğlu, Bursa, Türkiye
Sotirios N. Prapas, Athens, Greece
Shahbudin Rahimtoola, Los Angeles, CA, USA
Vedat Sansoy, İstanbul, Türkiye
Muhammed Saric, New York, USA
Murat Sezer, İstanbul, Türkiye
Mark V. Sherid, New York, USA

Horst Sievert, Frankfurt, Germany
İlke Sipahi, İstanbul, Türkiye
Hulki Meltem Sönmez, Aydın, Türkiye
Richard Sutton, London, UK
Ahmet Şaşmazel, İstanbul, Türkiye
Zeynep Tartan, İstanbul, Türkiye
Oğuz Taşdemir, Ankara, Türkiye
Ahmet Temizhan, Ankara, Türkiye
Adam Timmis, London, England
S. Lale Tokgözoğlu, Ankara, Türkiye
Oktay Tutarel, Hannover, Germany
Murat Tuzcu, Cleveland, OH, USA
Volkan Tuzcu, İstanbul, Türkiye
Sabahattin Umman, İstanbul, Türkiye
Dilek Ural, Kocaeli, Türkiye
Ahmet Ünalır, Eskişehir, Türkiye
Marc A. Vos, Utrecht, Netherlands
Galen Wagner, Durham, NC, USA
Hein Wellens, Maastricht, Netherlands
Nuran Yazıcıoğlu, İstanbul, Türkiye
Murat Yeşil, İzmir, Türkiye
Remzi Yılmaz, Şanlıurfa, Türkiye
Kiyoshi Yoshida, Okayama, Japan
Mehmet Yokuşoğlu, Ankara, Türkiye
Jose L. Zamorano, Madrid, Spain
Wojciech Zareba, New York, USA



Genel Yayın Yönetmeni / Executive Editor
İbrahim KARA

Yayın Koordinatörleri / Publication Coordinators
Sevilay ARDIÇ NAYIR
Gökhan ÇİMEN
Ali ŞAHİN

Proje Asistanları / Project Assistants
Sinan Gökborü BÜNCÜ
Ulaş ÖZGÜR

Grafik Departmanı / Graphic Department
Ünal ÖZER
Neslihan YAMAN
Merve KURT

Yayıncı / Publisher

AVES
Adres/Address: Kızılelma Cad.
No:5/3 34096 Fındıklı / İstanbul
Telefon/Phone: +90 212 589 00 53
Faks/Fax: +90 212 589 00 94
E-posta/E-mail: info@avesyayincilik.com

Basım Tarihi / Printing Date
Mayıs 2013 / May 2013

Yayın Türü / Publishing Type
Yerel Süreli / Local Periodical

ISSN 1302-8723 • E-ISSN 1308-0032

Baş Editör Ofis Asistanı:

Betül TUNTAŞ
Tel: +90 222 229 15 65
Faks: +90 222 229 15 85
E-posta: info@anakarder.com
btimur@ogu.edu.tr

Baskı / Printing
ADA Ofset Matbaacılık
Tic. Ltd. Şti., Litros Yolu
2. Matbaacılar S. E Blok
No: (ZE2) 1. Kat
Topkapı, İstanbul
Tel: +90 212 567 12 42

Anadolu Kardiyoloji Dergisi

Eskişehir Osmangazi Üniversitesi (ESOGÜ)
tarafından kısmen desteklenmektedir.

The Anatolian Journal of Cardiology is partly supported by University of Eskişehir Osmangazi (ESOGÜ).

ESKİŞEHİR OSMANGAZİ ÜNİVERSİTESİ
MEŞELİK KAMPÜSÜ 26480 ESKİŞEHİR
Tel: +90 222 239 71 48
Faks: +90 222 239 54 00

AMAÇ VE KAPSAM

Anadolu Kardiyoloji Dergisi kardiyoloji konulu, yayın dili hem Türkçe hem İngilizce olan, bağımsız ve önyargısız çift-kör hakemlik (peer-review) ilkelerine dayanan uluslararası, periyodik bir dergidir. Anadolu Kardiyoloji Dergisi Şubat, Mart, Mayıs, Haziran, Ağustos, Eylül, Kasım ve Aralık aylarında olmak üzere yılda 8 sayı olarak yayınlanır.

Anadolu Kardiyoloji Dergisi'nin hedefi uluslararası düzeyde nitelikli, sürekli ve kardiyoloji konusunda özgün bir periyodik olarak klinik ve bilimsel açıdan en üst düzeyde orijinal araştırmaları yayınlamaktır. Bununla birlikte eğitim ile ilgili temel yenilikleri kapsayan derlemeler, editöryel kısa yazılar, olgu sunumları, orijinal görüntüler ve geniş kardiyoloji kesimlerinin konular hakkındaki deneyimlerini ve eleştirilerini içeren mektuplar ve sosyal kardiyoloji konulu yazılar yayınlamaktır.

Derginin hedef kitlesi kardiyoloji, çocuk kardiyoloji, kardiyovasküler cerrahi ve iç hastalıkları uzmanları, pratisyen hekimler ve tüm ilgili branşlardaki uzmanlardır.

Derginin editöryel ve yayın işleyişi ICMJE, COPE ve HEART Grubu standartları çerçevesinde yürütülmektedir.

Telif Hakkı, Çıkar Çatışma Bildirimi ve Yazar Katkı formları www.anakarder.com adresimizde mevcuttur.

Anadolu Kardiyoloji Dergisi; Science Citation Index Expanded, Journal Citation Reports, Index Medicus/Medline/PubMed, EMBASE, Scopus, CINAHL, Gale/Cengage Learning, EBSCO, DOAJ, ProQuest, Index Copernicus ve Tübitak/Ulakbim Türk Tıp Dizini tarafından indekslenmektedir.

Anadolu Kardiyoloji Dergisi'nin gelirleri abone ücretleri ve ticari firmalardan sağlanan reklamlardan oluşmaktadır.

Abone İşlemleri

Derginin tüm sayılarının tam metinlerine ücretsiz olarak www.anakarder.com adresinden ulaşılabilir. Basılı dergiye abone olmak isteyen kişiler web sayfasındaki abone formunu doldurmalı ve Yayınevine başvurmalıdır.

Yayınevi : AVES-İbrahim Kara
Adres : Kızılelma cad. 5/3 34096
Findıkzade-İstanbul
Tel. : 0212 589 00 53
Faks : 0212 589 00 94
Web sayfası : www.avesyayincilik.com
E-posta : info@avesyayincilik.com

Baskı İzinleri ve Tekrar Baskılar

Baskı izinleri ve Tekrar Baskılar için başvurular Yayınevi'ne yapılmalıdır.

Yayınevi : AVES-İbrahim Kara
Adres : Kızılelma Cad. 5/3 34096 Findıkzade-İstanbul
Telefon : +90 212 589 00 53
Faks : +90 212 589 00 94
Web sayfası : www.avesyayincilik.com
E-posta : info@avesyayincilik.com

Reklam

Reklam ile ilgili başvurular Yayınevine yapılmalıdır.

Yayınevi : AVES-İbrahim Kara
Adres : Kızılelma cad. 5/3 34096
Findıkzade-İstanbul
Tel. : 0212 589 00 53
Faks : 0212 589 00 94
Web sayfası : www.avesyayincilik.com
E-posta : info@avesyayincilik.com

Yazarlara Bilgi

Yazarlara Bilgi dergi sayfalarında ve www.anakarder.com web sayfasında yayınlanmaktadır.

Materyal Sorumluluk Reddi

Anadolu Kardiyoloji Dergisi'nde yayınlanan tüm yazılarda görüş ve raporlar yazar(lar)ın görüşüdür ve Editör, editöryel kurul ya da yayıncının görüşü değildir; Editör, editöryel kurul ve yayıncı bu yazılar için herhangi bir sorumluluk kabul etmemektedir.

Dergimizde asitsiz kağıt kullanılmaktadır.

AIMS AND SCOPE

The Anatolian Journal of Cardiology is the double-blind peer-reviewed, published in Turkish and English languages international periodical on cardiology. The Anatolian Journal of Cardiology is published 8 times per year (February, March, May, June, August, September, November and December).

The aim of the Anatolian Journal of Cardiology is to publish research articles on original issues of cardiology of the highest clinical and scientific quality at the international level. Along with this, it publishes reviews covering fundamental innovations and dealing with education, short editorial articles, original case reports and images, letters on experience relevant to broad cardiology issues and critiques, as well as issues on social cardiology.

The journal's audience includes cardiologists, pediatric cardiologists, cardiovascular surgeons, internal medicine specialists, practitioners and specialists of all relevant disciplines.

The journal's editorial and publishing process is adherent to standards of ICMJE, COPE, and HEART Group.

Copyright Transfer, Conflict of Interest Declaration and Authorship Contributions forms are available at www.anakarder.com.

The Anatolian Journal of Cardiology is indexed in Science Citation Index Expanded, Journal Citation Reports, Index Medicus/Medline/PubMed, EMBASE, Scopus, CINAHL, Gale/Cengage Learning, EBSCO, DOAJ, ProQuest, Index Copernicus and Tübitak/Ulakbim Turkish Medical Database.

The funding sources of the journal are advertising and subscription.

Subscription information

The access to all full-text issues of the journal is free at www.anakarder.com. To subscribe to the print issues of the journal please fill the subscription form at www.anakarder.com and contact the Publisher.

Publisher : AVES-İbrahim Kara
Address : Kızılelma cad. 5/3 34096
Findıkzade-İstanbul
Phone : +90 212 589 00 53
Fax : +90 212 589 00 94
Web page : www.avesyayincilik.com
E-mail : info@avesyayincilik.com

Permissions and Reprints

Permissions for reproduction of materials published and Reprints in the Anatolian Journal of Cardiology should be requested at Publisher:

Publisher : AVES-İbrahim Kara
Address : Kızılelma Cad. 5/3 34096 Findıkzade-İstanbul-Turkey
Phone : +90 212 589 00 53
Fax : +90 212 589 00 94
Web page : www.avesyayincilik.com
E-mail : info@avesyayincilik.com

Advertising

For requests concerning advertising, please contact Publisher.

Publisher : AVES-İbrahim Kara
Address : Kızılelma cad. 5/3 34096
Findıkzade-İstanbul
Phone : +90 212 589 00 53
Fax : +90 212 589 00 94
Web page : www.avesyayincilik.com
E-mail : info@avesyayincilik.com

Instructions for authors

Instructions for authors are published in the journal pages and could be accessed at the web site of the journal - www.anakarder.com

Material Disclaimer

Statements or opinions expressed in the manuscripts published in the Anatolian Journal of Cardiology reflect the views of the author(s) and not the opinions of the editors, the editorial board and the publisher; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials.

The journal is printed on an acid-free paper.

YAZARLARA BİLGİ

Baş Editör: Prof. Dr. Bilgin TİMURALP

Yazışma Adresi: Anadolu Kardiyoloji Dergisi
Kızılcama Cad. 5/3 34096 Fındıkzade-İstanbul / Türkiye
Tel.: 0222 229 15 65 - 0533 966 48 67
Faks: 0222 229 15 85
Web sayfası: www.anakardder.com
E-posta: btimur@ogu.edu.tr - info@anakardder.com

Anadolu Kardiyoloji Dergisi (AKD), çift-kör "peer-review" dergi olarak kardiyoloji alanında kesinlikle klinik kardiyoloji uygulamaları ile ilişkili olabilecek deneysel, temel bilimler, orijinal klinik çalışmaları, mezuniyet sonrası kardiyoloji eğitimi, özellikle Türkiye toplum sağlığı ile ilgili incelemeler, olgu sunumları, bunlara yönlendirilen çeşitli soru, cevapları ve katkılar, kardiyoloji tarihi, yayın ve araştırma etiği ile Devlet kurumlarının hekimleriyle ilgili kardiyoloji konularındaki düşünceleri, uygulanan, değişen ilişkileri ile Türk ve tüm Dünya Kardiyoloji Derneklerinin çalışmaları ve gelişmelerini yayımlar. Editörün yazı seçimine temel teşkil edecek hakem heyeti, dergide belirtilen danışmanlar ile yollanan yazı için yurt içi-dışı bağımsız otoritlerden seçilir. Anadolu Kardiyoloji Dergisi Şubat, Mart, Mayıs, Haziran, Ağustos, Eylül, Kasım ve Aralık aylarında olmak üzere, yılda 8 sayı çıkar.

Türk dilini iyi kullanmak çok önemlidir. Türk Dil Kurumu'nun Türkçe sözlüğü ve yazın klavuzu ile Türk Kardiyoloji Derneği'nin Kardiyoloji Terimler Sözlüğü yazıda temel alınmalıdır. İngilizce yazılan yazılar özellikle desteklenmektedir.

Deneysel, klinik ve ilaç araştırmaları için ilgili uluslararası anlaşmalara uygun (Helsinki Declaration of 1975, revised 2008- <http://www.wma.net/en/30publications/10publications/b3/index.html>, "Guide for the care and use of laboratory animals-www.nap.edu/catalog/5140.html) etik komisyon raporu gerekmektedir.

Tüm otoriler bilimsel katkı, oran ve ilgili sorumlulukları, ayrıca çıkar çatışması olmadığını bildiren toplantı inza ile yayına katılmaları. Araştırmalara yapılan kısmi de olsa nakdi ya da ayni yardımları hang kurum, kuruluş, ilaç-geçer firmalınca yapıldığı dip not olarak bildirilmelidir. (ICMJE Potansiyel Çıkar Çatışmaları Bildirim Formu ve Yazarlık Katkı formu www.anakardder.com/dan_ulasilabilir). Derginin yayın ve araştırma etiği ile ilgili uygulamaları ICMJE, COPE ve HEART Grubu kuralları ile uyumludur.

Özgün Araştırma, hasta bazlı Olgu Sunumları için genel etik kuralları çerçevesinde yayının yapıldığı kurumun yetkililerinin hazırladığı etik kurul onayı ya da eşdeğeri bir kabul yazısının sunulması şarttır. Olgu sunumları ve Özgün Görüntüler için sınırlı yer ayırıldığında, yüksek bilimsel ve akademik kalitesi özgün araştırma ve derleme yazıları öncelikli kabul edilmekteyiz.

Yazılardaki düşünce ve öneriler tümüyle yazarların sorumluluğunda olup, editör ve yardımcıların kanaatlerini yansıtmaz.

Yazılar başka yerde yayınlanmamış olmalıdır. Daha önce bilimsel toplantılarda 200 kelimeli geçmeyen özet sunumlarının yayınlama, durumu belirtilmek koşulu ile kabul edilebilir.

İşlemleri yürütülüp karar aşamasına yaklaşmış olan yazıların, makul bir neden olmadan geri çekilme talebi "ret" kapsamına girmektedir.

Yayına kabul edilen yazılar için birinci yazar, Türkiye ve İngilizce açısından olduğu gibi, metinde temel değişiklik yapmamak kaydı ile düzeltmelerin editörlerce yapılmasını kabul etmiş sayılır.

Yazıların dergide yayınlanmak üzere kabul edilmesi için; atfı alabilme olasılığı, orijinal ve bilimsel akademik üst düzeyde olması ön koşullardır.

Genel Kurallar

Yazarlar derginin çevrimiçi makale kabul sistemi www.anadolukardiyologderg.com aracılığı ile Baş Editör ofisine gönderilebilir. Ayrıntılı bilgi www.anakardder.com. Yayına kabul edilmeyen yazılar, sanatsal resimler hariç geriye yollanmaz. Tüm yazılar, editörler başta olmak üzere, editör danışmanı, istatistik danışmanları ve en az üç danışman-hakem tarafından incelenir. Yazı konusunun en önce gelen otorü olan, fakat çalışmanın dışında olup yazarlarla ve kurulları ile ilişkisi-bilgisi olmayan üç kişisinden iki yazar tarafından - hakem olarak önerilmesi dergi için çok önemlidir. Daha önce başka bir dergiyeye yollanan ve yayınlanmasını yazanlar, hakem raporlarının da birlikte yollanması zorunludur ve alınacak kararların çabuklaştırılmasına yardımcı olacaktır.

Editör, hakemlere yazıyı göndermeden önce aşağıda bildirilen biçimsel kurallara uygunluğunu araştırır. Düzeltmeler orijinal metin değil, düzeltilmesi istenen bölümlere kısıtlı olmalıdır. Yazılar yollanmadan önce yazın ve çizim hatalarından tam olarak arındırılmalıdır.

Yazın Kurallarına uygun hazırlanmayan makaleler değerlendirmeye alınmayacaktır. Yazardan revizyon bekleme süresi 24 gün, hakemlerde bekleme süresi 21 gündür.

Makalelerin formatı "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (<http://www.icmje.org/>)" kurallarına göre düzenlenmelidir.

Makale ile birlikte doldurulmuş Yazarlık Katkı Formu sunulması gerekir. Derginin Yazarlık Katkılar ile ilgili kuralları CSE (<http://www.councilscienceeditors.org/4a/pages/index.cfm?pageid=3376>) ve ICMJE (http://www.icmje.org/ethical_1author.html) önerileri ile uyumludur.

Özgün Araştırmalar ve Derlemeler'in sunumu çalışma bildirimci kılavuzlarına göre düzenlenmelidir: randomize çalışmalar için CONSORT, gözlemsel çalışmalar için STROBE, tanısal değeri çalışmalar için STARD, sistematik derleme ve meta-analizler için PRISMA, hayvan deneyli çalışmalar için ARRIVE, randomize olmayan davranış ve halk sağlığına müdahale çalışmalar için TREND.

Haziran 2012 tarihinden itibaren Anadolu Kardiyoloji Dergisi'nde basımlık isteği ile yollanan olgu sunumları ve özgün görüntülerini incelemeye başlanılması için birinci yazarının Anadolu Kardiyoloji Dergisi'ne bir yıllık abone olması gerekmektedir. Bu abone koşulu yalnız yazının incelemeye başlanması için olup, hiçbir şekilde basıma kabul ya da basım için öncelik sağlamamaktadır.

Abone olan otorün yazısı genel kurallara ve özel bölümler başlığındaki usul ve esaslara göre değerlendirilmeye alınır, kabul garantisi sağlanmaz. Abonelik ücreti 120 TL olup işlemler için yayıneviyle temas kurulmalıdır: AVES- 0212 589 00 53 - info@avesyayincilik.com

Araştırma Yazıları

1. Özgün Araştırma: Yazının tümünün 5000 kelimeden az ve yalnızca anlamada gerekli olan sayı ve içerikte tablo ve grafik desteği olmalıdır. Kaynakların 50'den az olması inandırıcılık için genelde yeterlidir.

1.1- Kapak sayfası: Birinci sayfadır ve aynı WinWord dosyası olarak düzenlenir. Yazarların tam ve açık isimleri, son aldıkları akademik unvanları ile 50 karakteri geçmeyecek şekilde yazının başlığı yazılır. Yazarların ilgili oldukları kurum, bölüm ve şehir sıra ile bildirilir. Birden fazla yerde yapılan çalışmalar sembollerle açıklanır. Bu sayfadan altına yazıya yetkili, düzeltmeleri yapacak yazının açık adı, posta ve e-posta adresi, telefon ve faks numaraları yazılır. Ayrıca çalışma bilimsel toplantıda önceden bildirilen koşullarda tebliğ edildi ya da özetі yayımlandı ise açıklama yapılır.

1.2- Özgün araştırma makalesi için bölümlü özet: Mutlaka 250 kelimeden kısa hazırlanmalıdır. Özet Amaç, Yöntem, Bulgular, Sonuç şeklinde alt başlıklara düzenlenir. NLM MESH terimleri (<http://www.nlm.nih.gov/mesh/MBrowser.html>) adresinde bulunabilir) ile uyumlu 6 tane anahtar kelime bölümlü özetin altında verilmelidir.

1.3- İngilizce bölümlü özet: 1.2 maddenin kurallarına uymak koşulu ile hazırlanan İngilizce bölümlü özetir.

1.4- Metin: Makale Başlığı, Giriş, Yöntemler (alt başlıklı), Bulgular, Tartışma, Çalışma kısıtlamaları ile Sonuçlar ve Kaynaklar kısımlarını içermelidir. Metnin özellikle yöntemler, bulgular ve tartışma kısmının alt başlıklara bölünmesi yararlı olabilir. Metnin toplam 5000 kelimeli geçmemeli ve 12 Times New Roman yazım stili ile yazılmalıdır. En sona teşekkür yazılacak ise, ciddi bilimsel katkı dışında araştırmayı yürütülmesine önemli katkıda bulunanlarla, yazının son şeklini vermesine yardım edenler zikredilir. Bu bilginin e-posta ile gönderilmesi gerekir veya aynı WinWord dosyasında "Teşekkür Notu" olarak sisteme yüklenir.

1.5- İstatistiksel analiz: Tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7; 1489-93). İstatistiksel analiz için kullanılan yazılım tanımlanmalıdır. Sürekli değişkenlerin karşılaştırılmasında parametrik testler kullanıldığında zaman verilerin ortalaması-standart sapma olarak bildirilmesi gerekir, parametrik olmayan testler için de Medyan (Minimum-maksimum) veya Medyan (25inci ve 75inci persentiler) değerleri olarak bildirilmesi gerekir. İleri ve karmaşık istatistiksel analizlerde, göreceli risk (RR, relative risk), olasılık (OR, odds ratio) ve tehlike (HR, hazard ratio) oranları güven aralıkları (confidence intervals) ve p değerleri ile desteklenmelidir.

1.6- Kaynaklar: Metin içinde geçiş sırasına göre numaralandırılır. Aynı sayfada çift aralıklı düzenlenir. Kişisel bilgi, yayınlanmamış veriler, baskıda gibi ulaşılamayan kaynaklar burada değil, metin içinde parantez ile sunulur. İlk yılan eski özetler kaynakçaya alınmaz; alınarak parantezde (abstr) şeklinde verilir. Kaynakların geçişliğinden yazarları sorumludur.

Periyodikler: Standart makale: Dergi isimlerinin kısaltmaları Index Medicus listesine göre yapılır (dergilerin kısaltmaları için NLM tarafından her yıl yayınlanan MEDLINE dergilerin listesine <http://www.nlm.nih.gov/tsd/serials/lji.html> adresinden ulaşılabilir). Altı yazar ve daha az olan makalelerde tüm otorler yazılır. Yedi ve fazla olan otorlerden ilk altısı yazılır ve "et al." ilave edilir.

Yazar isimlerinden sonra, o yazının tam başlığı, yıl, cilt ve sayfaları sıralanır.

Örnek: Müller C, Büttner HJ, Petersen J, Roskomun H. A randomized comparison of dipyridol and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000; 101: 590-3.

Kıtaplar

Kıtap içinde bölüm: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St.Louis: Mosby; 1974. p.273-85.

Tek yazarlı kitap: Cohn PF Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1983.

Yazar olarak editör (ler): Norman LJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Toplantıda sunulan makale:

Bengtsson S, Sotheman BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Pienne TE, Rienhoff Q, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P 1561-5.

Bilimsel veya teknik rapor:

Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHS/IGOE 169200860.

Tez:

Kaplan SL. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Elektronik formatta makale:

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: <http://www.cdc.gov/ncidod/EID/cid.htm>.

1.7- Şekiller, Tablolar ve Resimler: Şekil ve resimler, hasta, doktor, kurum isimleri görülmeyecek şekilde hazırlanmalıdır. Metinden ayrı olarak, metin içinde geçiş sırasına göre numaralanarak verilir. Başlık ve altbaşlık ayrı bir sayfada sunulur. Grafiklerde yeterli kalınlıkta çizgi kullanılır. Böylece gerekli küçükletmelerde kayıplar

en aza iner. Genişlikler 9 cm. ya da 18 cm. olmalıdır. Çizimlerin profesyonellerce yapılması uygundur. Gri renkler kullanılmamalıdır. Kullanılan kısaltmalar alt kısmında alfabetik sıra ile mutdaka açıklanmalıdır. Tablo ve Şekil başlıklarında ve tablounun yazı içinde anılmasında Roma rakamları kullanılmamalıdır. Metin, Tablo ve Şekillerde kullanılan andalık sayılar nokta ile ayrılmalıdır. Özellikle tabloları metni açıklayıcı ve kolay anlaşılır hale getirme amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır. Siyah/beyaz, gri tonlarda resimler/sanat eserleri yazarlara ek maliyetisiz basılmaktadır. Ancak renkli resimler/ sanat eserlerinin baskısı için yazarlardan ödemeleri istenecektir. Ayrıntılar için Baş Editör Ofisi ya da AVES Yayıncılık ile temasa geçiniz.

Not: Dergimizin web sayfasında (www.anakardder.com), derginin baskı versiyonunda olgu sunumu ve orijinal görüntülerine yer alan resimlere ek olarak video/hareketli görüntüler ve ekstra imaj/statik görüntüler yayınlanacaktır.

1. İmaj/statik görüntü formatında sunumlar: JPG, GIF, TIFF, BMP
2. Video/hareketli görüntü formatında sunumlar: MPEG, VME
3. Dosya boyutu maksimum 2 MB olmalıdır.
4. Resimlerde ve özellikle video görüntülerinde doktor, kurum, şehir ve hasta tanımlanılan tümü ile silinerek yollanmalıdır.

Makalenizde yer alan tablolar, şekiller ve resimler için orijinal oldukları ayrıca bildirilmeli. Orijinal dışında ve başka kaynaktan alındıkları durumunda mutlaka alınan kaynağa atıfta bulunulmalı ve orijinal görüntülerini "hardcopy" veya elektronik formatta (*.* pdf) versiyonları Telif Hakkı sahiplerinden (yayınevi, dergi veya otor) baskıya alınan izniler ile birlikte Baş Editör ofisine sunulmalıdır.

Kaynaklar, şekiller ve tablolar ile ilgili kurallara tüm makale türleri için geçerlidir.

Özel Bölümler

2. Derlemeler: Doğrudan ya da davetli otorler tarafından hazırlanabilir. Bir bilgi ya da konunun kiniktik kullanılması için son vardığı düzeyi anlatan, tartışan, değerlendiren ve ilerde yapılacak çalışmalara yön belirleyen bir yazıdır. Yazının konusunda otor olması ve atıfta bulunulmuş yazıları gerekir.

Bölümsüz özet: 250 kelime ile sınırlıdır. NLM MESH terimleri (<http://www.nlm.nih.gov/mesh/MBrowser.html>) adresinde bulunabilir) ile uyumlu 6 tane anahtar kelime bölümlü özetin altında verilmelidir. Kelime sayısı 5000, kaynak sayısı 50 ile sınırlıdır.

3. Editöryel Yorum: Dergide çıkan bir araştırmanın o konunun otorü veya iyi değerlendirilen yapan hakem tarafından kısaca değerlendirilmesini amacı güder. Sonunda, klinik anlam ve kısa özet bulunur.

4. Olgu Sunumları: Otorlerce de çok nadir görülen, tanı ve tedavide güçlük gösteren ya da uygulamada genellikle gözümüzden kaçtığı anlaşılır, yeni bir yöntem önerilen, textbook'larda olmayan bilgileri içeren çok ilgi çekici ve öğretici sunular yayınlanabilir. Bu özelliklere sahip olgular sınırlı sayıda basılmaktadır. Video görüntüsü olanları basılma şansı yüksektir. On kaynak ve 700 kelime ile sınırlıdır, özet bulunmama ile birlikte, İngilizce başlık içerir. Olgu sunumu formatını, Introduction/Giriş, Case Report/Olgu Sunumu, Discussion/ Tartışma, Conclusion/Sonuç başlıklarından oluşmaktadır.

5. Bilimsel Mektup: Yeni bilimsel buluş ve verileri duymayı amaçlayan, klinik açıdan önemli ancak ön bildiri niteliğinde olan yazılar bilimsel mektup olarak yayına kabul edilir. Bilimsel mektuplar içerik olarak altı başlıksız olup toplam 900 kelimeli aşmamalıdır. Referans sayısı 10, tablo ve resim sayısı ise 2 ile sınırlı olmalıdır.

6. Editöre Mektuplar: Derginin temel yayın amaçlarından birini oluşturmaktadır. Yayınlanan bir yazının önemi, gözden kaçan bir yazısı ya da olumsuz tartışır. Yazarlar, yayınlanan makaleler hakkında yorum içeren mektuplar dışında da okurların ilgi alanlarına giren konular veya özellikle eğitici vakalar hakkında da Editöre Mektup formatında yorumlarını sunabilir. Beşten fazla kaynak gösterilmez. Başlık ve bölümleri yoktur. En fazla 500 kelimeden oluşur.

7. Eğitim: Son yıllarda araştırma sonuçları ile kesinleşen, akademik düzeydeki eğitimde yerini alan ve klinik uygulamada yer bulan bilgiler ayrıntılı ile sunulur.

Bölümsüz özet: 250 kelime ile sınırlıdır. NLM MESH terimleri (<http://www.nlm.nih.gov/mesh/MBrowser.html>) adresinde bulunabilir) ile uyumlu 6 tane anahtar kelime bölümlü özetin altında verilmelidir. Kelime sayısı 5000, kaynak sayısı 50 ile sınırlıdır.

8. Orijinal Görüntü: Klinik bilime dayalı önemli bulguları yansıtan, kardiyovasküler hastalıklardan temel mekanizmalarına ışık tutan, anormallikleri vurgulayan veya yeni tedavi yöntemlerini aydınlatan çarpıcı ve nadir görüntüler yayına kabul edilir. Video görüntüsü olanların basılma şansı yüksektir. Başlığı ile beraber tanımlayıcı metin ve resim alt yazıları (kaynaksız) toplam 250 kelimeli geçmemelidir. Orijinal görüntü kurallara göre hazırlanan makale yalnızca e-sayfa olarak yayınlanır.

9. Tarihten Notlar: Türkiye için özellikle, Kardiyoloji ve ilgili branşlardaki önemli tarihi olayları açıklayan, hastalığın tan ve tedavisinin tarihi ile ilgili yeni bilgileri ortaya çıkaran makalelerdir. Yeni tarihsel bulgular konu ile ilgili uygun araştırma çalışmalarından sonucu olmalıdır. Tarihten notların içeriği atıf başlıksız olmalıdır ve 900 kelime, kaynak sayısı 10 ile sınırlıdır.

10. Yayın Etiği: Derginin bu bölümünde yayınlanan içerik yayın etiği ile ilgili aktüel bilgileri aktaran makalelerdir ve etik ihlali vakalarıdır. Makaleler 900 kelime ve kaynak sayısı 10 ile sınırlıdır. Yayın Etiği konusunda Prof. Dr. Arif Akşit'in tercüme ettiği "COPE Yayın Etiği Komitesinin Akış Şeması" örnek alınabilir.

11. Tansal Bilimce: Okuyucuları dikkatini çekecek, nadir görülen olguların doğrudan, görüntülenme yöntemleri, EKG ya da operasyonda elde edilen fotoğrafları makroskopik-mikroskopik anatomik, patolojik bulgularla yayınlanabilir. Özgün görüntülerden farklı olarak olgu ve resmin tanısı- sonucu önce gizlenir; çoktan seçmeli şeklinde 4 soru hazırlanır. Derginin sonraki sayhalarında kesin tanı-sonuç, açıklama ve öğretici resimlerle doğru cevap bildirilir; tartışma ile değerlendirilir. Gönderilen olgu sunumu veya özgün görüntüleri Baş Editör, yazının izni ile farklı bilimce formatta çevirebileceği gibi, yazarları 500 kelimeli geçmeyecek şekilde 8 kelimelik başlık ve üç kaynak, beş resim ve video ekleyerek bilimce yazılarına yollayabilir.

INSTRUCTIONS TO AUTHORS

Editor-in-Chief: Professor Dr. Bilgin TIMURALP
Address of Correspondence: Anadolu Kardiyoloji Dergisi
Kızılcıkma Cad. 5/3 34096 Fındıklı-Zade-Istanbul / Turkey
Phone : +90 222 229 15 65 - +90 533 966 48 67
Fax : +90 222 229 15 85
Web page: www.anakardercer.com
E-mail: btimur@ogu.edu.tr - info@anakardercer.com

The Anatolian Journal of Cardiology, being a double-blind peer-reviewed journal, publishes all articles on clinical cardiology with clear clinical relevance including experimental, fundamental and original clinical studies, postgraduate education on cardiology, investigations concerning especially Turkish public health, case reports, relevant letters with questions, answers and contributions, history of cardiology, publication and research ethics, as well as letters on expected, applied and changed relations between State institutions and physicians, works and developments of Turkish and World Societies of Cardiology. The referee's board that advises the selection of papers for publication by Editor consists of the elected advisory experts of the journal and is selected from independent national and international experts in the relevant field. The Anatolian Journal of Cardiology is published 8 times per year, including February, March, May, June, August, September, November and December.

Proper use of Turkish language is of special importance. Turkish Language Institution dictionary and orthography guide together with dictionary of cardiology terms published by Turkish Society of Cardiology should be taken as basic for literary language. Papers written in English language are particularly supported and encouraged.

An approval of research protocols by Ethics Committee in accordance with international agreements (Helsinki Declaration of 1975, revised 2008 - available at <http://www.wma.net/en/30publications/10policies/b3/index.html>), "Guide for the care and use of laboratory animals - www.nap.edu/catalog/5140.html") is required for experimental, clinical and drug studies.

The submission of a written document with institutional approval of Ethics Committee or equivalent confirming the research protocol, even some case reports, are performed in frame of general ethical rules, is mandatory.

The signed statement of scientific contributions and responsibilities of all authors and statement on absence of conflict of interests are required. (ICMJE Form for Disclosure of Potential Conflicts of Interest and Authorship Contributions form is available at www.anakardercer.com). The journal's policy on publication and research ethics is in compliance with ICMJE, COPE and HEART Group rules.

The authors should acknowledge and provide information on grants, contracts or other financial support of the study provided by any foundations and institutions or firms.

The priority in acceptance of manuscripts for publication is given to original research manuscripts and reviews of high scientific and academic quality, in addition limited number of case reports and original images and other types of manuscripts are accepted for publication.

Statements and suggestions published in manuscripts are under the authors responsibility and do not reflect opinions of editors and their associates.

Manuscripts are considered for review only in cases if they have not been published previously elsewhere or are not currently under consideration in other journals. Only those data presented at scientific meetings (notification of scientific conference of session is required) in form of preliminary results - abstracts that does not exceed 200 words - could be accepted for consideration.

The retraction requests of manuscripts, being under consideration and close to the final decision, without reasonable explanation will result in "reject" decision.

The authors of the paper accepted for publication in AJC should be in consent of that editors could make corrections without changing the presented data or the basic meaning of the text of the manuscript written either in Turkish or English languages.

To be accepted for publication, it is required that manuscripts should be original and of high scientific and academic quality, with probability of being cited.

General Guidelines

Manuscripts and accompanying letters could be submitted to the Editor-in-Chief office through on-line manuscript submission system www.anadolukardiyolderg.com; you may find information at www.anakardercer.com

Rejected manuscripts, except artwork usually are not returned. All manuscripts are reviewed by editors, editor's consultant, statistical consultants and at least three experts/referees. Proposal of names of three independent referees, who are unaware of the study and had no relationship with authors or author's institutions, but are experts in the field of the study, by first author is important for the journal.

In case of previous submission of manuscripts for consideration to other journals, submission of manuscripts together with referee's reports is mandatory and will facilitate the consideration.

Before sending manuscript for review to referees editor checks the adherence of the manuscript's format to general guidelines. The spelling and grammar errors are required to be corrected before submission of manuscript. The revised versions of manuscripts should include incorporated revisions highlighted.

Authors are required to submit the revision within 24 days, and the referee's evaluation period is limited by 21 days.

Manuscripts format should be in accordance with Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (available at <http://www.icmje.org/>).

The filled authorship contributions form must be submitted along with manuscript. The journal's rules on authorship contributions are in compliance with CSE (<http://www.councilscienceeditors.org/44/pages/index.cfm?pageid=3376>) and ICMJE (http://www.icmje.org/ethics_1authort.html) recommendations.

Starting from June 2012, in order to be considered for review, it is obligatory for the case reports and original images submitted to the Anatolian Journal of Cardiology that

the first authors must subscribe to the journal for at least one year. This obligation is needed to begin the review process and does not provide any priority in acceptance or publication procedures. The manuscript of the subscriber author is reviewed according to the instructions and principles defined under the related titles, General Guidelines and Special Parts. One-year subscription price is 120 TL and it is necessary to contact with publication house: AVES - +90 212 589 00 53 - info@avesyayincilik.com

Original Investigations and Reviews should be presented according to the guidelines: randomized study - CONSORT, observational study - STROBE, study on diagnostic accuracy - STARD, systematic reviews and meta-analysis PRISMA, animal experimental studies - ARRIVE, nonrandomized behavioral and public health intervention studies - TREND.

Research Articles

1. Original research articles: Manuscript should not exceed 5000 words and should be accompanied by necessary number of tables and figures. Fifty references seem to be enough for confidence.

1.1 Title page is the first page of the manuscript, which should be uploaded as separate WinWord file and include: full names of authors with their last academic degrees and manuscript title consisted of no more than 50 characters. These should be followed by complete descriptions of the department, institutions and city, country where the work was done. If the study was performed at different institutions it should be noted by symbols. Full address for correspondence contains full name of the first author or responsible authors, postal and e-mail addresses, phone and fax numbers. If manuscripts content has been presented before, time and place of the conference should be denoted.

1.2 Structured abstract, in Turkish language should not exceed 250 words and consists of the Objective, Methods, Results and Conclusion sections. No more than 6 keywords concordant with NLM MeSH vocabulary terms (available at <http://www.nlm.nih.gov/mesh/MBrowser.html>) must follow the structured abstract.

1.3 Structured abstract in English language written due to the above mentioned in part 1.2 rules.

1.4 Main text includes Introduction, Methods, Results, Discussion, Study Limitations, Conclusions and References sections. It would be useful to present Methods, Results and Discussion parts with subsections and subtitles. Main text should not exceed 5000 words and should be written in Times New Roman 12 font style. Finally, acknowledgement to persons who significantly contributed to the study or assisted in preparing article should be done appropriately. The latter note should be sent by e-mail or uploaded to the system in form of separate "Acknowledgement" WinWord file.

1.5 Statistical analysis should be performed in accordance with guidelines on reporting statistics in medical journals (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7; 1489-93). Describe software used for analysis. For parametric tests represent continuous variables as Means±Standard Deviation, while for nonparametric tests represent data as Median and range (Minimum- Maximum) or Median and interquartile range (25th and 75th percentiles). Whenever complex analyses are used support the relative risk, odds or hazard ratios values by providing confidence intervals and p values.

1.6 References are numbered in order of citation in the main text and are typed on separate page in double space fashion. Personal communications, unpublished data, manuscripts under publication processing are cited in the main text in parenthesis, but not in list of references. Those abstracts that had been published more than 2 years ago are not accepted as references.

Publications in kind of abstracts are noted in parenthesis (abstr.). Authors are responsible for accuracy of references.

Periodicals:

Standard journal article: Abbreviations of journal titles should be done in accordance with journal abbreviations used in Index Medicus (for journal abbreviations consult List of Journals indexed for MEDLINE published annually by NLM at <http://www.nlm.nih.gov/tsd/serials/j.html>). In case of six or less authors numbers list of all authors is required. If number of authors exceeds seven, list first 6 authors followed by et al. A list of authors should be followed by the full title of the article, journal title, year, volume and page numbers.

Example: Muller C, Buttner HJ, Peterson J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after placement of coronary artery stents. Circulation 2000; 101: 590-3.

Books:

Chapter in a book: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. St Louis: Mosby; 1974. p. 273-85.

Personal author(s): Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor (s), compiler(s) as author: Norman LJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Conference paper:

Benignsson S, Sotheman BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Depuget P, Pienne TE, Riehoff Q, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P. 1561-5.

Scientific or technical report:

Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct Report No: HHSIGDE 16920860.

Dissertation:

Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Article in electronic format:

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar [cited 1996 June 5]; 1(1): (24 screens). Available from: <http://www.cdc.gov/ncidod/EID/cid.htm>.

1.7. Diagrams, Tables and Figures: The figures and pictures should not contain the names of patients, doctors or institutions. Figures and pictures should be sent to the Editor-in-Chief office. They should be printed in separate from main text pages and

numbered in order of citation in the text. The comments for tables, diagrams and figures are explained in a separate page with brief title. The sufficiently thick lines could be used while preparing of graphics, thus preventing the losses in the quality of graphics while decreasing their size. The largest appropriate and acceptable size of graphics is 8-9 cm or 16-17 cm in width. Figures should be done professionally and no gray colors be used. Used abbreviations should be explained in alphabetic order in the footnote of the table or figure's legend. Do not use Roman numbers in the numeration of tables and figures within text and their titles. The decimal numbers in the text, tables and figures should be separated by period. Especially, the text of tables should be easily understandable and explanatory and should not repeat the data presented in the main text. The pictures/art works in black and white, gray colors are published without additional costs for authors. The color pictures/art work will be published at additional costs - please contact the Editor-in-Chief office and AVES publishing house.

Note: In addition to printed version of pictures in case reports and original images published in the journal the video/movie images and additional static images are published in the journal's web site www.anakardercer.com. The requirements for web site video/movie and static images are:

1. Static images should be submitted in one of the following formats: JPG, GIF, TIFF, BMP
2. Video/movie images should be submitted in following formats: MPEG, VMF
3. The maximum size of the file should be no more than 2 MB
4. Video/movie images and figures/photos should be sent without description of doctor's or patient's names, institutions and places of origin.

The originality of tables and figures should be confirmed in the accompanying letter. In case of reproduction of tables and figures from other published sources, the appropriate citation should be done and the original source either in hardcopy or electronic (*.pdf) format along with the obtained permission for publication from Copyright owner (publisher, journal or author(s)) should be submitted to the Editor-in-Chief office.

The rules for title page, references, figures and tables are applicable for all types of manuscripts.

Special Parts

2. Reviews: are prepared by authors or by invited authors. This manuscript should contain the evaluation, discussion, analysis and synthesis of the newest and updated knowledge on topic, intended to be used in clinic, and should define the perspectives for further research. The author should be an expert and have cited published works in the area of interest.

2.1 Unstructured abstract limited to 250 words is required. No more than 6 keywords concordant with NLM MeSH vocabulary terms (available at <http://www.nlm.nih.gov/mesh/MBrowser.html>) must follow the unstructured abstract. Word count is limited by 5000 and references number is limited by 50.

3. Editorials: This type of article is a brief evaluation of published manuscripts by the author in the field of investigation other than referees of the journal. At the end of editorial usually a summary on clinical significance of the study is required.

4. Case reports: Interesting from diagnostic and educational point of view case reports concerning seldom, rare seen even by authorities, those one that usually diagnosed and managed with difficulties, and those cases which description is usually missing in clinical practice applications are published. Limited number of case reports is published. Articles accompanied by video/movie images have high priority for publishing. Case reports consist of introduction, case report, discussion and conclusion parts. Reference and word count numbers are limited (no more than 10 and 700 words), and no abstract is required.

5. Scientific letter: The articles in form of preliminary report aimed to announce the new scientific thoughts and data are accepted for publication as scientific letters. The content of the scientific letter should not contain subheadings and is limited by 900 words. The number of references is limited by 10, and number of figures and tables should not exceed 2.

6. Letter to the Editor: Letter to the Editor is one of the main reasons for publication of this journal. It discusses the importance of the published manuscripts, their missing and deficient sites and usually is limited by 5 references and do not exceed 500 words.

7. Education: Knowledge utilized in clinical applications, included in education curriculum of academic level and confirmed by recent research results should be represented.

7.1 Unstructured abstract limited to 250 words is required. No more than 6 keywords concordant with NLM MeSH vocabulary terms (available at <http://www.nlm.nih.gov/mesh/MBrowser.html>) must follow the unstructured abstract. Word count is limited by 5000 and references number is limited by 50.

8. Original image: The impressive and rare images reflecting important findings based on clinical science, shedding light on fundamental mechanisms of cardiovascular diseases, emphasizing anomalies, enlightening new treatment methods are accepted for publication. Articles with accompanying video/movie images have high priority for publishing. The article including the title, text and figure legends (without references) should not exceed 250 words. Original images are prepared according with the above-mentioned rules and are published in electronic only version.

9. Historical notes: The articles describing important historical events in cardiology (particularly for Turkey) and relevant disciplines, revealing new information on history of disease's diagnosis and treatment. The new historical findings should be the result of a proper research work on the topic. The content of the historical notes should not contain subheadings and is limited by 900 words. The number of references is limited by 10.

10. Publication Ethics: The material published in this section of the journal includes articles providing the contemporary information on publication ethics and cases of ethics misconduct. The articles are limited by 900 words and the number of references is limited by 10. You can find COPE charts on publication ethics at: http://www.publicationethics.org/files/u2/All_flowcharts.pdf.

11. Diagnostic Puzzle: Images which will be of interest for the readers, images of rare cases, obtained from ECG, imaging methods or operation photographs, microscopic-macroscopic anatomical and pathologic findings can be published. Unlike the original images, initial diagnoses of the cases are hidden; and four questions in multiple choice format are prepared. Definite diagnosis-result, explanation and correct answer with instructive images are declared on the ensuing pages of the journal. The Editor-in-Chief can change the format of the question by permission of the authors of original image or case report sent to journal. The authors can send puzzle article in a format not exceeding a total of 500 words, with a maximum of 8 words in the title and up to three references, five images/videos.

İÇİNDEKİLER / CONTENTS

EDİTÖRDEN / EDITORIAL

- Yayın dili ve uluslararası yayıncılık, Profesör Özeydin ve Anadolu Kardiyoloji Dergisi'nin başarısı, hakemlikler. Akademik Depresyon 202
On publication language and international publishing, success of Professor Özeydin and Anatolian Journal of Cardiology, peer-review and academic depression
Bilgin Timuralp, Eskişehir-Türkiye

EDİTÖRYEL-SICAK KONU / EDITORIAL-HOT TOPIC

- Shinya Yamanaka, M.D., Ph.D. - 2012 Nobel Prize Laureate: How his dream of a research career provides vision for the next generation of young scientists 204
2012 Nobel Ödül Laureat'ı Dr. Shinya Yamanaka'nın araştırma kariyeri düşleri gelecek nesil genç bilim adamlarına nasıl bir vizyon aktarıyor
Robert W. Mahley, California-USA

ÖZGÜN ARAŞTIRMALAR / ORIGINAL INVESTIGATIONS

- Use of cardiac CT angiography imaging in an epidemiology study - the Methodology of the Multicenter AIDS Cohort Study cardiovascular disease substudy 207
Kardiyak BT anjiyografik görüntülemenin epidemiyolojik bir çalışmada kullanımı - "The Multicenter AIDS Cohort Study" kardiyovasküler alt çalışmasının metodolojisi
Yalçın Hacıoğlu, Mohit Gupta, Tae-Young Choi, Richard T. George, Christopher R. Deible, Lisa P. Jacobson, Mallory D. Witt, Frank J. Palella, Wendy S. Post, Matthew J. Budoff, Torrance, CA, Baltimore, MD, Pittsburgh, PA, Chicago, IL-USA
- A new approach to the measurement of heart rate in patients with chronic heart failure-Heart rate performance index: an observational study 215
Kalp yetersizliği olan hastalarda kalp hızına yeni bir yaklaşım-Kalp hızı verim göstergesi: Gözlemsel bir çalışma
Aydın Akyüz, Şeref Alpsay, Dursun Çayan Akkoyun, Niyazi Güler, Tekirdağ-Turkey
- The relationship between adiponectin, NT-pro-BNP and left ventricular ejection fraction in non-cachectic patients with systolic heart failure: an observational study 221
Kaşıktık olmayan sistolik kalp yetmezlikli olgularda adiponektin, NT-pro-BNP ve sol ventrikül ejeksiyon fraksiyonu arasındaki ilişki: Gözlemsel bir çalışma
İstemihan Tengiz, Uğur Önsel Türk, Emin Alioğlu, Bahadır Kırılmaz, Gülden S. Tamer, Nurullah Tüzün, Ertuğrul Ercan, İzmir, Çanakkale, Kocaeli-Turkey
- Impaired coronary flow reserve evaluated by echocardiography is associated with increased aortic stiffness in patients with metabolic syndrome: an observational study 227
Metabolik sendromlu hastalarda ekokardiyografik olarak gösterilen bozulmuş koroner akım rezervi artmış aort sertliği ile ilişkilidir: Gözlemsel bir çalışma
Derya Tok, Firat Özcan, Iskender Kadife, Osman Turak, Kumral Çağlı, Nurcan Başar, Zehra Gölbaşı, Sinan Aydoğdu, Ankara-Turkey
- Editorial Comment/Editöryel Yorum: Relations between microvascular function and aortic stiffness in metabolic syndrome 235
Metabolik sendromda mikrovasküler fonksiyon ve aort sertliği arasındaki ilişki
Tae Joon Cha, Kyoung Im Cho, Busan-South Korea
- Relationship between hospital volume and risk-adjusted mortality rate following percutaneous coronary intervention in Korea, 2003 to 2004 237
2003 ve 2004 yılları arasında Kore'de perkütan koroner girişim sonrası hastane hacmi ve risk-ayarlı mortalite arasındaki ilişki
Yong Hoon Kim, Ae-Young Her, Chuncheon City-South Korea

İÇİNDEKİLER / CONTENTS

Editorial Comment/Editöryel Yorum: Hospital volume and mortality relation in PCI-Is there a need for modification of ACC/AHA percutaneous coronary intervention guidelines in Asia? <i>PKG'lerde hastane vaka sayıları ile mortalite ilişkisi-ACC/AHA'nın perkütan koroner girişim kılavuzlarında Asya ülkeleri için değişikliğe gerek var mı?</i> Ayhan Olcay, İstanbul-Turkey	243
► The effects of chronic usage of enzyme inhibitors and angiotensin receptor blockers on contrast-induced nephropathy in low-risk patients <i>Düşük riskli hastalarda anjiyotensin dönüştürücü enzim inhibitörleri ve anjiyotensin reseptör blokerlerinin kronik kullanımının kontrast madde nefropatisi üzerine etkileri</i> Nezihi Barış, Ebru Özpelit, Nazile Bilgin Doğan, Hande Kangül, Sefa Gül, Bahri Akdeniz, Sema Güneri, İzmir-Turkey	245
► Evaluation of right ventricular functions in patients with nasal polyposis: an observational study <i>Nazal polipozisli hastalarda sağ ventrikül fonksiyonlarının değerlendirilmesi: Gözlemsel bir çalışma</i> Eda Şimşek, Ziya Şimşek, M. Hakan Taş, Cüneyt Kucur, Ersin Günay, Harun Üçüncü, Erzurum, Afyon-Turkey	251
DERLEMELER / REVIEWS	
► Value of stress echocardiography in mitral stenosis <i>Mitral darlığının değerlendirilmesinde stres ekokardiyografinin değeri</i> Kadriye Orta Kılıçkesmez, Serdar Küçüköğlü, İstanbul-Turkey	257
► Epicardial adipose tissue: a review of physiology, pathophysiology, and clinical applications <i>Epikardiyal yağ dokusu: Fizyoloji, patofizyoloji ve klinik uygulamalar hakkında bir derleme</i> Cihan Şengül, Olcay Özveren, İstanbul-Turkey	261
EĞİTİM / EDUCATION	
► Kalp yetersizliği tedavisinde yeni açılımlar: Şimdi ve gelecek <i>Recent and future innovations in the treatment of heart failure</i> Alper Kepez, Bülent Mutlu, İstanbul-Türkiye	266
BİLİMSEL MEKTUP / SCIENTIFIC LETTER	
► The effect of distance-based learning on the fifth stage medical students' perception in peripheral vascular diseases course: a questionnaire survey <i>Periferik damar hastalıkları stajında uzaktan eğitim sisteminin beşinci sınıf tıp öğrencilerinin algılaması üzerine etkisi: Anket çalışması</i> Mustafa Saçar, Gökhan Önem, Akile Sarioğlu Büke, Ahmet Baltarlı, Çanakkale, Denizli-Turkey	275
OLGU SUNUMLARI / CASE REPORTS	
► Acute coronary syndrome with intraventricular thrombus after using erythropoietin <i>Eritropoietin kullanımı sonrası intraventriküler trombüs ile birlikte akut koroner sendrom</i> Alparslan Kurtul, Mustafa Duran, Onur Kadir Uysal, Ender Örnek, Ankara, Kayseri-Turkey	278
► Variant high origin of both right and left coronary arteries from the ascending aortic wall <i>Çıkan aort duvarından yüksek kökenli hem sağ ve sol koroner arter</i> Raghavendra Rao, Bondel Shwetha, Karnataka, Bangalore-India	279

İÇİNDEKİLER / CONTENTS

- Miyokart enfarktüsü sonrası implante edilen ICD tarafından sağ ventrikül uyarılmasına bağlı kötüleşen kalp yetersizliğinin resenkronizasyon ile tedavisi 281
Worsening of heart failure due to right ventricular apical pacing by ICD implanted after myocardial infarction and treatment with resynchronization
Ali Deniz, Mehmet Kanadaşı, Mesut Demir, Ayhan Usal, Adana-Türkiye
- Renal coloboma syndrome associated with double- chambered right ventricle 282
Renal kolobom sendromu ile çift odacıklı sağ ventrikül birlikteliği
Gökçen Gökçe, Yalçın Gökoğlan, Volkan Hürmeriç, Fazıl Cüneyt Erdurman, Osman Melih Ceylan, Ali Hakan Durukan, Güngör Sobacı, Kars, Ankara-Turkey
- Thoraco-Omphalopagus conjoined 284
Torako-Omfalopaguslu yapışık ikizler
Kadir Şerafettin Tekgündüz, Haşim Olgun, İbrahim Caner, Naci Ceviz, Erzurum-Turkey
- EDİTÖRE MEKTUPLAR / LETTERS TO THE EDITOR**
- Letters to Editor-in-Chief 286
Baş Editöre mektuplar
- Ischemic stroke in the course of thrombolytic treatment of prosthetic valve thrombosis: thrombolysis is suggested 286
Protez kapak trombozunun trombolitik tedavisi sırasında iskemik inme: Tromboliz önerilir
Fidel Manuel Caceres-Loriga, Havana-Cuba
- Influence of gender, C- reactive protein and triglycerides in risk prediction of coronary heart disease 287
Koroner arter hastalığı riskini öngörmeye cinsiyet, C-reaktif protein ve trigliseridin etkisi
Roberto Lozano, Reyes Marin, M-Jesus Santacruz, Zaragoza-Spain
- Can isolated ST elevation in aVR lead be a sign of acute pulmonary embolism? 288
aVR'de izole ST yükselmesi akut pulmoner emboli belirtisi olabilir mi?
Anita Sadeghpour, Azin Alizadeasl, Tehran, Tabriz-Iran
- A deadly chain of events in a case; Deep venous thrombosis, pulmonary embolism, patent foramen ovale and cerebral embolism 289
Bir vakada ölümcül olaylar zinciri; derin ven trombüsü, pulmoner emboli, patent foramen ovale ve serebral emboli
Murat Eroğlu, Murat Yalçın, Zafer Işılak, Murat Velioğlu, Ankara-Turkey
- Komplike akut Tip B diseksiyonla başvuran Marfan sendromlu hastada başarılı endovasküler greft-stent tedavisi 291
Successful endovascular stent-graft treatment in a patient with Marfan syndrome presenting with complicated acute Type B dissection
Can Yücel Karabay, Cihan Dünder, Kürşat Tigen, Cevat Kırmacı, İstanbul-Türkiye
- Warfarin kullanan hastalara ilaca ilişkin verilen grup eğitiminin bilgi düzeylerine etkisi 292
The effect of group education about drug usage in the patient's on warfarin therapy
Türkan Özcan, Meral Altıok, Fatma Babalıklı, Mersin-Türkiye
- Çok düşük doğum ağırlıklı prematüre bir bebekte başarılı aortopulmoner pencere cerrahisi 294
Successful surgical closure of aortopulmonary window in a very low birth weight premature infant
Önder Doksöz, Savaş Demirpençe, Timur Meşe, Osman Nejat Sarıosmanoğlu, İzmir-Türkiye

İÇİNDEKİLER / CONTENTS

ALMANAC SERİLERİ / ALMANAC SERIES

- Almanac 2012: congenital heart disease. The journals present selected research that has driven recent advances in clinical cardiology 295
Michael Burch, Nathalie Dedieu, London-UK

ANISINA / IN MEMORIAM

- Prof. Dr. A. Mithat Özer'in ardından 304
In memoriam of Prof. Dr. A. Mithat Özer
İstemi Nalbantgil, İzmir-Türkiye

E-SAYFA ÖZGÜN GÖRÜNTÜLER / E-PAGE ORIGINAL IMAGES

- Coexistence of accessory mitral papillary muscle and ventricular septal defect E-15
Aksesuar mitral papiller kas ve ventriküler septal defekt birlikteliği
Zafer Işılak, Onur Sinan Deveci, Murat Yalçın, Mehmet İncedayı, İstanbul-Turkey 
- All-in-one case: constrictive pericarditis, secundum atrial septal defect, persistent left superior vena cava and anomalous drainage of hemiazygos vein to coronary sinus E-16
Hepsi bir vakada: Konstrüktif perikardit, sekundum atriyal septal defekt, persistan sol süperiyor vena kava ve hemiazigos venin koroner sinüse açılması
Abdurrahman Tasal, Osman Sönmez, Ercan Erdoğan, Ömer Göktekin, İstanbul-Turkey
- Severe pulmonary vein stenosis due to invasion of metastatic lung cancer E-17
Metastatik akciğer kanseri invazyonuna bağlı gelişen ciddi pulmoner ven darlığı
Mehmet Mustafa Can, Malatya-Turkey
- Free-floating intra-aortic thrombus causing coronary artery occlusion: appearance in ECG-gated computed tomography with cine-images E-18
Sine-görüntüleri ile EKG-gated BT'de koroner arter tıkanmasına neden olan intra-aortik serbest-yüzen trombüs
Terman Gümüş, Sergin Akpek, Genco Yücel, İstanbul-Turkey 
- Interventricular septal cardiac hydatid cyst mimicking hypertrophic cardiomyopathy E-19
Hipertrofik kardiyomiyopatiyi taklit eden interventriküler septal kist hidatik
Turhan Turan, Abdulkadir Çakmak, Mustafa Çapraz, Ahmet Çağrı Aykan, Trabzon, Amasya-Turkey 

Yayın dili ve uluslararası yayıncılık, Profesör Özaydın ve Anadolu Kardiyoloji Dergisi'nin başarısı, hakemlikler Akademik Depresyon

On publication language and international publishing, success of Professor Özaydın and Anatolian Journal of Cardiology, peer-review and academic depression

Hayatı biz mi kurguluyoruz, yoksa aktörleri miyiz sadece?..

Türkçemizin gelişmesi açısından ulusal ve uluslararası eğitimin etkisinin çok önemli olduğu yadsınamaz. Dilimizin bilim dalı olarak gelişmesinde bilim insanlarımızın birinci derecede sorumlu olduğunu biliyoruz. Bizler "dilci" olmasak da, bize destek sağlayacak, eğitim verecek Türk dili uzmanlarının desteğine bu konuda da büyük gereksinimiz var. Gerek hayranlık, gerek duygusal, gerek tembellik ve kolaya kaçmak nedeni ile; bilimdeki yeni gelişmelerle, uluslar arası toplantı ya da yayınlarda gözümüze çarpan ve öğrendiğimiz yabancı terimleri olduğu gibi, hemen ve aynen kullanmayı yeğlemekteyiz. Osmanlı'nın son devirlerinde, o zamanın yeni romancıları, Fransız hayranlığı ve görgü-bilgi alış-verişimizin hızlanması ile, Fransa'da eğitim gören her düzey ve konudaki gençlerin taşıdığı Fransızca deyim ve sözleri pek acı bir şekilde hicvetmişlerdi. Ama Türkiyemizde göğüslerinde yabancı yazılı "T-shirt"lerle gezen gençler (benim tüm torunlarım dahil) Türk dili konusunda ne kadar geliştirmişiz en güzel!!! örnektir. Bugün düştüğümüz bu çukur için daha birçok başka neden ve bahanemiz de ayrıca bulunabilir.

Diğer bir pencereden Anadolu Kardiyoloji Dergisi'ne baktığımızda, 12 yıl önce Tam Türkçe'li olarak başladığımız bu bilim yayıncılığı, globalleşmenin en önemli yararı olan bilimdeki bilgi-alışverişinin kolay ve çok hızlanması ile Mart sayımızda özgün araştırma-derlemelerde tek bir Türkçe yazı varken, Mayıs sayısı tümü ile İngilizce çıktı. Bu dil seçimi konusunda bir zorlamamız ve önyargımız olmadı. Ama şunu irdelemeler sonunda gördüm ki, Türkçe yazılar atıf almıyor, diğer bir deyişle Anadolu Kardiyoloji Dergisi'nin "Etki Faktörü"nü yükseltmiyor. IF yükselmeyince de gelen yazı sayısı azalıyor, Anadolu Kardiyoloji Dergisi yazı yollama seçiminde alt sıralara düşüyor. Bu durumu yazarlara bildirerek emeklerimizi daha geniş bir bilim alanına yaymaları açısından, seçimlerini öneriyorum. Geçmiş yüzyılda, Dr. Behçet adını Tıp Tarihine yazdırabilirdi ise üstün hekimliği ve gözlem gücünden de öte, Almanca yayın yapan bir dergiyi seçtiği içindir. O sıralarda Türkçe bilim dergilerinin varlığı konusunu Tıp Tarihçileri bırakıyorum; her ne kadar meslekte tam yarım yüzyılı doldurmuş

olsam bile. Sayın Mustafa Aydoğan bir yayınında da "Alman doktor Ganslenn, makalesinde diyabet tedavisinde kullanılan insülinin hastalara soluma yolu ile verilmesini önerdi. Ancak Ganslenn'in bu makalesi, Almanca yazıldığı ve yıllarca başka dile çevrilmediği için değeri 1970'lere kadar anlaşılamadan kaldı" demiştir.

Dostlara hatırlarını sorarken "Nasılsın?" dediğimde biri "Türkiye gibi" diyerek cevaplandırdı. Ağzımdan büyük bir "eyvahhh" çıktı. Esasında çevremdeki akademisyenlerde "Batsın bu Dünya" havasını görüyorum. Hem de "Baba"nın bahtsız ölümünden daha bile önce. Bu şarkı devir devir söylenir. Bazen nedeni "yönetenler" bazen de " yönetilen-akademisyen"ler olur. Ama halen *Akademik bir depresyon* yaşadığımızı biliyorum. Allah'tan bu konuda (Anadolu Kardiyoloji Dergisi dışında) hiçbir ciddi akademik sorumluluk ve yetkim yok.

Yapılan en iyi bir araştırma dahi kullanılmadığı (yayınlanmadığı) takdirde bilimsel değer taşımaz. Okunacak ki; hipotezi sorgulansın, yeni varsayımlar üretilsin, temel alınarak araştırmalar yapılsın ve ya sonuçlar kanıtlanılsın ya da reddedilsin. Varsayım-sorgulama-araştırma-kanıtlama. Darılmayın; Anadolu Kardiyoloji Dergisi'ne gelen ve maalesef haberleri olmadan çok değerli ve deneyimli, üst düzey bilim insanı hocalarımızın da adlarını taşıyan bazı "özgün araştırma" yazıları günlük gazetelerdeki başlıklar ve içerikler gibi yazılmış, adeta bir "demeç". Seçtiği konudaki temel bilgileri yeteri kadar incelemeyen, neden bu araştırmayı yaptığını ve neler beklediğini belirten sağlam bir hipotez kurmadan, ne kanıtlayacağını açıklamadan "hadi bir de buna bakalım" tarzındaki yazılar beni temelden çok üzüyor. Dergimiz ve özümü aşağılanmış hissediyorum. Bazı akademik kadrolar için zorunlu olmasa, YÖK dayatmasa, yönetim kurulları şart koşmasa bu arkadaşlarımızın kesinlikle ciddi bir araştırma ve bilgi üretme gibi gayretleri olmayacak.

Yukarıdaki acı gerçeklere karşı Prof. Dr. Mehmet Özaydın ve arkadaşlarının "N-3 polyunsaturated fatty acids administration does not reduce the recurrence rates of atrial fibrillation and

Yazışma Adresi/Address for Correspondence: Prof. Dr. Bilgin Timuraltı, Kızılelma Cad. 5/3 34096 İstanbul-Türkiye

Tel: +90 212 589 00 53 Faks: +90 212 589 00 94 E-posta: btimur@ogu.edu.tr

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.135



inflammation after electrical cardioversion: A prospective randomized study "başlıklı, 2011-Haziran sayılı Anadolu Kardiyoloji Dergisi'ndeki yazısı hem JAMA, hem de Circulation'dan atıf aldı. Büyük onur duydum, kutlarım.

Hakemler esastır diyordum önceki pek çok yazımda. Onlar bilimsel merak ve ciddiyetleri açısından hakemliği işlerinde öncelikli sıraya koyuyorlar. Acı bir kelime; "angarya"yı meslek olarak almışlar, hiçbir ciddi getirisi olmasa da. Zaten hakemliğin ne kadar önemli bir iş olduğunu geçen haftaki maçta gördük; ölümden döndü. Ben olsam o işi yapmam. Çünkü benim hakem-

lerimi bile o kadar koruyan çıkmıyor. Ne var ki; bu konudaki Editör'e mektubu 286. sayfada lütfen okuyun; özetle -hem yazı yollayıp Baş Editöre 10 hakem seçtiriyor yazarım, hem de hakemlik önerime cevap bile vermiyor.

Olur böyle şeyler.

Bilgin Timuralp
Baş Editör
Eskişehir, Türkiye



Cumhuriyet Kitap Eki, 31 Ocak 2013
Sayın Semih Poroy üstadımın izni ile.

Shinya Yamanaka, M.D., Ph.D. - 2012 Nobel Prize Laureate: How his dream of a research career provides vision for the next generation of young scientists

2012 Nobel Ödül Laureat'ı Dr. Shinya Yamanaka'nın araştırma kariyeri düşleri gelecek nesil genç bilim adamlarına nasıl bir vizyon aktarıyor

Robert W. Mahley

Senior Investigator, Gladstone Institute of Cardiovascular Disease and Gladstone Institute of Neurological Disease, President Emeritus/Founder, Gladstone Institutes, and Professor, Departments of Pathology and Medicine, University of California, San Francisco, California-USA

The career path of Dr. Shinya Yamanaka started with a dream to be a scientist and led to him receiving the 2012 Nobel Prize in Physiology or Medicine. Dr. Yamanaka discovered how to convert skin fibroblasts into induced pluripotent stem (iPS) cells, which are embryonic-like stem cells that could become any of the more than 120 different cell types in the body. His ground-breaking finding, made through hard work, dedication, and a willingness to follow the research wherever it led him, has changed medicine forever. There is much to be gained by young scientists around the world, including Turkey, from Dr. Yamanaka's career path and lessons learned, which can be summarized in just a few words: develop a vision and work hard to achieve it.

Postdoctoral Fellowship at the Gladstone Institutes in San Francisco

The year was 1993, and no one was returning Dr. Shinya Yamanaka's phone calls. The physician and recent Ph.D. graduate of Osaka City University had given up a promising career as an orthopedic surgeon to pursue his dream as a research scientist. But now he was not receiving any responses to his application to become a postdoctoral research fellow in the United States.

Until, that is, Dr. Yamanaka's application came across the desk of Thomas Innerarity, Ph.D., a senior investigator focused on cardiovascular research at the Gladstone Institutes in San Francisco. "I applied to many, many research institutes in the United States, but I received no responses," recalled Dr. Yamanaka. "The one exception was Tom, who invited me to come to Gladstone and be a part of his research laboratory."

It was a wise decision. Founded in 1979, Gladstone is an independent, nonprofit research institute that focused primarily on

research into cardiovascular and viral diseases at the time (later adding a third focus on neurological diseases in the mid-1990s) (www.gladstoneinstitutes.org). The work Dr. Yamanaka undertook as a Gladstone postdoctoral fellow – and the Gladstone notion that researchers must follow science wherever it leads – would form the basis for his subsequent discovery of how to reprogram adult skin cells into iPS cells. Now back at Gladstone as a senior investigator, this former Gladstone postdoctoral fellow has won the 2012 Nobel Prize in Physiology or Medicine.

When Dr. Yamanaka first arrived at Gladstone for his postdoctoral training more than 20 years ago, stem cells were far from his mind. Rather, Dr. Yamanaka focused his research on finding new ways to decrease the levels of low-density lipoproteins (LDL), a major risk factor for coronary artery heart disease. It was widely known among scientists that a protein called apolipoprotein (apo) B was the principal component of LDL. Gladstone scientists were investigating two forms of the apoB protein that existed in the body. The longer form (apoB100), normally found in the liver, is the structural protein of LDL and is recognized by LDL receptors that take up cholesterol. Another shorter form, apoB48, is the structural protein of chylomicrons and is synthesized in the intestine. Importantly, it does not bind to LDL receptors, making it less likely to contribute to cardiovascular disease. Dr. Yamanaka sought to understand how both forms were synthesized. If he could understand that, he reasoned, he could then find ways to change the longer form so that it would resemble the shorter and harmless form and reduce the risk of heart disease.

In early experiments, Dr. Yamanaka studied an enzyme called APOBEC-1, which facilitates synthesis of the shorter apoB48 form. In the liver, APOBEC-1 is normally inactive, and the

Address for Correspondence/Yazışma Adresi: Dr. Robert W. Mahley, M.D., Ph.D., President Emeritus, The J. David Gladstone Institutes, 1650 Owens Street, San Francisco, CA 94158-USA

Phone: +1 (415) 734-2061 Fax: +1 (415) 863-2250 E-mail: rmahley@gladstone.ucsf.edu

Available Online Date/Çevrimiçi Yayın Tarihi: 22.04.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.132





Figure 1. Dr. and Mrs. Robert Mahley and Dr. and Mrs. Shinya Yamanaka
(Photo taken in Stockholm, Sweden, on the occasion of the awarding of the 2012 Nobel Prize in Physiology or Medicine.)

longer apoB is synthesized in this organ. Working under Dr. Innerarity's guidance, Dr. Yamanaka and the other scientists in the laboratory thought that by activating the APOBEC-1 enzyme in the liver, they could mimic the intestinal process to create a shortened form of the apoB protein that would lower LDL levels and thus decrease the incidence of heart disease.

A failed scientific experiment?

The entire laboratory staff began planning and carrying out the experiments needed to test this hypothesis. Twenty years ago, experiments were very labor intensive because many of the reagents had to be prepared in the laboratory – things that today can easily be ordered from chemical supply catalogues. The research team would line up along the entire laboratory bench like an assembly line, with each person, including Dr. Yamanaka, taking on a different step in the experiment. The team's experiments on mice did show a reduction in LDL but, unpredictably, the experiments also had an unintended side effect – the mice developed hepatocellular carcinoma (1), which was a big disappointment to all. Obviously, this approach would not be useful in treating heart disease. Instead of getting discouraged, Dr. Yamanaka, who had worked the hardest on this project, got curious. He wanted to understand what went wrong.

The Gladstone philosophy has always been to give scientists-in-training, like Dr. Shinya Yamanaka, the freedom to follow wherever their curiosity and the science lead, even if that means switching research focus, primary methods, or disease expertise. So for Dr. Yamanaka, this latest turn of events did not constitute a failed experiment; but instead led to the beginning of a new project. This curiosity and willingness to pursue a research project, even in the face of what others would consider a failure, have played a big part in making him the scientist and the person he is today.

Lessons learned by a young scientist

One of my roles as director of the Gladstone Institute of Cardiovascular Disease and president of the Gladstone Institutes was to encourage young scientists like Dr. Yamanaka. One year at our scientific retreat I told them about the secret of having a successful scientific career: "VW." It had nothing to do with the fact that I always drive a Volkswagen (VW) vehicle; rather, VW stands for vision (V) and hard work (W). Dr. Yamanaka has often said that one of the important lessons he learned at the Gladstone was the notion of VW, which guided him even through difficult times. By moving on from what some considered a failed project with a new vision and hard work, he truly embodied this notion. Today, Dr. Yamanaka frequently stresses to young scientists that being a successful researcher and human being requires a clear vision and a willingness to work hard to fulfill it.

A new path opens new doors

Dr. Yamanaka wondered if switching on APOBEC-1 in the liver was responsible for the tumor growth in the liver. Further research refined his theory: he found that switching on APOBEC-1 in the liver altered NAT1, a protein that, when modified, causes tumors to develop. Dr. Yamanaka had therefore found the cause of the tumor growth: expression of a dysfunctional NAT1 (2). Now he wanted to find the solution.

Dr. Yamanaka wanted to study mice that lacked NAT1 to see whether they would still develop cancer. But to do so, he needed to develop genetically modified mice – a process that required embryonic stem (ES) cells. ES cells are called pluripotent, meaning that they have the ability to develop into any type of cell, such as skin, muscle, heart, or blood cells. To obtain the ES cells he needed for his study, Dr. Yamanaka collaborated with Robert Farese, M.D. a Gladstone investigator whose laboratory was the only one with the tools to develop ES cell cultures. He learned every aspect of this relatively new technique, from generating and culturing the human ES cells to inserting the specific constructs lacking NAT1 into mouse eggs. However, he was not able to reach the last stage of creating the genetically modified mice because the NAT1-lacking ES cells that he developed never matured; they just multiplied over and over again. Thus, by accident, he discovered that NAT1 was key to helping stem cells transform into individual cell types. After he made this important observation, he turned his central research focus to discovering the genetic factors involved in this process.

Back to Japan to forge his vision for the future

His new direction eventually took him back to Japan where, armed with the expertise gained at Gladstone, he undertook what seemed to be an impossible undertaking: to find out which genetic factors from among hundreds of possibilities instruct ES cells to become other types of cells. He sought to understand the molecular mechanisms that underlie the pluripotency and rapid proliferation of ES cells and to identify the factors that induce reprogramming. This laborious task involved sorting through many different factors that influence cell development and using them to reprogram somatic cells into ES-like cells. Dr.

Yamanaka selected the most likely ones and began examining them in various combinations. With what was widely seen as stunning speed, he first announced the four genetic factors behind his iPS breakthrough in mice in 2006 (3).

Dr. Yamanaka reported that adult mouse fibroblasts could be induced to form pluripotent cells by expressing just four genes (Oct4, Sox2, Klf4, and c-Myc). The next question Dr. Yamanaka addressed was whether his method would work with human cells. In the past, attempts to translate other findings (e.g., nuclear transfer) from mouse to human cells had been extremely difficult to carry out. However, in November 2007, Dr. Yamanaka electrified the world with the news that iPS cells could be made from human skin cells with the same factors used in mice (4). The ease with which the iPS cell discovery was translated to human cells emphasizes the fundamental importance of his original work in mice. Dr. Yamanaka subsequently found that one of the factors, c-Myc, was not needed, and that reprogramming could occur in the absence of any genomic integration events, and this was confirmed by others. Also in 2007, he showed that iPS cells can produce fully reproductive mice – definitive proof that iPS cells are pluripotent (5).

Dr. Yamanaka's original report was met with surprise and disbelief. The vast majority of scientists believed that nuclear reprogramming would require the use of early ES cells, via nuclear transfer or cell fusion. Major efforts on three continents to make nuclear transfer work in human cells had limited success. Most biochemical efforts focused on identifying complex combinations of "reprogramming factors" in the cytoplasm of fertilized eggs. Thus, Dr. Yamanaka's announcement that he could induce iPS cells from skin cells with a simple cocktail of four genes seemed too good to be true. His method (starting with skin fibroblasts) was radically different from those of other scientists (nuclear transfer, cell fusion), and the combination of genes seemed much too simple. However, in short order, Dr. Yamanaka provided reagents to other laboratories, and his results were rapidly confirmed.

Dr. Yamanaka's discovery altered the way scientists think about the processes that control activation and repression of genes: only three factors are sufficient to epigenetically "erase and re-mark" the entire genome. The simplicity of the final method emphasizes the beauty and complexity of human beings.

Dr. Yamanaka returns to his scientific roots: Gladstone

Dr. Yamanaka was recruited to Gladstone in 2007, this time as a senior investigator and a professor of anatomy at the University of California, San Francisco, with which Gladstone is affiliated, while still maintaining a laboratory in Kyoto.

The development of iPS cell technology by Dr. Yamanaka represents an entirely new platform for studying the fundamental mechanisms of human diseases and for developing therapies to overcome them. Rather than using models made in yeast, flies, or mice, which do not always recapitulate the features of human disease, this technology allows human stem cells to be created directly from patient tissues. As a result, these cells contain a complete set of the genes that resulted in a specific

disease, potentially offering a far-superior human model for studying disease and testing new drugs and treatments.

While the application of iPS cells to regenerative therapies will require refinement, iPS technology is fundamentally altering the way scientists work. Dr. Yamanaka's discovery of iPS cells is transforming multiple disciplines, from basic biology to regenerative medicine, and its simplicity has encouraged other researchers into this field, thereby accelerating progress in this field of research. Today, laboratories across the world are racing to generate iPS cells from humans with all types of disease, investigating cellular pathologic mechanisms in cells containing the disease-causing genetic background, and differentiating disease-specific iPS cells to screen for novel therapeutic agents. Finally, iPS technology provides the exciting possibility of harnessing the benefits of stem cells by producing patient-specific pluripotent cells for cell-based therapies that can avoid immunorejection and other biochemical issues.

Today, Dr. Yamanaka splits his time between San Francisco and Japan, where he is director of the Center for iPS Cell Research and Application at Kyoto University. After years of hard work and international recognition, his principal desire—to find workable solutions to pressing medical problems has never wavered.

On winning the 2012 Nobel Prize in Physiology or Medicine, Dr. Yamanaka stated: "The best part about this prize is that it will bring attention to, and will likely spur, the important stem cell work that scientists around the world are conducting. This iPS technology is for patients, and the more scientists who build on it, the faster we can help those who live with chronic or life-threatening diseases."

Advancement of science by nurturing the next generations

Mentoring, encouraging, and instructing young scientists is like planting trees, which give shade that extends beyond what we might imagine. There is no greater reward for a professor or teacher than participating in planting careers of young scientists in fertile soil. The benefit of the shade has the potential to relieve the suffering of our patients from multiple diseases.

Congratulations, Shinya Yamanaka, for making a difference!

References

1. Yamanaka S, Balestra ME, Ferrell LD, Fan J, Arnold KS, Taylor S, et al. Apolipoprotein B mRNA-editing protein induces hepatocellular carcinoma and dysplasia in transgenic animals. *Proc Natl Acad Sci USA* 1995; 92: 8483-7. [\[CrossRef\]](#)
2. Yamanaka S, Poksay KS, Arnold KS, Innerarity TL. A novel translational repressor mRNA is edited extensively in livers containing tumors caused by the transgene expression of the apoB mRNA-editing enzyme. *Genes Dev* 1997; 11: 321-33. [\[CrossRef\]](#)
3. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; 126: 663-76. [\[CrossRef\]](#)
4. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131: 861-72. [\[CrossRef\]](#)
5. Okita K, Ichisaka T, Yamanaka S. Generation of germline-competent induced pluripotent stem cells. *Nature* 2007; 448: 313-7. [\[CrossRef\]](#)

Use of cardiac CT angiography imaging in an epidemiology study - the Methodology of the Multicenter AIDS Cohort Study cardiovascular disease substudy

Kardiyak BT anjiyografik görüntülemenin epidemiyolojik bir çalışmada kullanımı - "The Multicenter AIDS Cohort Study" kardiyovasküler alt çalışmasının metodolojisi

Yalçın Hacıoğlu, Mohit Gupta, Tae-Young Choi, Richard T. George¹, Christopher R. Deible², Lisa P. Jacobson³, Mallory D. Witt, Frank J. Palella⁴, Wendy S. Post^{1,3}, Matthew J. Budoff

Harbor UCLA Medical Center and the Los Angeles Biomedical Research Institute, Torrance, CA-USA

¹Johns Hopkins University, School of Medicine, Baltimore, MD-USA

²University of Pittsburgh, School of Medicine, Pittsburgh, PA-USA

³Johns Hopkins Bloomberg School of Public Health, Baltimore, MD-USA

⁴Northwestern University, School of Medicine, Chicago, IL-USA

ABSTRACT

Objective: The methodology for use of cardiac CT angiography (CTA) in low risk populations is not well defined. In order to present a reference for future studies, we present CTA methodology that is being used in an epidemiology study- the Multicenter AIDS Cohort Study (MACS).

Methods: The Multicenter AIDS Cohort Study (MACS) is an on-going multicenter prospective, observational cohort study. The MACS Cardiovascular Disease substudy plans to enroll 800 men (n= 575 HIV seropositive and n=225 HIV seronegative) age 40-70 years for coronary atherosclerosis imaging using cardiac CTA. The protocol includes heart rate (HR) optimization with beta blockers; use of proper field of view; scan length limitation; prospective ECG-gating using the lowest beam voltage possible. All scans are evaluated for presence, extent, and composition of coronary atherosclerosis, left atrial volumes, left ventricular volume and mass and non-coronary cardiac pathology.

Results: The first 498 participants had an average radiation dose of 2.5 ± 1.6 milliSieverts (mSv) for the cardiac CTA study. Overall quality of scans was fair to excellent in 98.6% of studies. There were three significant adverse events-two allergic reactions to contrast and one subcutaneous contrast extravasation.

Conclusion: Cardiac CTA was safe and afforded a low effective radiation exposure to these asymptomatic research participants and provides valuable cardiovascular endpoints for scientific analysis. The cardiac CTA methodology described here may serve as a reference for use in future epidemiology studies aiming to assess coronary atherosclerosis and cardiac anatomy in low risk populations while minimizing radiation exposure. (*Anadolu Kardiyol Derg 2013; 13: 207-14*)

Key words: CT angiography, radiation dose, epidemiological study

ÖZET

Amaç: Kardiyak BT anjiyografinin düşük riskli popülasyonlardaki kullanımı ile ilgili metodolojisi belirsizdir. Gelecekteki bu tür çalışmalara referans oluşturmaya amacıyla bu makalede "The Multicenter AIDS Cohort Study" kardiyovasküler hastalık (MACS-KAH) alt çalışmasının metodolojisi sunulmaktadır.

Yöntemler: MACS-KAH alt çalışması birçok merkezli, prospektif ve gözlemsel-kohort çalışmadır. Bu çalışmada 40-70 yaş arası 575'i HIV seropozitif ve 225'i HIV seronegatif olmak üzere toplam 800 erkeğin kardiyak BT aracılığıyla koroner görüntülemesi planlanmaktadır. Çalışma protokolü beta blokerlerle kalp hızının optimizasyonu, uygun görüntüleme alanının seçimi, scan uzunluğunun sınırlanması, prospektif EKG tetiklemenin ve olası en düşük ışın voltajının kullanımını içermektedir. Tüm olgular koroner aterosklerozun varlığı, yaygınlığı ve içeriği, sol atriyum hacmi, sol ventrikül hacmi ve kitlesi ve koroner dışı kalp patolojilerinin varlığı açısından incelenmektedir.

Bulgular: Çalışmaya alınan ilk 498 deneğin kardiyak BT'sinde ortalama radyasyon dozu 2.5 ± 1.6 milliSievert olarak bulundu. Scanlerin görüntü kalitesi deneklerin %98.6'sında orta ve mükemmel arasında değişmekteydi. İki kontrast maddeye alerjik reaksiyon ve biri de kontrast ekstrasvazasyonu olmak üzere toplam üç olguda beklenmeyen yan etki görüldü.

Address for Correspondence/Yazışma Adresi: Dr. Yalçın Hacıoğlu, Harbor UCLA Medical Center and the Los Angeles Biomedical Research Institute, Torrance, CA-USA 1124 West Carson St, E3, Torrance, CA 90502 Phone: +1 301 2223204 E-mail: yhacioglu@yahoo.com

Accepted Date/Kabul Tarihi: 31.10.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 30.01.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.065



Sonuç: Bu metodolojinin kullanımı ile kardiyak BT anjiyografinin bilimsel analizlerde değerli kardiovasküler verilerin elde edilmesi amacıyla semptomsuz araştırma deneklerinde düşük etkin radyasyon dozu sağlayarak güvenli kullanımı olasıdır. Dolayısıyla bu metodoloji, gelecekte düşük riskli popülasyonlarda koroner aterosklerozun ve kalp anatomisinin incelenmesini amaçlayan benzer epidemiyolojik çalışmalara referans olarak ışık tutabilir. (*Anadolu Kardiyol Derg 2013; 13: 207-14*)

Anahtar kelimeler: BT anjiyografi, radyasyon dozu, epidemiyolojik çalışma

Introduction

Human immunodeficiency virus (HIV) infection may be associated with increased risk for coronary artery disease, dilated cardiomyopathy, myocarditis, endocarditis, pericardial effusion, and pulmonary arterial hypertension (1-3). Inflammatory changes, endothelial dysfunction and prolonged exposure to antiretroviral protease inhibitor drugs resulting in metabolic changes such as dyslipidemia and lipodystrophy have been suggested as some of the probable predisposing factors. The evidence for accelerated atherosclerosis was chronologically provided by autopsy series, case reports, cross sectional studies using carotid Doppler ultrasound, coronary artery calcium imaging and a few small-scale studies using cardiac computed tomography angiography (CTA) (4-7). At present, there are no published large-scale epidemiology studies that include cardiac CTA to evaluate the prevalence or progression of subclinical coronary atherosclerosis among asymptomatic HIV patients.

Cardiac CTA is a robust non-invasive imaging modality with proven accuracy in diagnosis and quantification of coronary atherosclerosis (8). Besides coronary luminal narrowing, it provides important information about plaque composition (calcified vs. non-calcified) as well as other cardiac or extra-cardiac structures that may be adversely affected by HIV infection (i.e., cardiac chambers, myocardial mass, valves, pericardium, pulmonary vasculature, etc.). However, due to concerns of radiation exposure hazards based on relatively high dose estimates obtained during the early experience with 64-slice CCTA, experts in the field have recommended against its use in the screening of asymptomatic populations, as well as its use in epidemiology studies (8-12).

Nevertheless, the past several years witnessed the development of newer CT technologies and dose reduction protocols (i.e., use of lower field of view, prospective image acquisition protocol, use of lower kV and mA, and dose modulation techniques) that resulted in substantially lower radiation exposures (as low as 1 mSv per study in some reports) than those reported earlier (13-20). Therefore, it is conceivable that the routine implementation of these new techniques could significantly diminish the radiation hazards associated with cardiac CTA imaging, eventually leading to its wider applicability in a broader spectrum of clinical and research settings.

We describe the cardiac CTA methodology used in the Multicenter AIDS Cohort Study (MACS) Cardiovascular Disease (CVD) substudy, so that it may serve as a reference for the use of cardiac CTA in future epidemiology studies.

Methods

Cardiac CTA methodology in the MACS cardiovascular substudy

The MACS-CVD substudy is a prospective multi-center observational epidemiology study that aims to compare the prevalence and progression of subclinical CVD between HIV seropositive and HIV seronegative men. The specific hypothesis of this study is that the metabolic, inflammatory, immunologic, and anthropomorphic changes associated with HIV infection and/or antiretroviral therapy lead to increased risk for subclinical CVD. This is one of the first prospective studies to utilize cardiac CTA in an asymptomatic population, to identify the presence, size, and composition of coronary plaques (including the degree of coronary artery stenosis). The complete study protocol also involves additional limited CT scanning of the abdomen and thigh for adiposity, non-contrast CT for coronary artery calcium (CAC), carotid ultrasound for carotid intimal thickness, carotid plaque, and carotid artery distensibility, as well as phlebotomy for various blood biomarkers. The current manuscript will focus only on the methodology of the coronary atherosclerosis CT imaging acquired with CTA.

The research protocol was approved by the Institutional Review Boards at each clinical site and participants signed informed consent prior to enrolling in the study. This research on human subjects is in accordance with ethical standards of their institution and with the Helsinki Declaration of 1975, as revised in 1983.

Participants

The MACS Cardiovascular Disease (CVD) substudy plans to enroll up to 800 men (n=575 HIV-positive and n=225 HIV-negative) aged 40-70 years, most of whom have already participated in the original coronary artery calcium (CAC) MACS CVD substudy (4).

Eligibility criteria include the ability to give informed consent, age 40-70 years old (inclusively); absence of history of heart surgery (coronary artery bypass graft or valve surgery) or history of coronary angioplasty with or without stent placement and weight ≤ 300 lbs. Participants are excluded from the contrast CT portion of this study, but can participate in the non-contrast portion (which includes coronary artery calcium) if one of the following is present: estimated glomerular filtration rate by the Modification of Diet in Renal Disease equation (GFR/MDRD) obtained within a month of the scan < 60 mL/min or urine protein > 3 g/L creatinine using a spot urine test; history of contrast allergy; or atrial fibrillation at the time of the scan.

CT scanners/centers

While the original MACS substudy included noncontrast coronary artery calcium (CAC) scanning with either electron beam tomography (EBT) or multidetector computed tomography (MDCT), the current cardiac CTA study utilizes only 64+ detectors MDCT scanners. CT scanning equipment includes General Electric (GE) LightSpeed VCT (64-slice MDCT, General Electric, USA) at Harbor-UCLA Medical Center and University of Pittsburgh, Siemens Definition 64-slice Dual Source CT (DSCT, Siemens, Germany) at Northwestern University and Toshiba Aquilion One, 320-slice MDCT (Toshiba, Japan) at Johns Hopkins Hospital.

Participant recruitment, screening and preparation

Potentially eligible participants are mailed a brochure describing the MACS cardiovascular substudy. Recruitment and screening occurs in person at a MACS study visit or by phone. Screening is performed for eligibility as described above. All participants undergo serum creatinine testing within a month prior to CT scanning in order to be eligible for IV contrast on the day of their CT scan visit (acceptable estimated GFR is ≥ 60 mL/min using the *MDRD* equation) (21). Men with contraindications for contrast (e.g. estimated GFR < 60 mL/min or with contrast allergy) receive a non-contrast CT scan only.

On the day of the CT scan, participants are interviewed by a technologist, nurse or physician's assistant at least 30 minutes prior to the procedure. Screening for contraindications for beta-blockers and nitroglycerin is performed. Blood pressure and heart rate are measured and peripheral IV access is obtained. Participants have one intravenous line placed (typically 20 gauge), preferably in an antecubital vein for contrast administration. The participant lies in supine position on the scanner table and is attached to a 12-lead electrocardiographic monitor and an automated blood pressure monitor. Baseline EKG, heart rate, and blood pressure are recorded and reviewed by study personnel. A physician is present at all times during contrast-enhanced MDCT imaging.

Heart rate optimization

Except for the participants undergoing DSCT studies all other participants with initial heart rates of ≥ 65 beats per minute (BPM) are given beta blocker therapy according to local proto-

cols. Generally, 50 mg of metoprolol is given orally up to one hour prior to the MDCT. If the HR remains > 65 BPM, the physician then has an option to either try another oral dose of 50 mg or proceed directly to intravenous metoprolol 2.5 - 5 mg every 5 minutes (maximum 40 mg) until a heart rate of 50-65 BPM is achieved (as long as blood pressure tolerates). Participants may receive IV or oral diltiazem or verapamil if there is a contraindication to using β -blockers (e.g. severe reactive airway disease).

Pre-procedural nitroglycerin

Unless the participant is hypotensive (systolic BP < 90 mm Hg supine), nitrate intolerant or received sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra) within 24-48 hours of the study, every participant receives 0.4 mg of sublingual NTG one minute prior to contrast administration in order to improve epicardial vasodilation.

Contrast administration

Based on the preference of each scanning center, either a low osmolar v.s iso-osmolar, non-ionic, iodinated contrast (either iohexol, iopamidol, or iodixanol) is usually administered at a rate of 5 mL/sec as an IV infusion of, on average, 50-60 mL (max. 70 mL), based on the participant's size after completion of the non-contrast CT studies. Based on the preference of each scanning center either a test bolus or an automated bolus tracking feature is used to assess contrast bolus arrival and optimize image quality. Participants are asked to hold their breath during scanning for up to 10 seconds.

CT image acquisition and radiation dose reduction methods

The main radiation dose reduction methods used in the MACS Cardiovascular Substudy are listed in Table 1. First, scout images are obtained in order to determine the scan range in the anterior-posterior and lateral views. In addition, all CTAs are preceded by a non-contrast cardiac CT scan, which is also used to determine the range of the CTA. Whenever possible the field of view (FOV) on the axial plane is limited to 25 cm in addition to using a proper size cardiac bowtie filter (small for GE scanners and medium for Toshiba Aquilion One scanner) so that the X-ray beam can be limited mostly to cardiac structures (20-22). Utmost effort is exerted to limit the scan length (the z-axis of the chest area imaged) as well.

Table 1. Radiation dose reduction methods used in the MACS Cardiovascular substudy

Dose Reduction Technique	Description
Limitation of the field of view	Limit xy field of view (FOV) using proper size cardiac bowtie filter during image acquisition (FOV 25 cm with small bowtie filter for GE and medium bowtie filter for Toshiba). The FOV is centered on the heart with very minimal display of non-cardiac structures
Limitation of the scan length	Limit scan length (z-axis of chest coverage). This requires efficient use of scout or CAC images for determination of the shortest optimal scan length (usual range 128-160 mm) so that all cardiac structures are optimally visualized along the z-axis starting from 1cm above the left main artery origin to 1 cm below the diaphragm
Prospective ECG triggered image acquisition	Obtaining images only during one phase ($\pm$ padding) of cardiac cycle (mid-diastole), rather than continuous imaging during the entire cardiac cycle for the majority of studies
Low tube voltage settings	Using the lowest tube voltage possible (preferably 80-100 kV, max. 120kV) based on body habitus

CAC - coronary artery calcium, ECG - electrocardiogram, FOV - field of view, kV - kilovolt

This requires efficient use of the scout and/or CAC images for determining the shortest scan length (usual range 128-160 mm) that includes all cardiac structures along the z-axis, starting from 1cm above the left main artery origin to 1 cm below the diaphragm.

The goal is for all studies to use prospective ECG triggering. This technique requires obtaining images only during one phase range of the cardiac cycle with or without some limited padding (75% phase $\pm$ 5% padding), rather than continuous helical imaging (retrospective ECG-gating) during the entire cardiac cycle. This technique is preferred over retrospective ECG-gating imaging unless the heart rate is elevated or there is significant heart rate variability. For the Toshiba scanner, the goal is to perform a "one beat" prospective ECG-triggered scan. If the heart rate is elevated, then a "two beat" prospective ECG-triggered scan is performed.

The fourth method is the use of a reduced tube voltage (use of 80 or 100 kVp for participants with a body mass index <25 kg/m², rather than the typically employed 120 kVp), which has been

shown to reduce radiation exposure by up to 44.8% independent of other techniques (23, 24).

Each measure undertaken contributes to reducing radiation doses to a range acceptable for use in asymptomatic cohorts. The radiation dose per participant was estimated to fall in the range of 2-5 mSv depending on body mass index (BMI), cardiac height and heart rate. The specific scanning settings at each CT center are shown in Table 2.

Data transmission

When studies are completed they are transmitted to the core CT reading center (Los Angeles Biomedical Research Institute at Harbor/UCLA Medical Center) and are read using a dedicated workstation (GE Advantage Workstation® (AW)-version 4.4, GE Healthcare, Milwaukee, WI) by one experienced reader (>10 years of expertise) who is blinded to participant demographic information.

Table 2. CTA scanning parameters by CT site

	Center 1	Center 2	Center 3	Center 4
Scanner type, # of detectors	GE LightSpeed, 64	GE LightSpeed, 64	Siemens Somatom Definition, 64	Toshiba Aquilion One, 320
Image acquisition protocol	Prospective for all if HR<65/min; otherwise retrospective	Prospective for all if HR<65/min; otherwise retrospective	Prospective for all [§]	Prospective for all; two beats scanning [‡] if HR $\geq$ 65/min
Tube voltage, kV	For BMI<25: 80-100 For BMI $\geq$ 25: 100	100	For BMI <25: 80-100 For BMI $\geq$ 25: 100	For BMI<25: 100 For BMI $\geq$ 25: 120
Tube current, mA	mA (BMI) 350 (<25) 550 (25-30) 750/650* (>30)	mA (BMI) 350 (<25) 550 (25-30) 750 (>30)	200	mA (BMI) 550 (<25) 500/490 [¶] (25-30) 580/490 [¶] (>30)
Collimation, mm	64x0.625	64x0.625	64x0.6	320x0.5
Rotation time, s	0.35	0.35	0.33	0.35
Reconstruction kernel	Standard	Standard	B26	FC43 (standard)
Acquisition window (phase) [£]	70-80%	70-80%	70-80%	70-80%
Reconstructed slice thickness, mm	0.625	0.625	0.75	0.5
Reconstruction interval, mm	0.625	0.625	0.40	0.25
Contrast medium	Omnipaque®	Visipaque®	Isovue-370®	Isovue-370®
Contrast rate, mL/s	4-5	5	Determined by Medrad P3T software	5-6
Contrast amount, mL	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg	Determined by Medrad P3T software based on weight	Based on weight: 50 for <60 kg 60 for 60-99 kg 70 for >100 kg

[§]Exceptions require approval by the radiologist

[‡]Prospective ECG gated scanning with total exposure time of 700 ms over portions of two R-R intervals

[†]This is the current protocol since January 2011; prior to that it was BMI based, in the range of 80-120 kV

*For retrospective ECG gated imaging protocol

[¶]For two beats scanning with Toshiba Aquilion One scanner

[£]For prospective ECG gated imaging

BMI - body mass index, CT - computerized tomography, CTA - computerized tomography angiography, ECG - electrocardiogram, HR - heart rate

Curved maximum intensity projection (MIP) and multiplanar reconstructions are performed for each coronary artery segment at the end-diastolic frame or the frame with the least motion artifact. Based on the curved MIP, the reader identifies an area of abnormality and determines the point of minimum luminal diameter within the abnormal area. Multiplanar reformatting is also used to generate cross-sectional images of coronary segments using semi-automated software (AW 4.4, GE Healthcare, Milwaukee, WI). This yields a vessel centerline using the full-width-half-maximum standard method to delineate the contrast-filled vessel, as well as automatic maximum and minimum diameters at any cross-section along the vessel centerline. A cross-sectional 5 mm MIP image is reconstructed at this location and semi-automatic software is used to outline the intimal surface providing cross-sectional vessel area. In cases where coronary segments are normal, the most proximal cross-sectional image is used for analysis. CT values are measured using the most visible images at each site of the coronary arteries, such as axial source or multiplanar images of the long-axis. All data sets are evaluated based on the modified 15-segment model of the American Heart Association (25). The right coronary artery is defined to include segments 1-4, the left main artery and the left anterior descending (LAD) artery to include segments 5-10, and the left circumflex artery (LCX) to include segments 11-15. The intermediate artery (ramus artery), if present, is designated as segment 16. Side branches are used as anatomical landmarks to define coronary segments.

Assessment of the presence and extent of coronary artery plaque and stenosis

The CT reader interactively uses axial images, multi-planar reconstructions and maximum intensity projections to assess the presence and size of plaque and the degree of luminal narrowing and stenosis in all assessable coronary segments. Each segment is graded as to whether it has sufficient diameter and image quality to be accessed. The size of plaque and the percentage of coronary arterial stenosis are estimated from cross-sectional images obtained from a curved multiplanar CTA reconstruction of standardized coronary segments. Plaque size is graded as 0=no plaque, 1=mild, 2=moderate, or 3=severe. Segment stenosis is defined as 0=no plaque, 1=1-29% (minimal) stenosis, 2=30-49% (mild) stenosis, 3=50-69% (moderate) stenosis, or 4=>70% (severe) stenosis. Diameter stenosis is reported by selecting the most narrowed diameter even if the plaque is eccentric. The extent of atherosclerosis is expressed as the total plaque score (TPS) and is determined by summing the plaque size scores for all assessable coronary segments with any plaque (either calcific, noncalcific, or mixed) up to a maximum score of 45. The stenosis scores of all 15 individual segments are summed to yield a total stenosis score (TSS) ranging from 0 to 60.

Composition of coronary atherosclerotic plaque

Plaque is evaluated from both axial source images and multiplanar reconstruction images of the long axis at each site of the coronary arteries. Calcified atherosclerotic plaque is defined as any structure with a density greater than the contrast-enhanced

lumen that can be visualized separately from the lumen, can be assigned to the coronary artery wall, and can be identified in at least two independent planes. Non-calcified atherosclerotic plaque is defined as any discernible structure that can be clearly assignable to the vessel wall (which has a CT density less than the contrast-enhanced coronary lumen but greater than the surrounding connective tissue) and can be identified in at least two independent planes (26). Each coronary segment is classified as either normal or containing non-calcified plaque, mixed plaque (<50% of plaque area occupied by calcium) or calcified plaque. Standard display settings are used for the evaluation of the contrast-enhanced CT scans (window width 800 Hounsfield units; window center 250 HU). Reviewers independently evaluate the contrast-enhanced scans by assessment of the axial slices of multiplanar reformations and of three thin-slab maximum intensity projections. Oriented along the heart axis, the thin-slab (5 mm thickness, 1-mm increment) maximum intensity projections are reconstructed perpendicular to one another.

Left ventricular volume and mass

Measurements are made for left ventricular (LV) volume, mass and left atrial (LA) volumes using Simpson's method of discs, which has been previously validated (27). Estimation of end-diastolic LV volume is possible with the help of a prediction model using LV and LA volumes at the 75% phase [LV EDV=(1.021×75% phase LV volume) + (0.259×75% phase LA volume), adjusted R (2)=0.995] (28).

Non-coronary cardiac findings

Cardiac CTAs are also evaluated for major non-coronary cardiac findings that may alter patient management: aortic disease, valvular disease, pericardial disease, interatrial and interventricular shunts, and aneurysms. According to individual institutional practice, scans are read for non-cardiac incidental findings by a radiologist and/or for findings of clinical importance that are referred to a radiologist for interpretation, and then reported to the PI. The clinical follow-up of lung nodules is advised based on the Fleischner Society Recommendations (29).

Assessments for quality assurance and contrast medium, and radiation dose safety

Quality assurance of CT images is performed using five distinct measures. First, each CT scan is visually inspected by the data manager at the core CT lab for compliance with the protocol, including appropriate kilovolts (kVs), milliAmperes (mAs), reconstruction field of view, slice thickness and phase reconstructions, as well as radiation dose length product. Then the expert CT reader analyzes each image for adequate breath hold, presence of motion artifacts, and inclusion of all parts of the heart and descending thoracic aorta. Third, a contrast-to-noise ratio of the distal left anterior descending artery is calculated for each scan as a quantitative metric of image quality. Fourth, a randomly selected 5% of cases are measured for image quality assurance by the primary investigator as well as the CT reader. Fifth, CT scanners at each site perform daily calibration.

Image quality is assessed by looking at the axial data (representative of the X- and Y-axes resolution) and the coronal reformat slice (representative of the Z-axis resolution). All CTA scans are evaluated for presence or absence of slab, blurring, and partial volume-averaging artifacts. Image quality is graded for individual coronary artery segments and for the entire study.

One reader, blinded to clinical and scan parameters, scores each study. Parameters assessed include participant motion, respiratory motion, cardiac motion, image noise (signal to noise ratios), contrast opacification and segment-based interpretability. Overall image quality is scored using a four-point Likert scale (30). Segments that cannot be evaluated are given a score of 4, which corresponds to a lack of vessel wall definition due to marked motion artifacts, poor vessel opacification, prominent structural discontinuity, or high image noise-related blurring. A score of 3 corresponded to some motion artifacts or noise-related blurring, fair vessel opacification, or minimal structural discontinuity; a score of 2 indicates minor motion artifacts or noise-related blurring, good vessel opacification, and no structural discontinuity; and a score of 1 implies absence of motion artifacts or noise-related blurring, excellent vessel opacification, and no structural discontinuity.

Each participating center is required to monitor vigilantly patient radiation and contrast doses via field site data collected and intervene to improve safety on a timely and ongoing basis. The contrast and radiation dosage of each scan is reviewed. If CTA mean radiation doses exceed 7 mSv or contrast doses exceed 100 cc, the CTA control liaison (CTA-CL) will initiate remedial actions at the enrolling site. Feedbacks that may be provided to the scanner technologist include suggestions for X-ray beam voltage reduction, adherence to prospective gating, limiting the field of view or scan length and improvement of heart rate optimization methods. The CTA-CL is also required to notify the site primary investigator regarding any of these issues.

Results

Radiation safety and quality assurance survey results

The initial survey for quality assurance and radiation safety including estimated effective dose (ED), dose length product (DLP), X-ray beam voltage (kV), image quality, image noise and aorta attenuation was based on findings from the first 498 participants (mean age 54 ± 6 years, all men) of the MACS CVS sub-study (Table 3). Optimal heart rate ($HR < 65$ BPM) was achieved in 74.5% (371/498) of participants. Prospective gating was performed in 96.8% of participants (482/498). The effective radiation dose (ED) was calculated using the following formula: $ED = DLP \times \text{Conversion factor}$ (0.014 for chest; 0.015 for abdomen; 0.0008 for legs), was 2.5 ± 1.6 mSv (mean $\pm$ SD) for cardiac CTA studies; and total of 4.6 ± 1.9 mSv for all CT studies combined, including CAC, cardiac CTA, abdominal and thigh scans.

Radiation doses delivered were low for all scanners used in the study, with mean doses of 1.8 ± 1.6 mSv for scans obtained using the General Electric VCT (64 detector system), 2.6 ± 1.6 mSv for the Siemens DSCT, and 3.3 ± 1.2 mSv for studies obtained with the Toshiba Aquilion One (320 detector system) (Table 3). The

image noise was low and proportional to the effective radiation doses. There have been 7 cardiac CTA procedures with doses over 7 mSv. Six of these studies involved retrospective protocols undertaken because of variable heart rates or heart rates above threshold, and some after a prospective scan was felt to be inadequate. Only 3 scans involved radiation exposures > 10 mSv (including the non-contrast portion) with the highest exposure being 17.6 mSv. The seventh was a scan using a "two beat" prospective ECG-gated protocol (dose for the cardiac CTA was 7.8 mSv). Further training and clarification of the research protocol (only one CTA per participant) subsequently minimized these protocol deviations, with one site deciding not to perform any further retrospective scans (Northwestern).

Generally the CT scans were well tolerated. There were only two reported allergic reactions to contrast-one involving urticaria, and other nasal congestion and itchy throat. Both reactions resolved with conservative medical therapy. One participant experienced contrast extravasation due to an infiltrated IV line and this resolved with conservative therapy.

To date, there have been no cases of contrast induced nephropathy or radiation induced cancers detected. We did not measure DNA fracture rates as part of this study.

Discussion

We herein describe a cardiac CTA methodology that implements multiple radiation-reducing measures as well as undertakes numerous careful cardiovascular structural measurements that, in sum, provide valuable cardiovascular endpoint data for scientific analysis while minimizing the radiation exposure per study (< 7 mSv). The mean effective radiation dose for the cardiac portion of the CTA was only 2.5 ± 1.6 mSv. In addition, there were very few participants who received CTA radiation doses over 7 mSv (7/498 or 1.4%). Similarly, the incidence of significant adverse events (a mild allergic reaction and IV contrast extravasation) was low (3/498=0.6%) and had been described in the study consent form.

The efficacy and safety of the measures undertaken in our study to reduce radiation dose have been previously evaluated in numerous other reports. For example, the use of a proper bowtie filter was suggested as an important measure for limiting radiation dose in a letter communication by Budoff et al. (20) in which it was proposed that reducing the FOV by using a small instead of a medium cardiac bowtie filter may result in up to a 40% radiation dose reduction (from 13.4 mSv to 8 mSv with retrospective imaging, and to a level as low as 1 mSv with prospective imaging) (19). Use of bowtie filters also result in lower radiation exposure.

In another study by Gopal et al. (14) the CAC scan was used in order to limit the cranio-caudal coverage scan length (ideally covering only the area from ~ 1 cm above the visualized top of the coronary arteries extending down to 1 cm below the distal border of posterior descending artery). Using this method the scan length was reduced by ~ 3 -4 cm per study, which translated into a $\sim 30\%$ overall radiation dose reduction, despite the added 1.2 mSv radiation due to CAC scanning.

Table 3. Quality and radiation safety data of first 498 CTA studies by CT scanner type

Variables		All participants (n=498)	GE LightSpeed (n=205)	Siemens DSCT (n=149)	Toshiba 320 (n=144)
Age , years		55.5±6.5	54.7±6.5	55.2±5.9	57.1±6.8
Heart rate, bpm		60±8	60±7	63±8	57±7
DLP - Cardiac CTA only, mGycm		178.5±114	131±112.5	188.7±114.1	235.5±83.9
Effective dose - Cardiac CTA only, mSv		2.5±1.6	1.8±1.6	2.6±1.6	3.3±1.2
DLP - Entire study*, mGycm		330.3±135.6	276.6±131.4	348.6±149.6	387.9±91.2
Effective dose - Entire study*, mSv		4.6±1.9	3.9±1.9	4.9±2.1	5.4±1.3
Tube voltage, kV, frequency (%)	80	22/498 (4.4)	21/205 (10.2)	1/149 (0.7)	0/144 (0)
	100	337/498 (67.7)	181/205 (88.3)	93/149 (62.4)	63/144 (43.8)
	120	139/498 (27.9)	3/205 (1.5)	55/149 (36.9)	81/144 (56.2)
Overall image quality, frequency (%)	Excellent	268/498 (53.8)	95/205 (46.3)	89/149 (59.7)	84/144 (58.3)
	Good	185/498 (37.2)	85/205 (41.5)	53/149 (35.6)	47/144 (32.6)
	Fair	38/498 (7.6)	21/205 (10.2)	5/149 (3.4)	12/144 (8.4)
	Poor	7/498 (1.4)	4/205 (2)	2/149 (1.3)	1/144 (0.7)
Image noise		33.4±9.8	36.9±9.5	31.6±8.9	30.7±9.8
Aortic attenuation, HU		444.1±82.4	429.8±88.5	456.5±85.9	450.6±66.7

Data are presented as mean±SD and percentage values
 * Also includes non-contrast CT scans, including coronary artery calcium, and single slices through the abdomen and thigh.
 bpm - beats per minute, CT - computerized tomography, CTA - computerized tomography angiography, DLP - dose length product, DSCT - dual source CT, HU - Hounsfield unit,
 SD - standard deviation

Moreover, Shuman et al. (16) showed that, without using any other dose reduction technique, prospective ECG-triggering could reduce the mean radiation dose by 77% compared to retrospective ECG-gating (4.2 mSv vs. 18.1 mSv, $p<0.01$), without compromising image quality or diagnostic accuracy (15). Another study similarly reported that the use of prospective ECG-triggering reduced radiation exposure by 79% without compromising image quality when compared to traditional retrospective ECG-gated acquisition (16).

The fourth method employed in our study, which is the use of a reduced tube voltage (use of 80-100 kV for participants <85 kg rather than typically employed 120 kV) was previously studied by Hausleiter et al. (18) in patients undergoing retrospective ECG-gating CTA with either 16-slice or 64-slice CT scanners. In this study researchers demonstrated that, compared to 120 kV voltage, the use of 100 kV could lower the radiation exposure by 22% when using 16 slice-scanners and 43% with 64-slice scanners, independent of any other techniques.

Further technologic advances in radiation dose reduction with cardiac CTA have been implemented since the inception of this trial. Iterative reconstruction is now available on all scanners, resulting in the achievement of additional radiation dose reductions of 30-40% (31). Furthermore, new detectors are now being introduced that allow for further radiation dose reductions, that will further enhance the safety of this tool in large cohort studies and patient populations.

Conclusion

If proven feasible and efficient, the methodologies that we describe in this report may enable the use of cardiac CTA as a safe and effective screening tool of choice for detection of sub-clinical coronary atherosclerosis and structural cardiac pathologies, even in low risk populations such as in those that participate in epidemiologic population-based studies.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - W.S.P., M.J.B., L.P.J.; Design - W.S.P., M.J.B., L.P.J.; Supervision - F.J.P., C.R.D., W.S.P., M.J.B.; Resource - M.G., T.Y.C., W.S.P., M.J.B., M.D.W., C.R.D.; Material - M.D.W., F.J.P., C.R.D.; Data collection&/or Processing - Y.H., M.G., T.Y.C., C.R.D.; Analysis &/or interpretation - Y.H., L.P.C., M.J.B.; Literature search - Y.H., W.S.P., R.T.G.; Writing - Y.H., W.S.P., R.T.G., M.J.B.; Critical review - W.S.P., R.T.G., M.J.B.

Acknowledgements

The MACS Cardiovascular Substudy is supported by National Heart Lung and Blood Institute grant (NHLBI) R01 HL095129 (Post), National Center for Research Resources (NCRR) grant (M01 RR00425) awarded to the GCRC at LA Biomedical Research Institute at Harbor-UCLA and grant (UL1 RR 025005) from NCRR awarded to Johns Hopkins Medical Institutions, a component of

the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The MACS is funded by the National Institute of Allergy and Infectious Diseases (NIAID), with additional supplemental funding from the National Cancer Institute (NCI) U01-AI-35042, UL1-RR025005 (GCRC), U01-AI-35043, U01-AI-35039, U01-AI-35040, U01-AI-35041. Website located at <http://www.statepi.jhsph.edu/mac/s/mac.html>.

References

1. Khunnawat C, Mukerji S, Havlichek D Jr, Touma R, Abela GS. Cardiovascular manifestations in human immunodeficiency virus-infected patients. *Am J Cardiol* 2008; 102: 635-42. [\[CrossRef\]](#)
2. Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. *Eur Heart J* 2011; 32: 945-51. [\[CrossRef\]](#)
3. DAD Study Group, Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte Ad, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* 2007; 356: 1723-35. [\[CrossRef\]](#)
4. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, Lazar J, et al. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. *AIDS* 2008; 22: 1615-24. [\[CrossRef\]](#)
5. Kingsley LA, Cuervo-Rojas J, Muñoz A, Palella FJ, Post W, Witt MD, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS* 2008; 22: 1589-99. [\[CrossRef\]](#)
6. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS* 2010; 24: 243-53. [\[CrossRef\]](#)
7. d'Ettore G, Franccone M, Mancone M, Ceccarelli G, Ascarelli A, Vullo F, et al. Significant coronary stenosis detected by coronary computed angiography in asymptomatic HIV infected subjects. *J Infect* 2012; 64: 82-8. [\[CrossRef\]](#)
8. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. *Heart* 2008; 94: 1386-93. [\[CrossRef\]](#)
9. Hausleiter J, Meyer T, Hermann F, Hadamitzky M, Krebs M, Gerber TC, et al. Estimated radiation dose associated with cardiac CT angiography. *JAMA* 2009; 301: 500-7. [\[CrossRef\]](#)
10. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation* 2006; 114: 1761-91. [\[CrossRef\]](#)
11. Bluemke DA, Achenbach S, Budoff M, Gerber TC, Gersh B, Hillis LD, et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention, and the Councils on Clinical Cardiology and Cardiovascular Disease in the Young. *Circulation* 2008; 118: 586-606. [\[CrossRef\]](#)
12. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. *JAMA* 2007; 298: 317-23. [\[CrossRef\]](#)
13. Raff GL, Chinnaiyan KM, Share DA, Goraya TY, Kazerooni EA, Moscucci M, et al. Radiation dose from cardiac computed tomography before and after implementation of radiation dose-reduction techniques. *JAMA* 2009; 301: 2340-8. [\[CrossRef\]](#)
14. Gopal A, Mao SS, Karlsberg D, Young E, Waggoner J, Ahmadi N, et al. Radiation reduction with prospective ECG-triggering acquisition using 64-multidetector computed tomographic angiography. *Int J Cardiovasc Imaging* 2009; 25: 405-16. [\[CrossRef\]](#)
15. Gopal A, Budoff MJ. A new method to reduce radiation exposure during multi-row detector cardiac computed tomographic angiography. *Int J Cardiol* 2009; 132: 435-6. [\[CrossRef\]](#)
16. Shuman WP, Branch KR, May JM, Mitsumori LM, Lockhart DW, Dubinsky TJ, et al. Prospective versus retrospective ECG gating for 64-detector CT of the coronary arteries: comparison of image quality and patient radiation dose. *Radiology* 2008; 248: 431-7. [\[CrossRef\]](#)
17. Hirai N, Horiguchi J, Fujioka C, Kiguchi M, Yamamoto H, Matsuura N, et al. Prospective versus retrospective ECG-gated 64-detector coronary CT angiography: assessment of image quality, stenosis, and radiation dose. *Radiology* 2008; 248: 424-30. [\[CrossRef\]](#)
18. Hausleiter J, Meyer T, Hadamitzky M, Huber E, Zankl M, Martinoff S, et al. Radiation dose estimates from cardiac multislice computed tomography in daily practice: impact of different scanning protocols on effective dose estimates. *Circulation* 2006; 113: 1305-10. [\[CrossRef\]](#)
19. Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, et al. Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. *Eur Heart J* 2010; 31: 340-6. [\[CrossRef\]](#)
20. Budoff MJ. Ethical issues related to lung nodules on cardiac CT. *AJR Am J Roentgenol* 2009; 192: 146. [\[CrossRef\]](#)
21. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461-70.
22. Geleijns J, Salvadó Artells M, de Bruin PW, Matter R, Muramatsu Y, McNitt-Gray MF. Computed tomography dose assessment for a 160 mm wide, 320 detector row, cone beam CT scanner. *Phys Med Biol* 2009; 54: 3141-59. [\[CrossRef\]](#)
23. Budoff MJ, Waggoner J, Ahmadi N, Pal RS, Sarlak B, Honoris L, et al. Substantial radiation dose reduction in 64-multidetector cardiac computed tomographic angiography by using lower X-ray energy during scanning. *J Am Coll Cardiol* 2008; 51: 148.
24. Blankstein R, Bolen MA, Pale R, Murphy MK, Shah AB, Bezerra HG, et al. Use of 100 kV versus 120 kV in cardiac dual source computed tomography: effect on radiation dose and image quality. *Int J Cardiovasc Imaging* 2011; 27: 579-86. [\[CrossRef\]](#)
25. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975; 51: 5-40. [\[CrossRef\]](#)
26. Iwasaki K, Matsumoto T, Aono H, Furukawa H, Samukawa M. Prevalence of subclinical atherosclerosis in asymptomatic diabetic patients by 64-slice computed tomography. *Coron Artery Dis* 2008; 19: 195-201. [\[CrossRef\]](#)
27. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Cardiac chamber volumes, function, and mass as determined by 64-multidetector row computed tomography: mean values among healthy adults free of hypertension and obesity. *JACC Cardiovasc Imaging* 2008; 1: 782-6. [\[CrossRef\]](#)
28. Khatri PJ, Tandon V, Chen L, Yam Y, Chow BJ. Can left ventricular end-diastolic volumes be estimated with prospective ECG-gated CT coronary angiography? *Eur J Radiol* 2012; 81: 226-9. [\[CrossRef\]](#)
29. MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005; 237: 395-400. [\[CrossRef\]](#)
30. Brodoefel H, Tsiiflikas I, Burgstahler C, Reimann A, Thomas C, Schroeder S, et al. Cardiac dual-source computed tomography: effect of body mass index on image quality and diagnostic accuracy. *Invest Radiol* 2008; 43: 712-8. [\[CrossRef\]](#)
31. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. *J Cardiovasc Comput Tomogr* 2011; 5: 198-224. [\[CrossRef\]](#)

A new approach to the measurement of heart rate in patients with chronic heart failure-Heart rate performance index: an observational study

Kalp yetersizliği olan hastalarda kalp hızına yeni bir yaklaşım-Kalp hızı verim göstergesi: Gözlemsel bir çalışma

Aydın Akyüz, Şeref Alpsoy, Dursun Çayan Akkoyun, Niyazi Güler

Department of Cardiology, Faculty of Medicine, Namık Kemal University, Tekirdağ-Turkey

ABSTRACT

Objective: In order to evaluate the utility of the heart rate performance index (HRPI), which is obtained by dividing HR mean by the difference of HR max and HR min in the context of Holter monitoring, we sought to determine whether there was any correlation or relationship between the HRPI and LVEF values as determined by echocardiography and to compare the HRPI between the study and control groups.

Methods: This study is a cross-sectional, controlled observational study. Thirty-two patients with symptomatic or asymptomatic left ventricular systolic dysfunction (LVEF <45%) were included as study group and 32 subjects without chronic heart failure (CHF) were included as a control group. In the study group, 10 patients were in NYHA class I (31.2%), 12 - were in NYHA class II (37.6%) and 10 - were in NYHA class III (31.2%). Heart rate analysis was measured using 24-hour Holter ambulatory electrocardiography. To determine the HRPI, the difference between maximum (HR max) and minimum heart rate (HR min) was divided by mean heart rate (HR mean) (beats/minute): $HRPI = (HR \text{ max} - HR \text{ min}) / HR \text{ mean}$. Statistical analysis was performed using t-test for independent samples, Mann-Whitney U test, Chi-square test, Kruskal-Wallis test, Pearson's correlation and linear regression analyses.

Results: The HRPI index value was markedly decreased [0.83 (0.58-1.1) and 1.10 (0.74-1.3), $p < 0.001$] in the study group as compared to the control group. The data collected for the study group and the control group ($n=64$) demonstrated a positive correlation between the HRPI and LVEF ($r=0.62$, $p < 0.001$) as well as a negative correlation between the HR mean and LVEF ($r=-0.39$, $p < 0.003$). The HR mean was higher (80.2 ± 11.3 and 75.2 ± 6.7 , $p < 0.007$) and HR max-HR min (67.9 ± 11.6 and 83.3 ± 14.3 , $p < 0.001$) were lower in the study group as compared to the control group. Linear regression analysis demonstrated no significant relationship between LVEF and HRPI and other heart rate derivatives (unstandardized $\beta=42.43$ 95% CI: 21.98-50.51, $p=0.231$).

Conclusion: According to our findings, patients with CHF exhibited higher HR mean values, reduced HR max-min values and significantly decreased HRPI values. There is a positive correlation between HRPI and LVEF; a decreased HRPI is associated with a decreased LVEF, but there is no relationship between these two variables. Therefore HRPI values may represent a viable option for assessing daily exercise activity and potentially sympathetic activation in patients with CHF. The assessment of HRPI may be helpful the evaluation of CHF patients, as well as resting HR. (*Anadolu Kardiyol Derg 2013; 13: 215-20*)

Key words: Congestive heart failure, ambulatory electrocardiography, heart rates, ventricular ejection fraction, regression analysis

ÖZET

Amaç: Yirmi dört saatlik Holter EKG incelemede kalp hızı verim göstergesi (KHVG), en yüksek kalp hızı ile en düşük kalp hızı arasındaki farkın ortalama kalp hızına bölünmesi ile elde edildi. KHVG çalışma ve kontrol grupları arasında karşılaştırıldı ve ekokardiyografi ile ölçülen sol ventrikül fırlatma yüzdesi arasında bir ilişki olup olmadığını araştırıldı.

Yöntemler: Bu çalışma kesitsel ve gözlemsel bir çalışmadır. Kapak hastalığı olmayan 32 kalp yetersizliği hastası ile birlikte, kalp yetersizliği olmayan 32 kişi alındı. KHVG'ni tespit etmek için Holter EKG de ölçülen en yüksek kalp hızı ile en düşük kalp hızı arasındaki fark (EYKH-EDKH) ortalama kalp hızına (OKH) bölündü. KHVG=(EYKH-EDKH) / OKH (vuru/dk). İstatistiksel analizde eşleştirilmemiş t-testi, Mann-Whitney U testi, Ki-kare testi, Kruskal-Wallis testi, Pearson korelasyon ve lineer regresyon analizleri kullanıldı.

Address for Correspondence/Yazışma Adresi: Dr. Aydın Akyüz, Namık Kemal Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Tekirdağ- Türkiye Phone: +90 542 411 65 50 Fax: +90 282 262 68 10 E-mail: ayakyuzq5@gmail.com

Accepted Date/Kabul Tarihi: 21.11.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 30.01.2013

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.066



Bulgular: Konjestif kalp yetersizliği (KKY) hastalarında OKH daha yüksek (80.2 ± 11.3 ve 75.2 ± 6.7 , $p < 0.007$) iken, EYKH ve EDKH arasındaki farkı ise daha az (67.9 ± 11.6 ve 83.3 ± 14.3 , $p < 0.001$) bulundu. KHVG kontrol grubuna göre KKY grubunda azalmıştı [0.83 ($0.58-1.1$) ve 1.10 ($0.74-1.3$), $p < 0.001$]. KKY ve kontrol grubu verileri birlikte analiz edildiğinde KHVG ve SVFY arasında pozitif bir korelasyon vardı ($r = 0.62$, $p < 0.001$). Lineer regresyon analizinde SVFY ve KHVG arasında ilişki bulunmadı ($\beta = 42.43$ 95% CI: $21.98-50.51$, $p = 0.231$).

Sonuç: KKY hastalarında KKY olmayanlara göre OKH değerleri daha yüksek iken EYKH ile EDKH değerleri arasındaki fark ise daha azdır ve KHVG değerleri daha düşüktür. KHVG ve SVFY arasında pozitif yönde korelasyon vardır, fakat ilişki yoktur. KHVG, KKY hastalarının günlük egzersiz aktivitelerinin ve olasılıkla sempatik aktivasyonlarının değerlendirilmesinde kullanılabilir. KKY hastalarında SVFY ve KHVG'nin istirahat kalp hızının yanısıra kullanılması faydalı olabilir. (*Anadolu Kardiyol Derg 2013; 13: 215-20*)

Anahtar kelimeler: Konjestif kalp yetersizliği, ambulator elektrokardiyografi, kalp hızları, ventrikül ejeksiyon fraksiyonu, regresyon analizi

Introduction

An increased resting heart rate (HR) is an independent risk factor in patients with coronary artery disease (CAD) and chronic heart failure (CHF). The accurate measurement of resting HR is therefore of elevated importance in patients with CHF and CAD (1, 2). One of the most important adaptations in patients with CHF is activation of the sympathetic nervous system, which occurs early in the course of CHF (3). The changes of HR mean, HR max and HR min is expected in CHF patients due to a decreased capacity for exercise and an increased sympathetic tone.

Ambulatory Holter electrocardiogram monitoring (H-ECG) has been routinely used to determine the analysis HR derivatives such as HR min, HR max and HR mean, as well as arrhythmias, heart rate variability (HRV), heart rate turbulence, QT dispersion, T-wave alternans, signal-averaged ECG and late potentials (4-10). Various H-ECG methods have been proposed to predict mortality in patients with CHF, but only left ventricular ejection fraction (LVEF) and resting HR are practical for using in CHF patients.

The measurement of resting HR and LVEF is very simple and also important in predicting of mortality, but up to now studies are very limited to show whether a relationship between the resting HR and LVEF or between the HR max-HR min and LVEF. HR mean indicates a variety of resting HR, is a predictor of mortality in CHF, and HR max-HR min reflects a kind of heart rate reserve which is known as the difference of HR baseline and HR max on treadmill exercise testing and shows a chronotropic insufficiency (11).

Dividing HR mean by HR max and HR min yields a new index, which here is denoted as the heart rate performance index: $HRPI = (HR \text{ max} - HR \text{ min}) / HR \text{ mean}$. We want to investigate whether a correlation or relationship between LVEF and heart rate derivatives.

In the present study, we sought to determine whether there was any correlation or relationship between the HRPI and LVEF values as determined by echocardiography and to compare the HRPI between the study and control groups.

Methods

Study design

Study was designed as a cross-sectional observational controlled study.

Study population

The study was conducted in our cardiology clinic. Participants enrolled in the study were selected among patients not requiring hospitalization and subjects from January 2011 to June 2011. We selected the patients who had undergone routine clinical and laboratory examinations, including H-ECG, transthoracic echocardiography and routine blood tests.

The inclusion criteria for the CHF were as follows: New York Heart Association (NYHA) Class I-II and III, the patients with low LVEF, and Holter-ECG for 24 hours. Exclusion criteria were defined as the following: presence of atrial fibrillation or flutter, acute coronary syndromes, moderate -severe valvular disease, severe CAD, or any systemic disease as well as those on beta-blocker (BB) medication, digoxin and ivabradine. Ten of them were hypertensive, 3 of them were smoking, and 8 of them have CAD. They were using only diuretics, Angiotensin II receptor blockers (ARB) and/or angiotensin-converting-enzyme inhibitors (ACEI).

Subjects in control group were not taking digoxin or BB medication and nine of them were using diuretics, ARB and/or ACEI due to hypertension. They were selected among the subjects who had no cardiac any arrhythmias, CAD, CHF and any valvular heart disease.

Diabetes mellitus, hyperlipidemia, any congenital or pericardial disease, any thyroid disease, stroke, malignancies, pulmonary embolism or any systemic disease were the other exclusion criteria for the both groups.

All patients gave oral and written informed consent. The study was approved by the local ethics committee and was conducted according to the Helsinki declaration.

Study protocol

Our study included 32 patients (15 female) with mild-moderate non-valvular CHF (LVEF $< 45\%$) in sinus rhythm as study group and 32 subjects (14 female) without heart failure and CAD as control group. First, we planned to compare the values of HR mean, HR max-min and HRPI between the subjects without CHF and the patients with CHF. Second, we planned to combine the two groups' data for better observation the correlation or relationship between LVEF and HR derivatives.

Study variables

The clinical variables including age, gender, body mass index (BMI), and major risk factors for CAD, functional capacity according to NYHA and medication variables are summarized in Table 1.

Predictor variable was presence of CHF: the subjects with LVEF <45% were accepted as those with CHF. The outcome variables of study were HR mean, HR max-min and HRPI. Confounding factors were: age, gender, BMI, smoking, hypertension, and CAD. The subgroup analysis was performed according to NYHA functional class, treatment with ARB, ACEI and diuretics.

Holter monitoring and HRPI

Twenty four-hour Holter ECG was performed without hospitalization and analyzed using a three-channel ambulatory recorder (MT-101, Schiller AG, Baar, Switzerland). Since, the number of RR intervals taken from the calculation of the maximal and the minimal heart rate is generally optional and very important, recordings were analyzed by two independent investigators utilizing a 24 h two-channel full disclosure. Finally, the analysis was performed by deleting ECG signal artifacts in the calculation of HR min, HR max and HR mean. Dividing HR mean by the difference of HR max and HR min yields an HRPI, which here is denoted as the heart rate performance index: $HRPI = (HR \text{ max} - HR \text{ min}) / HR \text{ mean}$.

Echocardiography

Transthoracic echocardiographic examinations were performed using commercially available instruments in combination with a cardiac probe (2.5-3.5 MHz) (Esaote, My Lab 50, Florence, Italy). Echocardiograms were obtained in standard parasternal long-axis and short-axis views as well as apical two-, four-, and five-chamber views. LVEF estimations were performed using the modified Simpson's method (12). Two cardiologists agreed upon a diagnosis of CHF based upon an LVEF <45%.

Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Categorical variables were reported as numbers (n) and percentages (%), whereas continuous variables were expressed as mean and standard deviation (SD) and median and minimum-maximum where appropriate. Student's t-test, Mann-Whitney U test and Chi-square test were used to compare differences between two groups. Kruskal-Wallis test was performed for comparing ejection fraction and HR derivatives in the study group's subgroups. Correlations between the HR derivatives and LVEF were analyzed using Pearson's test. Linear regression analysis was performed to find whether the relationship between HRPI and LVEF, HR mean and LVEF, HR max-mean and LVEF, respectively. A $p < 0.05$ was considered significant.

Results

Baseline characteristics of the population and heart rate derivatives

The study group included 17 male (53.1%) and 15 female (46.9%) subjects with systolic CHF, while the control group consisted of 18 male (56.2%) and 14 female (43.8%) without CHF. The study group did not differ significantly from the control group with regard to age, sex, smoking, hypertension, blood

pressure, or BMI. Ten patients were classified as having NYHA class I (31.2%), 12 patients were classified as NYHA class II (37.6%), and 10 patients were classified as NYHA Class III (31.2%). Eight patients had CAD (25%), and 24 patients (75%) had non-ischemic heart failure. The characteristics of the two groups are summarized in Table 1.

In a subgroup analysis, there were differences between NYHA class I-III subgroups in LVEF, HR mean, HR max, HR min, HR max-min and HRPI, respectively, ($p=0.020$; $p=0.030$, $p=0.011$, $p=0.041$, $p=0.028$ and $p=0.025$) (Table 2).

HR mean was higher ($p < 0.007$) and the difference between HR max and HR min was lower in the study group as compared to control group ($p < 0.001$). HRPI values were markedly decreased in patients with CHF compared to control group [0.83 (0.58-1.1) and 1.10 (0.74-1.3), $p < 0.001$] (Table 3). The study and control groups were similar in terms of HR max and HR min ($p < 0.759$ and $p < 0.287$).

Relationship between HRPI and LVEF

When the two groups were analyzed together ($n=64$), there was a positive correlation between the HR max-min and LVEF ($r=0.42$, $p < 0.01$) and a negative correlation between HR mean and LVEF ($r=-0.39$, $p < 0.003$) (Fig. 1, 2). A significant positive correlation was observed between the HRPI and LVEF ($r=0.62$, $p < 0.001$) (Fig. 3).

Table 1. The demographics and baseline characteristics of the study participants

Variables	Study group (n=32)	Control group (n=32)	*p
Age, years	60±12	57±9	0.956
Male, n (%)	17 (53.1)	18 (56.2)	0.568
Female, n (%)	15 (46.9)	14 (43.8)	0.789
CAD, n (%)	8 (25)	0	<0.01
Smoking, n (%)	3 (9.3)	4 (12.5)	0.232
Hypertension, n (%)	10 (31.2)	9 (28.1)	0.453
SBP, mmHg	123.2±16.6	139.6±20.4	0.080
DBP, mmHg	81±9.3	85.2±9.4	0.569
BMI, kg/m ²	27.2±2.87	28.7±4.65	0.678
Medication, n (%)			
ARB/ACEI	29 (90.6)	9 (28.1)	<0.05
Loop diuretic	12 (37.5)	5 (15.6)	<0.01
Spironolactone	10 (31.2)	1 (3.1)	<0.01
Acetylsalicylic acid	25 (78.1)	7 (21.8)	0.765
NYHA functional capacity, n (%)			
Class I	10 (31.2)	0	<0.01
Class II	12 (37.6)	0	<0.01
Class III	10 (31.2)	0	<0.01

Data are presented as number (percentage) and mean±SD

* Unpaired Student t-test and Chi-square test.

ACEI - angiotensin-converting-enzyme inhibitors, ARB - angiotensin II receptor blockers, BMI - body mass index, CAD - coronary artery disease, DBP - diastolic blood pressure, EF - ejection fraction, SBP - systolic blood pressure

Table 2. Ejection fraction and HR derivatives in NYHA class subgroups

Variables	NYHA I (n=10)	NYHA II (n=12)	NYHA III (n=10)	*Chi-square	*p
Age, years	58 (33-74)	60 (35-76)	61 (38-78)	0.84	0.216
LVEF, %	40 (36-44) ^{a,b}	34 (30-38) ^c	28 (22-34)	26.8	0.020
HR mean, beats/min	74±12 ^{a,b}	79±5 ^c	89±8	7.43	0.030
HR max, beats/min	114±13 ^b	122±9	130±8	5.1	0.011
HR min, beats/min	50±6 ^b	52±6 ^c	62±9	10.3	0.041
HR max-HR min, beats/min	70±11 ^a	67±19	67±15	0.09	0.028
HRPI	0.85 (0.68-1.1) ^{a,b}	0.88 (0.64-1.02) ^c	0.75 (0.58-1.1)	6.5	0.025

Data are presented as mean ±SD and median (minimum-maximum) values.
*Kruskal-Wallis test, Mann-Whitney U test for the comparison between the groups: ^abetween NYHA I vs. NYHA II, ^bbetween NYHA I vs. NYHA III, ^cbetween NYHA II vs. NYHA III; p<0.05
HR mean - mean heart rate, HR max - maximal heart rate, HR min-minimal heart rate, HR max-min- the difference value between HR max and HR min, HRPI - heart rate performance index (maximum heart rate-minimum heart rate)/mean heart rate (beat per minute), LVEF - left ventricular ejection fraction

Table 3. 24- hour ambulatory electrocardiographic measurements in study and control groups

Variables	Study group (n=32)	Control group (n=32)	*p
Ejection fraction, %	34±6	59±5	0.018
HR mean, beats/min	80.2±11.3	75.2±6.7	0.007
HR max, beats/min	120.3±12.5	136.2±14.1	0.087
HR min, beats/min	32.4±7.6	53.6±9.3	0.759
HR max-HR min, beats/min	67.9±11.6	83.3±14.3	0.001
HRPI	0.83 (0.58-1.1)	1.10 (0.74-1.3)	0.001

Data are presented as number and mean±SD, and median (minimum-maximum) values
*Student t-test and Mann-Whitney U test.
HR mean-mean heart rate, HR max -maximal heart rate, HR min-minimal heart rate, HR max -min-the difference value between HR max and HR min, HRPI - heart rate performance index (maximum heart rate -minimum heart rate) /mean heart rate (beat per minute), LVEF - left ventricular ejection fraction

Table 4. Linear regression analysis of LVEF association with HR variables

Variables	Beta coefficient	95% confidence interval	*p
HR mean	-0.60	-1.30-0.86	0.084
HR max-mean	-0.46	-1.67-0.74	0.445
HRPI	31.59	-20.64-83.83	0.231

*Linear regression analysis
HR mean-heart rate mean, HRPI-heart rate performance index (Maximum Heart Rate-Minimum Heart Rate) /Mean Heart Rate (beat per minute), LVEF - left ventricular ejection fraction

However, in linear regression analysis we did not find a relationship between LVEF and HRPI (unstandardized $\beta=42$, 95% CI: 21.98-50.51, $p=0.231$), as well as there was no statistically a relationship between LVEF and HR mean, LVEF and HR max-min, respectively, (unstandardized $\beta=-0.22$, 95% CI: -0.52 -0.73, $p=0.225$ and unstandardized $\beta=-0.46$, 95% CI -1.66-0.73, $p=0.411$) (Table 4).

Discussion

In our study, we present the novel use of one aspect of heart rate as determined by H-ECG in the evaluation of patients with CHF. This parameter is denoted here as HRPI and correlates with LVEF in patients with CHF. Notably, we observed a greater difference between HR max and HR min among control subjects as opposed to CHF patients due to the former's increased capacity for exercise. HR mean was elevated in the CHF. We found that the HR mean was higher and the difference between HR max and HR min was lower in the study group as compared to control group. There was a positive correlation between the HRPI and LVEF ($r=0.62$, $p<0.001$) as well as a negative correlation between HR mean and LVEF ($r=-0.39$, $p<0.003$). There was no a relationship between LVEF and HRPI in linear regression ($\beta=42$, 95% CI: 21.98-50.51, $p=0.231$). The results of the investigation showed us that HRPI is a simple practical marker of daily exercise activity and potentially sympathetic activation.

The resting HR and LVEF are practical methods in the assessment of CHF patient, but the studies investigating a relationship between them are very limited. Improved tools will reduce the variability of these analyses and facilitate the evaluation of patients with CHF, particularly with respect to estimates of LVEF. Various heart rate parameters have been used to establish a relationship between autonomic tone and CHF. There is still a need in a new Holter ECG parameter, which could better show the relation between HR and clinical status of the patient. Some heart rate parameters such as heart rate turbulence and HRV are more useful in stratifying cardiovascular risk than in evaluating a given patient's clinical status (13, 14). Although some publications in the past demonstrated the predictive power of the resting heart rate (15, 16), this finding was largely buried beneath the wealth of data on HRV (5, 6, 17).

The increased HRPI values may be an alternative to a decreased resting HR as a target parameter in the assessment in patients with CHF who are only taking only ACEI, ARB or diuretics. The suppression of diurnal heart rate fluctuations in CHF patients results in reduced differences between minimal and maximal HR values as well as an increase in resting heart rate (3, 18). Numerous studies (CIBIS-II, MERIT-HF, COMET and SHIFT) have demonstrated a relationship among increased resting heart rate, mortality and health-related quality of life (2, 19-22). Specifically, the magnitude of HR reduction in patients with HF is associated with a reduction in mortality. Patients with HF and HR>70 beats/min have a significantly greater rate of cardiovascular mortality and risk of hospital admission than those with HR<70 beats/min, and the discrimination by HR is even more accurate in predicting coronary-related vascular outcomes (15). The target heart rate in the treatment of patients with heart failure is typically about 60-70 beats/min (2, 22). Heart rate can be easily determined during physical examination of the patient and therefore allows a simple hint on the prognosis and efficiency of therapy (23).

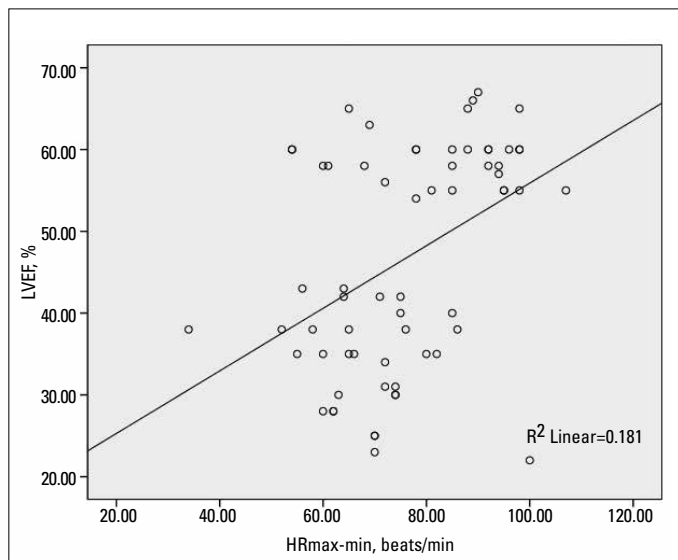


Figure 1. Correlation between HR max-mean and LVEF (Pearson's coefficient $r = 0.42$, $p < 0.01$)

HR max - maximum heart rate during 24 hours, HR min - minimum heart rate during 24 hours, LVEF - left ventricular ejection fraction

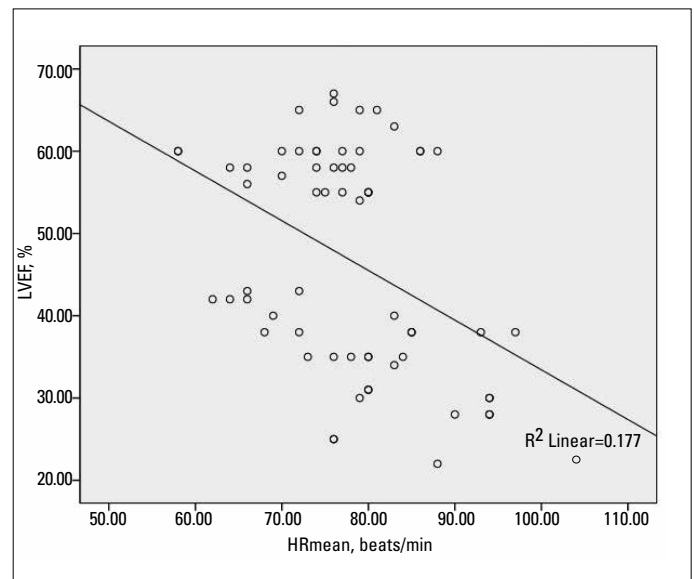


Figure 2. Correlation between HR mean and LVEF (%) (Pearson's coefficient $r = -0.39$, $p < 0.003$)

HR mean - averaged heart rate during 24 hours, LVEF - left ventricular ejection fraction

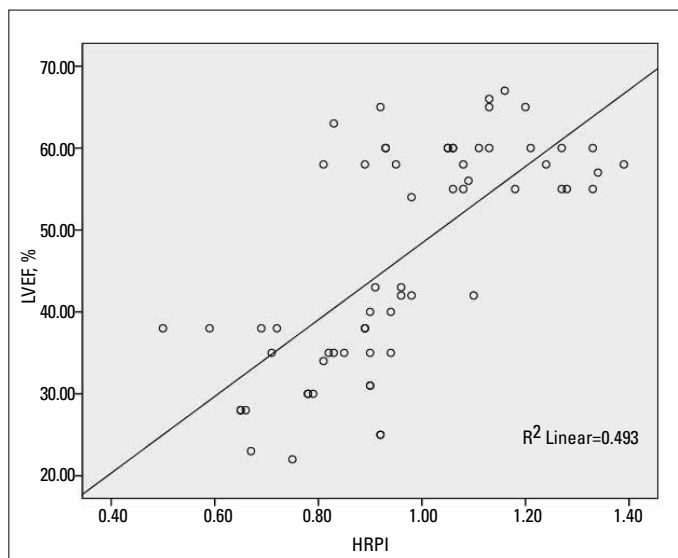


Figure 3. Correlation between HRPI and LVEF (%) (Pearson's coefficient $r = 0.62$, $p < 0.001$)

HRPI - heart rate performance index: $HR \text{ max} - HR \text{ min} / HR \text{ mean}$, LVEF - left ventricular ejection fraction

The first disadvantage of HRPI, the measurement of HR mean and HR max-min is not routinely very practical, because the true HR min values can be usually obtained in the sleeping phase and the true HR mean value needs during 24 hours recording. But it may be useful in some clinics with no optional commercial Holter ECG tools such as HRV, heart rate turbulence. The analysis of cardiac tone in bedside monitoring with memory capacity can be obtained by the HRPI method, especially in the clinics with the capabilities of ECG monitor having memory capacity and lack of Holter ECG tools. The second disadvantage of HRPI seems to be affected with medication BB, digoxin or ivabradine.

Relatively small number of the study group is the first limitation of the study. We could not find enough new untreated NYHA Class IV patients, especially with no medication on BB, digoxin or ivabradine, and also NYHA Class IV patients were excluded from the study for ethical reasons. Second, all CHF patients were taking medications such as ARB, ACEI and/or diuretics and some subjects of the control were hypertensive and have CAD. Finally, some authors concluded that HR parameters are affected by smoking, gender, physical inactivity and advanced age (24), but we did not take into account these mentioned factors.

Conclusion

We found that there is a positive correlation between LVEF and HRPI, which may be a new approach of the assessment of heart rate in patients with CHF. Our study shows that HRPI may potentially represent a valuable approach in assessing the daily exercise activity and potentially sympathetic activation among CHF patients examined by 24-hour Holter ECG analysis.

HRPI may also be better an alternative method to HR mean or resting HR for using as an indicator of the quality of autonomic cardiac function. The assessment of LVEF and HRPI together may facilitate the evaluation of CHF patients, as well as resting HR. Further studies will be necessary to confirm the utility of this clinical parameter in predicting autonomic activation or in supposing the clinical situation and LVEF in patients with CHF.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - A.A., N.G.; Design - A.A., N.G.; Supervision - A.A., N.G.; Data collection&/or Processing -

A.A., Ş.A., D.Ç.A.; Analysis &/or interpretation - A.A., N.G.; Literature search - A.A., Ş.A., D.Ç.A.; Writing - A.A.; Critical review - A.A., N.G., Ş.A., D.Ç.A.

References

1. Fox K, Borer JS, Camm AJ, Danchin N, Ferrari R, Lopez Sendon JL, et al. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol* 2007; 50: 823-30. [\[CrossRef\]](#)
2. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; 376: 886-94. [\[CrossRef\]](#)
3. Floras JS. Clinical aspects of sympathetic activation and parasympathetic withdrawal in heart failure. *J Am Coll Cardiol* 1993; 22: 72-84. [\[CrossRef\]](#)
4. Zimetbaum PJ, Josephson ME. The evolving role of ambulatory arrhythmia monitoring in general practice. *Ann Intern Med* 1999; 130: 848-56.
5. Tulppo M, Huikuri HV. Origin and significance of heart rate variability. *J Am Coll Cardiol* 2004; 43: 2278-80. [\[CrossRef\]](#)
6. Tekiner F, Gemici K, Emrehan B, Tekiner E, Jordan J. The efficacy and prognostic value of heart rate variability in 24-hour and short time recordings for determining cardiac autonomic dysfunction in congestive heart failure. *Anadolu Kardiyol Derg* 2007; 7: 118-23.
7. Koyama J, Watanabe J, Yamada A, Koseki Y, Konno Y, Toda S. Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. *Circ J* 2002; 66: 902-7. [\[CrossRef\]](#)
8. Barr CS, Naas A, Freeman M, Lang CC, Struthers AD. QT dispersion and sudden unexpected death in chronic heart failure. *Lancet* 1994; 343: 327-9. [\[CrossRef\]](#)
9. Klingenhöfen T, Zabel M, D'Agostino RB, Cohen RJ, Hohnloser SH. Predictive value of T-wave alternans for arrhythmic events in patients with congestive heart failure. *Lancet* 2000; 356: 651-2. [\[CrossRef\]](#)
10. Poll DS, Marchlinski FE, Falcone RA, Josephson ME, Simson MB. Abnormal signal-averaged electrocardiograms in patients with nonischemic congestive cardiomyopathy: relationship to sustained ventricular tachyarrhythmias. *Circulation* 1985; 72: 1308-13. [\[CrossRef\]](#)
11. Cheng YJ, Macera CA, Church TS, Blair SN. Heart rate reserve as a predictor of cardiovascular and all-cause mortality in men. *Med Sci Sports Exerc* 2002; 12: 1873-8. [\[CrossRef\]](#)
12. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005; 18: 1440-63. [\[CrossRef\]](#)
13. Francis J, Watanabe MA, Schmidt G. Heart rate turbulence: a new predictor for risk of sudden cardiac death. *Ann Noninvasive Electrocardiol* 2005; 10: 102-9. [\[CrossRef\]](#)
14. Malik M. Heart rate variability. *Curr Opin Cardiol* 1998; 13: 36-44. [\[CrossRef\]](#)
15. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R, et al. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomized controlled trial. *Lancet* 2008; 372: 817-21. [\[CrossRef\]](#)
16. Heusch G. Heart rate and heart failure. Not a simple relationship. *Circ J* 2011; 75: 229-36. [\[CrossRef\]](#)
17. May O, Arildsen H. Long-term predictive power of heart rate variability on all-cause mortality in the diabetic population. *Acta Diabetol* 2011; 48: 55-9. [\[CrossRef\]](#)
18. Panina G, Khot UN, Nunziata E, Cody RJ, Binkley PF. Assessment of autonomic tone over a 24-hour period in patients with congestive heart failure: relation between mean heart rate and measures of heart rate variability. *Am Heart J* 1995; 29: 748-53. [\[CrossRef\]](#)
19. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 1999; 353: 9-13. [\[CrossRef\]](#)
20. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL. Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001-7. [\[CrossRef\]](#)
21. Torp-Pedersen C, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, et al. COMET Investigators. Effects of metoprolol and carvedilol on cause-specific mortality and morbidity in patients with chronic heart failure-COMET. *Am Heart J* 2005; 149: 370-6. [\[CrossRef\]](#)
22. Ekman I, Chassany O, Komajda M, Böhm M, Borer JS, Ford I, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. *Eur Heart J* 2011; 32: 2395-404. [\[CrossRef\]](#)
23. Reil JC, Custodis F, Swedberg K, Komajda M, Borer JS, Ford I, et al. Heart rate reduction in cardiovascular disease and therapy. *Clin Res Cardiol* 2011; 100: 11-9. [\[CrossRef\]](#)
24. Bjerregaard P. Mean 24 hour heart rate, minimal heart rate and pauses in healthy subjects 40-79 years of age. *Eur Heart J* 1983; 41: 44-51.

The relationship between adiponectin, NT-pro-BNP and left ventricular ejection fraction in non-cachectic patients with systolic heart failure: an observational study

Kaşıktık olmayan sistolik kalp yetmezlikli olgularda adiponektin, NT-pro-BNP ve sol ventrikül ejeksiyon fraksiyonu arasındaki ilişki: Gözlemsel bir çalışma

İstemihan Tengiz, Uğur Önsel Türk¹, Emin Alioğlu¹, Bahadır Kırılmaz², Gülden S. Tamer³, Nurullah Tüzün¹, Ertuğrul Ercan

Department of Cardiology, Faculty of Medicine, İzmir University, İzmir-Turkey

¹Clinic of Cardiology, Central Hospital, İzmir-Turkey

²Department of Cardiology, Faculty of Medicine, Çanakkale Onsekiz Mart University, Çanakkale-Turkey

³Department of Microbiology, Faculty of Medicine, Kocaeli University, Kocaeli-Turkey

ABSTRACT

Objective: NT-pro-brain natriuretic peptide (NT-proBNP) has been shown to be an accurate diagnostic marker in patients with heart failure (HF). Adiponectin (Adp) levels are increased in HF but its diagnostic value is still uncertain in these patients. The study was designed to investigate the possible association of these markers in non-cachectic patients with newly diagnosed systolic heart failure.

Methods: Fifty-seven systolic HF patients and 20 matched controls were enrolled in an observational cross-sectional study. Physical and echocardiographic examinations were performed and serum Adp, NT-proBNP, tumor necrosis factor-alpha (TNF-α) levels were measured. Study variables were compared between the groups. Correlation analyses were done and the diagnostic validity of the markers was compared with ROC analysis.

Results: Adp and NT-proBNP levels were significantly higher in HF group (20.19±12.9 vs. 7.65±4.6 µg/mL; p<0.001 and 1051.74±606.2 vs. 222.53±65.6 pg/mL; p=0.002; respectively). TNF-α levels were similar between the groups (2.83±1.8 vs. 2.08±1.2 pg/mL; p=0.582). Correlation analysis showed significant association among Adp and NT-proBNP levels, (r=0.448; p<0.001), and left ventricular ejection fraction (LVEF) values (r=-0.466; p<0.001). The Adp and NT-proBNP showed comparable diagnostic performances with mean [95% confidence interval] areas under the curves of 0.857 (0.771-0.944) and 0.888 (0.815-0.960), respectively.

Conclusion: There were significant correlation between Adp levels with NT-proBNP levels and LVEF values but no any association between Adp levels with body mass index values and TNF-α levels in patients with newly diagnosed systolic heart failure. The result may arouse suspicion about the hypothesis, which proposes that Adp levels simply reflects disease severity or cardiac cachexia in patients with HF.

(Anadolu Kardiyol Derg 2013; 13: 221-6)

Key words: Heart failure, adiponectin, NT-ProBNP, cardiac cachexia, diagnostic accuracy

ÖZET

Amaç: Kalp yetmezliği (KY) olgularında NT-pro-beyin natriüretik peptid'in (NT-proBNP) tanısal değeri bilinmektedir. Adiponektin (Adp) düzeyleri bu olgularda yükselmektedir, ancak tanısal değeri henüz belirsizdir. Çalışma, yeni tanı almış, kaşıktık olmayan sistolik kalp yetmezlikli olgularda söz konusu serum göstergelerinin muhtemel ilişkisinin araştırılması için tasarlanmıştır.

Yöntemler: Sistolik KY tanısı konan 57 olgu ile yaş-cinsiyet uyumlu 20 kontrol olgusu gözlemsel kesitsel çalışmaya dahil edildi. Fizik muayene ve ekokardiyografik değerlendirmenin yanı sıra serum Adp, NT-proBNP, tümör nekrozis faktör-alfa (TNF-α) düzeyleri ölçüldü. Çalışma değişkenleri gruplar arasında karşılaştırıldı. Korelasyon analizleri yapıldı ve göstergelerin tanısal geçerliliği ROC analizi ile karşılaştırıldı.

Bulgular: Adp ve NT-proBNP düzeyleri KY grubunda anlamlı şekilde yüksek bulundu (sırasıyla 20.19±12.9'e karşılık 7.65±4.6 µg/mL; p<0.001 ve 1051.74±606.2'e karşılık 222.53±65.6 pg/mL; p=0.002). TNF-α düzeyleri her iki grupta benzerdi (2.83±1.8 vs. 2.08±1.2 pg/mL; p=0.582). Korelasyon analizi Adp ile NT-proBNP düzeyleri (r=0.448; p<0.001) ve Adp ile sol ventrikül ejeksiyon fraksiyonu (SVEF) değerleri arasında anlamlı korelasyon

Address for Correspondence/Yazışma Adresi: Dr. Uğur Önsel Türk, Central Hastanesi, Kardiyoloji Kliniği, İzmir-Türkiye

Phone: +90 232 341 67 67 Fax: +90 232 477 22 00 E-mail: droturk@yahoo.com

Accepted Date/Kabul Tarihi: 15.11.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 30.01.2013

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.067



olduğunu gösterdi ($r=-0.466$; $p<0.001$). ROC analizi ile Adp ve NT-proBNP seviyelerinin karşılaştırılabilir tanısal değere sahip olduğu saptandı: Eğri altında kalan alanlar sırası ile 0.857 (%95 GA; 0.771-0.944) ve 0.888 (%95 GA; 0.815-0.960) bulundu.

Sonuç: Yeni tanı almış sistolik kalp yetmezlikli olgularda Adp seviyeleri ile NT-proBNP ve SVEF arasında anlamlı korelasyon mevcut iken; Adp ile beden kitle indeksi ve TNF- α düzeyleri arasında herhangi bir ilişki saptanmamıştır. Bu sonuç Adp seviyelerinin KY olgularında ilerlemiş hastalığın veya kardiyak kaşeksinin bir göstergesi olduğu hipotezi ile çelişmektedir. (*Anadolu Kardiyol Derg 2013; 13: 221-6*)

Anahtar kelimeler: Kalp yetmezliği, adiponektin, NT-ProBNP, kardiyak kaşeksi, tanısal duyarlılık

Introduction

As more patients are diagnosed with heart failure (HF) each year, HF management has become a growing public health issue. Biomarkers, such as natriuretic peptides, offer consistent and cost-effective means of monitoring response to therapy. Considering that, HF is a systemic disease, biomarkers reflecting cardiac and systemic abnormalities in HF may add incremental diagnostic and/or prognostic information to natriuretic peptides. There is a growing interest in using newer biomarkers to obtain pathophysiological insight into and, possibly, to improve the management of HF.

Adiponectin (Adp) is an anti-inflammatory, insulin-sensitizing, and anti-atherogenic adipocytokine, which plays a fundamental role in energy homeostasis (1). Adp comprises 244 amino acids, and it is synthesized and secreted in large quantities from adipose tissue (1, 2). Paradoxically given its origin, circulating levels of Adp correlate inversely with body weight and body mass index (BMI), possibly as the result of a negative feedback interaction between the hormone and adipose tissue. It is well documented that high levels of circulating Adp have a favorable effect on metabolic processes and protect against derangements that lead to obesity, metabolic syndrome, atherosclerosis, and subsequent cardiovascular disease (2, 3). Epidemiological studies have shown that low Adp levels correlate with an increased risk of cardiovascular disease in obese individuals, in subjects with insulin resistance and in diabetes (2-5).

However, a paradoxical increase in Adp levels is observed in patients with systolic HF. Higher plasma concentrations of the hormone are associated with worse prognosis in HF, in contrast to what is seen in obese or diabetic patients (6-8). It is therefore not clear whether Adp is involved in the pathogenesis of HF or simply reflects the activation of complex and opposing maladaptive mechanisms. As a possible mechanism, previous studies proposed that in end-stage HF, wasting with the loss of adipose tissue (cardiac cachexia) might lead to increased levels of Adp (7, 9, 10). The mechanism raised suspicions about diagnostic values of Adp levels in HF patients without cardiac cachexia.

We, therefore, sought to investigate the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of non-cachectic patients with newly diagnosed systolic HF.

Methods

Study design

The current study has an observational cross-sectional design.

Study population

Our population is represented by a total of 57 consecutive patients with HF who were admitted to outpatient cardiology clinic of the Central Hospital between January and June 2009. All patients fulfilled the following inclusion criteria: I. Clinical congestive HF defined by Framingham criteria (11), II. Left ventricular (LV) systolic dysfunction (LV ejection fraction $<35\%$) documented by echocardiography, III. New York Heart Association (NYHA) functional capacity class 3-4.

This study also enrolled age- and sex-matched 20 control subjects without obvious heart disease who underwent cardiac catheterization for atypical chest pain in our hospital during the same enrollment period.

Patients were excluded if they had hemodynamically significant obstructive valvular disease, cor pulmonale, myocarditis, constrictive pericarditis, congenital heart disease, renal dysfunction (serum creatinine concentration >2.5 mg/dL), or if they had experienced myocardial infarction or unstable angina within the last 4 months.

Written informed consent was obtained from all patients with HF and control subjects prior to enrollment. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Local Ethics Committee.

Study protocol and definitions

All demographic and clinical features were collected from medical history of the patients. Baseline examination included a questionnaire involving gender, age and smoking status. BMI value was calculated as the ratio of the weight in kilograms to the height in squared meters. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure was >90 mmHg or if the individual was taking antihypertensive medications (12). The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies (12). Hyperlipidemia was defined by elevated total plasma cholesterol levels (>200 mg/dL) (12).

The medical history was obtained to document the etiology and the severity of HF symptoms according to the NYHA functional class. An ischemic etiology was defined by a history of myocardial infarction (electrocardiographic findings or positive troponin levels) and/or positive results from a noninvasive stress test or cardiac catheterization. Evidence-based therapy for systolic HF was started to HF patients.

We analyzed clinical, echocardiographic and laboratory parameters between the study groups and also investigated possible relationship between Adp, natriuretic peptide levels and left ventricular function.

Study variables

The following demographic, clinical, echocardiographic variables were evaluated: age, gender, weight, waist circumference, body mass index, smoking status, prevalence of diabetes mellitus, hypertension, hyperlipidemia, LV ejection fraction, LV fractional shortening, levels of NT-pro-brain natriuretic peptide (NT-proBNP), tissue necrosis factor alpha (TNF- α) and Adp. Primary end-point of the study was investigating the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of newly diagnosed systolic HF. The diagnosis of systolic HF was established as clinically defined by Framingham criteria (11) and confirmed by echocardiographic examination (LV ejection fraction <35%).

Echocardiography

Two-dimensional and Doppler echocardiographic examinations (Philips EnVisor C, Andover MA, USA) were performed and analyzed in a blinded manner. Measurements of the systolic and diastolic chamber dimensions and wall thickness were obtained from 2-dimensional imaging according to the recommendations of the American Society of Echocardiography (13). Left ventricular ejection fraction (LVEF) was measured by Simpson's modified biplane method (13). LV fractional shortening (FS) was calculated from the M-mode using the following equation:

$$FS (\%) = [(LVDD - LVDS) / LVDD] \times 100$$

Laboratory analyses

Venous blood samples were drawn at admission. Whole blood was collected in non-heparinized tubes and centrifuged at 1750 g for 10 minutes at 4°C. The obtained serum samples were stored at -20°C until they were assayed.

Serum Adp concentrations ($\mu\text{g/mL}$) were determined by a commercially available enzyme-linked immunosorbent assays (ELISA) kit (Biovendor, Heidelberg, Germany). The detection limit reported is 0.2 $\mu\text{g/mL}$. The antibodies used in this ELISA are specific for human adiponectin. No cross reactivity has been observed for human leptin, leptin receptor and resistin at 100 ng/mL. The intra-assay coefficient of variation measured was 5.9% and the inter-assay coefficient of variation was 6.3%.

NT-proBNP (pg/mL) was measured in plasma samples using commercially available kits from Biomedica (Vienna, Austria) with the intra- and inter-assay variation coefficient was 6% and 8%, respectively.

Serum TNF- α (pg/mL) was measured by a highly sensitive ELISA in a commercially available kit (Bender MedSystems, Vienna, Austria), with intra- and inter-assay coefficients of variation of 8.5% and 9.8%, respectively. The limit of detection was determined to be 0.13 pg/mL.

Statistical analysis

Statistical analysis was performed with the use of SPSS Statistics version 15.0. (SPSS, Inc., Chicago, IL, USA). Quantitative variables are expressed as mean $\pm$ standard deviation (SD), and

qualitative variables as percentages. Continuous variables were compared between the two groups using Mann-Whitney U test, whereas proportions were compared by Fisher's exact test. Correlation analyses were done by Spearman's test. Receiver operating characteristic (ROC) analysis was used to assess the diagnostic validity of the markers, and areas under the ROC curve (AUC) were compared. All results were considered statistically significant at the level of $p < 0.05$.

Results

Clinical characteristics

All HF patients had NYHA III or IV functional class at enrollment. Twenty-eight patients (49%) had ischemic etiology in HF group. Clinical characteristics of patients with HF and control subjects are shown in Table 1. Waist circumference was significantly higher in patients with HF than in control subjects (95.8 ± 10.8 vs. 87 ± 12 cm; $p = 0.015$; respectively).

Levels of biomarkers

Adp and NT-proBNP levels were significantly higher in HF group than in control group (20.19 ± 12.9 vs. 7.65 ± 4.6 $\mu\text{g/mL}$; $p < 0.001$ and 1051.74 ± 606.2 vs. 222.53 ± 65.6 pg/mL; $p = 0.002$; respectively). However TNF- α levels were similar between the groups (2.83 ± 1.8 vs. 2.08 ± 1.2 pg/mL; $p = 0.582$; respectively). Biomarker levels of the study groups are shown in Table 1.

Table 1. Clinical characteristics and biomarker levels of the study population

Variables	Patients with HF (n=57)	Control subjects (n=20)	*p
Age, years	63.6 $\pm$ 11.5	60.8 $\pm$ 9.5	n.s
Male gender, %	73	55	n.s
Weight, kg	79.7 $\pm$ 10.5	81.6 $\pm$ 10.2	n.s
Waist circumference, cm	95.8 $\pm$ 10.8	87 $\pm$ 12	0.015
Body mass index, kg/m ²	26.6 $\pm$ 4.3	30.5 $\pm$ 4.9	n.s
Diabetes mellitus, %	15.7	20	n.s
Hypertension, %	40.3	35	n.s
Smoking, %	35.1	40	n.s
Hyperlipidemia, %	40.3	50	n.s
LVEF, %	24.2 $\pm$ 4.7	57.9 $\pm$ 2.6	<0.001
LVFS, %	17 $\pm$ 5	39 $\pm$ 4	<0.001
Adiponectin, $\mu\text{g/mL}$	20.19 $\pm$ 12.9	7.65 $\pm$ 4.6	<0.001
NT-proBNP, pg/mL	1051.74 $\pm$ 606.2	222.53 $\pm$ 65.6	0.002
TNF- α , pg/mL	2.83 $\pm$ 1.8	2.08 $\pm$ 1.2	n.s

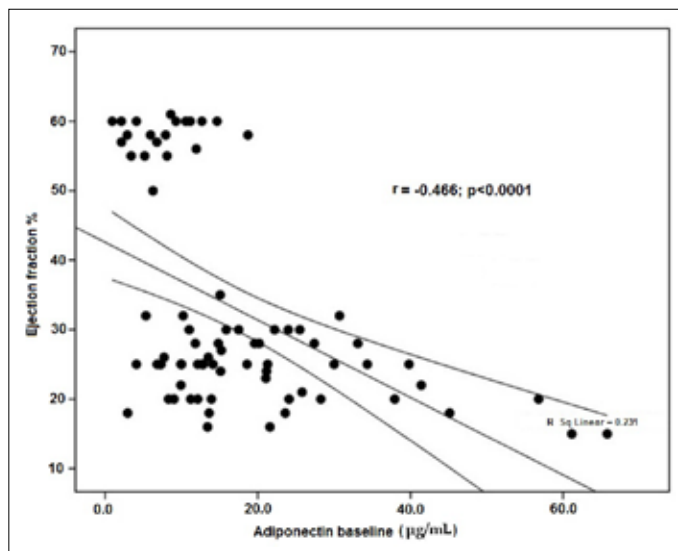
* Quantitative variables as mean $\pm$ standard deviation were compared by Mann-Whitney U test, **Qualitative variables as proportions were compared by Fisher's exact test.

HF - heart failure, LVEF - left ventricular ejection fraction, LVFS - left ventricular fractional shortening, NT-proBNP - N terminal-probrain natriuretic peptide, TNF- α - tumor necrosis factor-alpha

Table 2. The relationships of adiponectin levels with clinical, echocardiographic variables and other biomarkers in patients with systolic HF

Variables	Adiponectin, $\mu\text{g/mL}$	
	*r	*p
Age, years	0.173	0.134
Body mass index, kg/m^2	-0.110	0.417
LVedd, mm	0.291	0.01
LVesd, mm	0.424	<0.001
LAd, mm	0.170	0.139
IVS, mm	-0.221	0.053
PW, mm	-0.112	0.331
LVEF, %	-0.466	<0.001
LVFS, %	-0.470	<0.001
NT-proBNP, pg/mL	0.448	<0.001
TNF- α , pg/mL	0.114	0.326

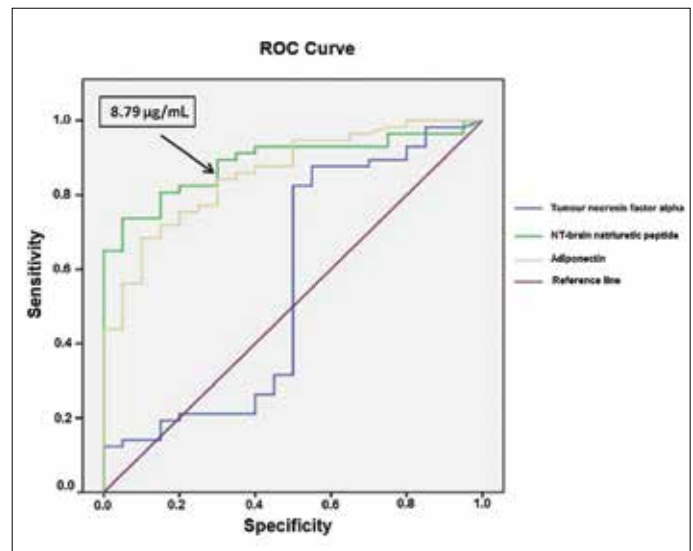
*Pearson correlation analysis

HF - heart failure, IVS - interventricular septum, LAd - left atrial diameter, LVedd - left ventricular end-diastolic diameter, LVesd - left ventricular end-systolic diameter, LVEF - left ventricular ejection fraction, LVFS - left ventricular fractional shortening, NT-proBNP - N-terminal proBrain natriuretic peptide, PW - posterior wall, TNF- α - tumor necrosis factor-alpha**Figure 1. The relationship between serum adiponectin levels and LVEF values in patients with systolic heart failure**

LVEF - left ventricular ejection fraction

Associations of Adp and other study variables

Correlation analysis showed positive association among Adp and NT-proBNP levels ($r=0.448$; $p<0.001$), LV end-diastolic ($r=0.291$; $p=0.01$), end-systolic diameters ($r=0.424$; $p<0.001$) and LV fractional shortening ($r=-0.470$; $p<0.001$) (Table 2). Furthermore, significant negative correlations were found between the LVEF and serum Adp (Fig. 1) and NT-proBNP levels ($r=-0.466$; $p<0.001$ and $r=-0.552$; $p<0.001$; respectively), but there was no any significant correlation between LVEF and TNF- α levels ($r=-0.73$; $p=0.527$). There was no any association between levels of Adp, NT-ProBNP and TNF- α in control subjects. Serum Adp was not

**Figure 2. ROC curves comparing the diagnostic performances of serum NT-proBNP, Adp and TNF- α level for identifying patients with heart failure. Adp and NT-proBNP showed comparable diagnostic performances with mean AUC of 0.857 (95% CI 0.771-0.944) and 0.888 (95% CI 0.815-0.960), respectively. Diagnostic performance of TNF- α levels were not statistically significant. [AUC: 0.557 (95% CI: 0.338-0.727), $p=0.447$] Optimum cut-off value of serum Adp level is shown**Adp - adiponectin, NT-proBNP - NT-pro-brain natriuretic peptide, TNF- α - tissue necrosis factor alpha

correlated with BMI in both patients and control subjects groups.

In patients with systolic HF, the Adp and NT-proBNP showed comparable diagnostic performances (Fig. 2) with mean [95% confidence interval (CI)] areas under the curves (AUC) of 0.857 (0.771-0.944, $p<0.001$) and 0.888 (0.815-0.960, $p<0.001$), respectively. At the optimal cut off value of 8.79 $\mu\text{g/mL}$ for Adp, sensitivity was 86% and specificity of 65% for predicting the presence of HF.

Discussion

In this study, we sought to investigate the Adp levels and its possible association with natriuretic peptide levels and left ventricular function in a cohort of non-cachectic patients with newly diagnosed untreated systolic HF. Our study has demonstrated that serum Adp levels were significantly increased in this population. Heart failure group of the study was selected meticulously and they had unique clinical characteristics. They were unaware that they had HF before the enrollment; the first hospital admission date due to HF symptoms of them was study enrollment time. Consequently, HF patients of the study had normal or overweight BMI ratios which confirming to exclude the cachectic HF patients from the study. The mean BMI was 26.66 ± 4.3 in patients with HF.

Previous studies concluded that Adp may be a marker of muscle wasting in HF and its levels are elevated in patients with cardiac cachexia (3, 9, 10). Kung et al. (14) asserted that elevated Adp levels were significantly associated with advanced disease

state and metabolic impairment. However, Adp levels were elevated in our HF group which had recently diagnosed and more reflective of early steps of metabolic disturbances due to HF.

The role of Adp in HF is controversial. Theoretically, progression of HF is closely associated with a reduction in total body weight as part of a wasting process. This decrease in body weight will result in an increase in Adp levels. Elevated Adp levels may compensate a state of impaired energy metabolic efficacy (a progressive shift from fatty acid utilization to glucose utilization) and malnutrition (15). Hence, functional adiponectin resistance has been observed in the skeletal muscle of patients with chronic HF (16). This would explain why, despite known cardiac and vascular protective effects (4). Adp is paradoxically associated with increased mortality in HF (2, 4, 8, 10). However, the hypothesis which asserts that the increased Adp levels is a marker of the advanced disease state and metabolic disturbances is controversial, because in our study, Adp levels were also increased in the HF population with non-cachectic patients. Adp is mainly expressed in adipose tissue; serum adiponectin level correlates negatively with BMI in stable CHF (2, 3, 10). In our study population, serum adiponectin concentrations were not correlated with BMI or waist circumference. Although the patients with HF had greater waist circumference than in control subjects, this may be as a result of hepatic or fluid congestion. Thus, major sources of circulating Adp are not thought to be adipose tissue in our HF population. Heart failure patients of the study were enrolled at the first hospital admission time due to HF symptoms and all of them at first days of stage C- HF. Recent studies have shown that Adp mRNA and protein are expressed in cardiomyocytes of rodents and humans and immunoreactive Adp was found in the myocardial tissues obtained from the autopsied heart (17-19). Takano et al. (20) showed significant transcardiac gradient of Adp levels in patients with HF. Adp may be released from the heart in patients with HF and the amount of heart-originated Adp may constituted significant part of serum levels. We have no data about the source of Adp in the present study.

The factors controlling Adp secretion in HF are still poorly understood and remain controversial. It is possible that increased proinflammatory cytokines may stimulate Adp secretion. Previous studies have proposed that TNF- α has been suggested to increase Adp secretion, although this literature is conflicting (21, 22). Heart failure population of the study had normal TNF- α levels and we did not find any relationship between serum Adp and TNF- α levels which supporting these conflicted results. However, our study demonstrated that serum Adp levels correlated positively with LVEF values and serum NT-proBNP levels. Takano et al. (20) proposed that Adp is released from the heart into the circulation in proportion to the severity of LV dysfunction in patients with HF irrespective of etiologies of HF. Accordingly; heart-originated Adp may at least partly contribute to the increased levels of Adp seen in patients with HF who had severe LV systolic dysfunction and normal BMI such as the study HF population.

Previous studies showed strong correlation between Adp and natriuretic peptide levels (20, 23). Whether the correlation between two markers simply reflects a parallel evolution of two biomarkers that mirror disease severity, or whether there is a causal association remains to be further explored. Moro et al. shown that atrial natriuretic peptide directly stimulates Adp production in adipocytes cultured under lipolysis inhibition (24). Thus, atrial natriuretic peptide and BNP, whose levels are increased in HF, might possibly stimulate adiponectin secretion resulting in increased adiponectin levels in patients with HF. Indeed, Tsukamoto et al. (25) demonstrated that natriuretic peptides increase the production of Adp by human adipocytes.

Study limitations

There are several limitations of the current study. First, the design was observational cross-sectional and measurements of serum biomarkers, BMI and LVEF values were performed at the same visit. The study was a single-center study performed in a relatively small sample of patients and restricted to Caucasian patients only. We measured Adp levels in peripheral venous samples, but not in coronary sinus samples. We were unable to determine transcardiac gradient of Adp. The assay used in our study measured total Adp levels and we have no data about the source of Adp. We were therefore unable to distinguish between the low molecular weight and the high molecular weight form. Finally, our study is not a diagnostic accuracy study; however, we found that Adp levels displayed to comparable diagnostic performance with NT-proBNP for diagnosis of systolic HF. Therefore, further studies are needed to explore its validity.

Conclusion

Major findings of our study were the presence of significant correlation between Adp levels with, NT-proBNP levels and LVEF values, but absence of any association between Adp levels with body mass index values and TNF- α levels in patients with newly diagnosed systolic heart failure. The result may arouse suspicion about the hypothesis, which proposes that Adp levels simply reflects disease severity or cardiac cachexia in patients with HF.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - İ.T., U.Ö.T., E.A.; Design - U.Ö.T.; Supervision - E.E., E.A.; Materials - B.K., G.S.T.; Data collection &/or Processing - B.K., N.T., U.Ö.T., İ.T.; Analysis &/or interpretation - E.E., U.T., Literature search - N.T., E.A.; Writing - U.Ö.T., G.S.T.; Critical review - G.S.T., İ.T., E.E.

References

1. Marinou K, Tousoulis D, Antonopoulos AS, Stefanadi E, Stefanadis C. Obesity and cardiovascular disease: from pathophysiology to risk stratification. *Int J Cardiol* 2010; 138: 3-8. [\[CrossRef\]](#)

2. Hopkins TA, Ouchi N, Shibata R, Walsh K. Adiponectin actions in the cardiovascular system. *Cardiovasc Res* 2007; 74: 11-8. [\[CrossRef\]](#)
3. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. *Endocr Regul* 2009; 43: 157-68.
4. Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. *Nat Clin Pract Cardiovasc Med* 2009; 6: 27-35. [\[CrossRef\]](#)
5. Persson J, Lindberg K, Gustafsson TP, Eriksson P, Paulsson-Berne G, Lundman P. Low plasma adiponectin concentration is associated with myocardial infarction in young individuals. *J Intern Med* 2010; 268: 194-205. [\[CrossRef\]](#)
6. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005; 112: 1756-62. [\[CrossRef\]](#)
7. Haugen E, Furukawa Y, Isic A, Fu M. Increased adiponectin level in parallel with increased NT-pro BNP in patients with severe heart failure in the elderly: A hospital cohort study. *Int J Cardiol* 2008; 125: 216-9. [\[CrossRef\]](#)
8. George J, Patal S, Wexler D, Sharabi Y, Peleg E, Kamari Y, et al. Circulating adiponectin concentrations in patients with congestive heart failure. *Heart* 2006; 92: 1420-4. [\[CrossRef\]](#)
9. von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. *Pharmacol Ther* 2009; 121: 227-52. [\[CrossRef\]](#)
10. McEntegart MB, Awede B, Petrie MC, Sattar N, Dunn FG, MacFarlane NG, et al. Increase in serum adiponectin concentration in patients with heart failure and cachexia: relationship with leptin, other cytokines, and B-type natriuretic peptide. *Eur Heart J* 2007; 28: 829-35. [\[CrossRef\]](#)
11. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. *Circulation* 1993; 88: 107-15. [\[CrossRef\]](#)
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42: 1206-52. [\[CrossRef\]](#)
13. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358 -67.
14. Kung T, Szabó T, Springer J, Doehner W, Anker SD, von Haehling S. Cachexia in heart disease: highlights from the ESC 2010. *J Cachexia Sarcopenia Muscle* 2011; 2: 63-9. [\[CrossRef\]](#)
15. Springer J, Anker SD, Doehner W. Adiponectin resistance in heart failure and the emerging pattern of metabolic failure in chronic heart failure. *Circ Heart Fail* 2010; 3: 181-2. [\[CrossRef\]](#)
16. Van Berendoncks AM, Garnier A, Beckers P, Hoymans VY, Possemiers N, Fortin D, et al. Functional adiponectin resistance at the level of the skeletal muscle in mild to moderate chronic heart failure. *Circ Heart Fail* 2010; 3: 185-94. [\[CrossRef\]](#)
17. Wang Y, Lau WB, Gao E, Tao L, Yuan Y, Li R, et al. Cardiomyocyte-derived adiponectin is biologically active in protecting against myocardial ischemia-reperfusion injury. *Am J Physiol Endocrinol Metab* 2010; 298: 663-70. [\[CrossRef\]](#)
18. Skurk C, Wittchen F, Suckau L, Witt H, Noutsias M, Fechner H, et al. Description of a local cardiac adiponectin system and its deregulation in dilated cardiomyopathy. *Eur Heart J* 2008; 29: 1168-80. [\[CrossRef\]](#)
19. Piñeiro R, Iglesias MJ, Gallego R, Raghu K, Eiras S, Rubio J, et al. Adiponectin is synthesized and secreted by human and murine cardiomyocytes. *FEBS Lett* 2005; 579: 5163-9. [\[CrossRef\]](#)
20. Takano H, Obata JE, Kodama Y, Kitta Y, Nakamura T, Mende A, et al. Adiponectin is released from the heart in patients with heart failure. *Int J Cardiol* 2009; 132: 221-6. [\[CrossRef\]](#)
21. Wang B, Trayhum P. Acute and prolonged effects of TNF-alpha on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture. *Pflugers Arch* 2006; 452: 418-27. [\[CrossRef\]](#)
22. Carey AL, Petersen EW, Bruce CR, Southgate RJ, Pilegaard H, Hawley JA, et al. Discordant gene expression in skeletal muscle and adipose tissue of patients with type 2 diabetes: effect of interleukin-6 infusion. *Diabetologia* 2006; 49: 1000-7. [\[CrossRef\]](#)
23. Van Berendoncks AM, Beckers P, Hoymans VY, Possemiers N, Coenen S, Elseviers MM, et al. Beta-blockers modify the prognostic value of adiponectin in chronic heart failure. *Int J Cardiol* 2011; 150: 296-300. [\[CrossRef\]](#)
24. Moro C, Klimcakova E, Lomède K, Berlan M, Lafontan M, Stich V, et al. Atrial natriuretic peptide inhibits the production of adipokines and cytokines linked to inflammation and insulin resistance in human subcutaneous adipose tissue. *Diabetologia* 2007; 50: 1038-47. [\[CrossRef\]](#)
25. Tsukamoto O, Fujita M, Kato M, Yamazaki S, Asano Y, Ogai A, et al. Natriuretic peptides enhance the production of adiponectin in human adipocytes and in patients with chronic heart failure. *J Am Coll Cardiol* 2009; 53: 2070-7. [\[CrossRef\]](#)

Impaired coronary flow reserve evaluated by echocardiography is associated with increased aortic stiffness in patients with metabolic syndrome: an observational study

Metabolik sendromlu hastalarda ekokardiyografik olarak gösterilen bozulmuş koroner akım rezervi artmış aort sertliği ile ilişkilidir: Gözlemsel bir çalışma

Derya Tok, Fırat Özcan, İskender Kadife, Osman Turak, Kumral Çağlı, Nurcan Başar, Zehra Gölbaşı, Sinan Aydoğdu

Clinic of Cardiology, Yüksek İhtisas Education and Research Hospital, Ankara-Turkey

ABSTRACT

Objective: Metabolic syndrome (MetS) is a strong predictor of cardiovascular events and coronary flow reserve (CFR), an indicator of microvascular function, has been found to be impaired in MetS. Aortic stiffness (AS) is a simple and effective method for assessing arterial elasticity. The aim of this study was to evaluate whether there is an independent association of impaired coronary flow and aortic elasticity in patients with MetS.

Methods: Forty-six patients (mean age 47.3±6.6 years) with the diagnosis of MetS according to the ATP III update criteria and 44 age and gender matched controls (mean age 46.0±6.1 years) were included into the cross-sectional observational study. Peak diastolic coronary flow velocities were measured in left anterior descending artery by pulsed wave Doppler at baseline and after adenosine infusion, and CFR was calculated as the ratio of hyperemic to baseline velocities. Aortic strain, distensibility and stiffness were calculated by M-mode echocardiography. Statistical analysis was performed by using Student t-test, Chi-square test, Pearson correlation and linear regression analyses.

Results: CFR was significantly lower in patients with MetS than in controls (2.3±0.2 vs 2.7±0.2, p<0.001). In the MetS group, aortic distensibility (10.4±3.5 cm².dyn⁻¹.10⁻⁶ vs. 12.7±3.4 cm².dyn⁻¹.10⁻⁶, p=0.002) was decreased and AS was significantly increased (6.5±2.0 vs. 3.2±0.8, p<0.001). In multivariate linear regression analysis, AS (β=-0.217, p=0.047), systolic blood pressure (β=-0.215, p=0.050) and waist circumference (β=-0.272, p=0.012) had an independent relationship with impaired CFR.

Conclusion: This study demonstrated that coronary flow reserve is impaired in patients with MetS and there is an independent relationship between impaired CFR and increased aortic stiffness, systolic blood pressure or waist circumference.

(Anadolu Kardiyol Derg 2013; 13: 227-34)

Key words: Metabolic syndrome, coronary flow reserve, aortic stiffness, echocardiography, regression analysis

ÖZET

Amaç: Metabolik sendrom (MetS) kardiyovasküler olayların güçlü bir belirleyicisidir. Koroner akım rezervi (KAR) mikrovasküler fonksiyonun göstergesidir ve MetS'de bozulduğu gösterilmiştir. Arteriyel elastikiyetin değerlendirilmesinde aortik sertlik (AS) basit ve önemli bir metottur. Bu çalışmada MetS'li hastalarda bozulmuş koroner akım ve aortik elastisite arasında bağımsız bir ilişki olup olmadığının değerlendirilmesi amaçlanmıştır.

Yöntemler: Enine kesitli gözlemsel çalışmaya güncellenmiş ATP III kriterlerine göre MetS tanısı alan 46 hasta (ortalama yaş 47.3±6.6 yıl) ve 44 kontrol (ortalama yaş 46.0±6.1 yıl) hastası alındı. Pik diyastolik koroner akım, distal sol ön koroner arterden adenosin infüzyonu öncesi ve sonrasında transtorasik nabız dalga Doppler ile ölçüldü ve hiperemik pik diyastolik hızın başlangıç zirve diyastolik hızı oranı KAR olarak kabul edildi. M-mode ekokardiyografi ile aortik strain, distensibilite ve sertlik hesaplandı. İstatistiksel analizde Student t-testi, Ki-kare testi, Pearson korelasyon ve lineer regresyon analizleri kullanıldı.

Address for Correspondence/Yazışma Adresi: Dr. Derya Tok, Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Sıhhiye, 06100 Ankara-Türkiye Phone: +90 312 306 10 00-1822 Fax: +90 312 312 41 20 E-mail: deryatok@hotmail.com

Accepted Date/Kabul Tarihi: 23.11.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 30.01.2013

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.068



Bulgular: MetS'li hastalarda kontrol grubuna kıyasla KAR'ı düşük (2.3 ± 0.2 'ye karşılık 2.7 ± 0.2 , $p < 0.001$), aortik distensibilite düşük (10.4 ± 3.5 'e karşılık 12.7 ± 3.4 , $p = 0.002$) ve sertlik ise anlamlı yüksek saptandı (6.5 ± 2.0 'e karşılık 3.2 ± 0.8 , $p < 0.001$). Lineer regresyon analizinde, AS ($\beta = -0.217$, $p = 0.047$), sistolik kan basıncı ($\beta = -0.215$, $p = 0.050$) ve bel çevresi ($\beta = -0.272$, $p = 0.012$) ile KAR'daki bozulma arasında bağımsız bir ilişki olduğu saptandı.

Sonuç: MetS'li hastalarda koroner akım rezervi bozulmuştur ve artmış aort sertliği, bel çevresi ve sistolik kan basıncı ile azalmış koroner akım rezervi arasında bağımsız bir ilişki vardır. (*Anadolu Kardiyol Derg 2013; 13: 227-34*)

Anahtar kelimeler: Metabolik sendrom, koroner akım rezervi, aortik sertlik, ekokardiyografi, regresyon analizi

Introduction

Metabolic syndrome (MetS) is defined as a clustering of multiple cardiovascular risk factors, including dyslipidemia, obesity, hypertension and impaired glucose tolerance (1). These factors contribute to a high incidence of cardiovascular disease in patients with MetS (2, 3). MetS impairs the ability of the coronary circulation to regulate vascular resistance and balance myocardial oxygen supply and demand (4, 5). Coronary microvascular dysfunction in MetS is evidenced by reduced coronary venous PO_2 , diminished vasodilation to endothelial-dependent and independent agonist and altered functional and reactive hyperemia (4-9). Alterations in coronary microvascular function could contributed to the increased cardiovascular morbidity and mortality observed in patients with MetS (10). Recently microvascular dysfunction characterized by impaired coronary flow reserve (CFR) has been identified in patients with MetS prior to overt atherosclerotic disease (7).

Aortic stiffness describes the elastic resistance that the aorta sets against its distension (11). Aortic stiffness is one of the most important cardiovascular risk factors predicting cardiovascular morbidity and mortality (12). Aortic elasticity can be assessed by various parameters measured by echocardiography, which is a non-invasive method (13). MetS causes an increase in arterial stiffness independently of other cardiovascular risk factors (14). Several components of the MetS, including high blood pressure, hyperglycemia, and abdominal fat, have been related to increased aortic stiffness (12, 15).

Aortic stiffening may cause an increase in aortic pulse pressure, left ventricular load, and ultimately left ventricular hypertrophy. This together with the decreased diastolic transmyocardial pressure gradient interacts with coronary flow and flow reserve (11). Significant correlations between coronary flow reserve and aortic stiffness parameters have been demonstrated in different populations such as hypertension, aortic valve stenosis, and hypercholesterolemia (16-19).

However, presence of an association between aortic stiffness (AS) and impaired CFR in MetS has never been evaluated.

The aim of this study was to evaluate whether there is an independent association of impaired coronary flow and aortic elasticity by utilizing transthoracic echocardiography in patients with MetS.

Methods

Study design

The present study was designed as a cross-sectional, observational study.

Study population

Forty-six patients (mean age 47.3 ± 6.5 years) with the diagnosis of MetS according to the Adult Treatment Panel III Final Report criteria (20) without clinical coronary artery disease were included in the study. Forty-four age and gender matched healthy subjects (mean age 46.0 ± 6.1 years) were recruited as the control group. Patients were excluded if they had coronary artery disease, severe valvular disease, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, malignancy, congenital heart disease, chronic heart failure, cardiac rhythm other than sinus, uncontrolled hypertension prior to study, systemic disease such as collagenosis, chronic autoimmune, hemolytic, hepatic and chronic renal disease, or inadequate transthoracic echocardiographic images.

The study protocol was approved by the local ethics committee and written informed consent was obtained from each subject.

Study variables

The baseline variables of study were as following: age, sex, smoking status, systolic (SBP) and diastolic (DBP) blood pressure, history of diabetes mellitus (DM), hypertension (HT), body mass index (BMI), waist circumference, fasting plasma glucose (FPG), total cholesterol, triglycerides, high-density (HDL) and low-density (LDL) lipoprotein cholesterol, high sensitive C-reactive protein (hsCRP), and echocardiographic measurements. In our study, presence of MetS was a primary predictor variable, the outcome variables were CFR and aortic stiffness and confounding variables were age, waist circumference, SBP, FPG, HDL-cholesterol, triglycerides, hs-CRP, and left ventricular mass index (LVMI).

Clinical and laboratory examinations

All patients underwent clinical and laboratory examinations. Demographic data including classical risk factors of atherosclerosis (HT, dyslipidemia, smoking) were noted. Blood samples were obtained after overnight fasting. Plasma glucose, total cholesterol, HDL and LDL cholesterol, triglyceride levels were measured using standard methods (HITACHI MODULAR EVO P800, Roche Diagnostics GmbH, Mannheim, Germany). The levels of hsCRP were measured with immunonephelometric method (IMMAGE Immunochemistry Systems; Beckman Coulter, California, USA).

Definitions

Metabolic syndrome was diagnosed if three or more of the followings were present according to the Adult Treatment Panel III Final Report criteria (20): (i) abdominal obesity: waist circumference >102 cm in men and >88 cm in women; (ii) plasma triglycerides: ≥ 150 mg/dL; (iii) plasma HDL cholesterol: <40 mg/dL in men and <50 mg/dL in women; (iv) SBP ≥ 130 mmHg or DBP ≥ 85

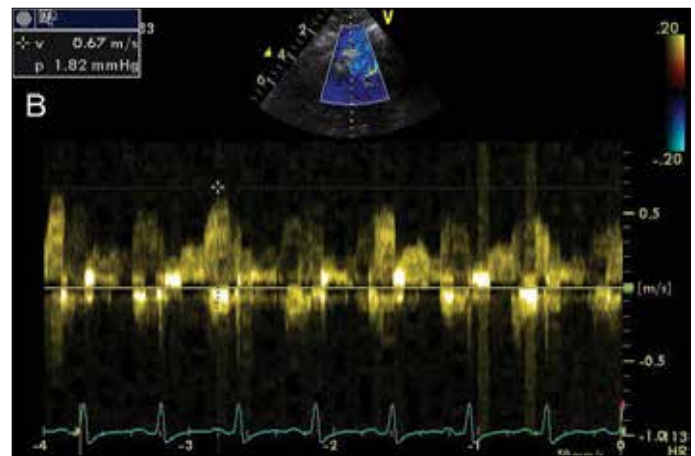
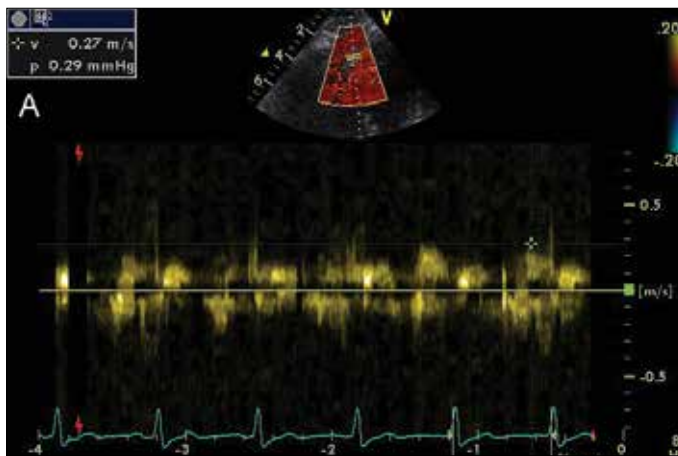


Figure 1. Demonstration of coronary flow velocity at (A) baseline and (B) hyperemia obtained by transthoracic pulsed wave Doppler echocardiography in the distal left anterior descending coronary artery

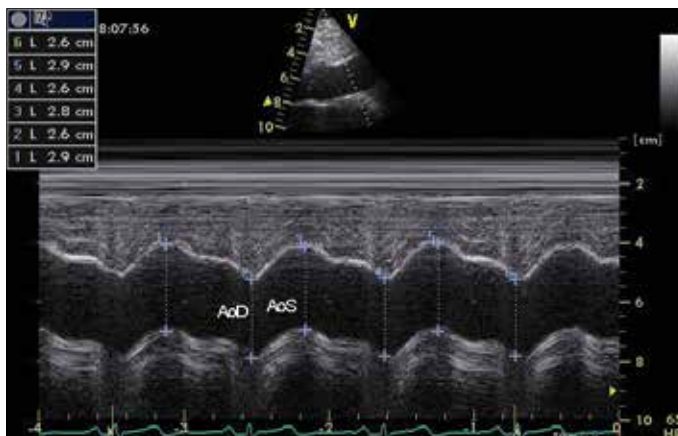


Figure 2. Measurements of aortic diameters shown on the M-mode tracing obtained at a level 3 cm above the aortic cusps

AoD - diastolic aortic diameter, AoS - systolic aortic diameter

mmHg or use of an anti-hypertensive medication; (v) FPG ≥ 110 mg/dL. Hypertension was defined as SBP > 140 mmHg or DBP > 90 mmHg or use of an antihypertensive medication (21). Diabetes mellitus was defined in case of a history of oral antidiabetics, insulin medication or fasting blood glucose ≥ 126 mg/dL at study entrance (22). Coronary artery disease was defined as the presence of 1 of the following: a past history of a myocardial infarction/revascularization, typical angina, ST-segment or T-wave changes specific to myocardial ischemia, Q waves on electrocardiogram, wall motion abnormality on echocardiography, a non-invasive stress test demonstrating ischemia or any perfusion abnormality, coronary artery stenosis on angiography. Height and weight were measured according to a standardized protocol. BMI was calculated as body weight divided by height squared (kg/m^2). Waist circumference was measured on bare skin during mid-respiration at the natural indentation between the tenth rib and the iliac crest to the nearest 0.5 cm.

Transthoracic echocardiography

All the patients underwent transthoracic echocardiography using a Vivid 7 Dimension Cardiovascular Ultrasound System

(GE Healthcare, USA) with a 3.5 MHz transducer. Two dimensional, M-mode and transthoracic Doppler echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography (23) and images were digitally stored and analyzed by an experienced echocardiographer blinded to the study protocol. Left ventricular mass was calculated from M-Mode records taken on parasternal long-axis images according to Devereux's formula (24). The LVMI was calculated as LVM/body surface area.

CFR determination

Left anterior descending (LAD) coronary artery was visualized using a modified, foreshortened, 2-chamber view, and an optimal alignment to the interventricular sulcus was obtained. The color gain was adjusted to provide optimal images and coronary flow in the distal LAD was examined by color Doppler flow mapping over the epicardial part of the anterior wall. By placing the sample volume on the color signal, spectral Doppler of the LAD showed the characteristic biphasic flow pattern with larger diastolic and smaller systolic components. Hyperemia was induced by intravenous infusion of adenosine at a rate of $0.140 \mu\text{g}/\text{kg}/\text{min}$ over 4 minutes. Coronary diastolic peak velocities were measured at baseline and after adenosine by averaging the highest 3 Doppler signals for each measurement. CFR was calculated as the ratio of hyperemic to baseline diastolic peak velocities (Fig. 1) (25).

Assessment of aortic stiffness

Aortic elasticity was assessed using a two-dimensional guided M-mode evaluation of systolic aortic diameter (AoS) and diastolic aortic diameter (AoD), 3 cm above the aortic valve (13, 26). AoD was obtained at the peak of the R wave on the simultaneously recorded electrocardiogram, while AoS was measured at the maximal anterior motion of the aortic wall; for each diameter, 3 measurements were averaged (Fig. 2). The following indexes of aortic elasticity were calculated: % aortic strain = $100 \times \text{AoS} - \text{AoD} / \text{AoD}$, aortic distensibility = $[2 \times (\text{AoS} - \text{AoD}) /$

AoD (pulse pressure)] ($10^{-6} \cdot \text{cm}^{-2} \cdot \text{dyn}^{-1}$); and aortic stiffness (AS) = $\ln(\text{SBP} / \text{DBP}) / [(\text{AoS} - \text{AoD}) / \text{AoD}]$, where SBP and DBP refer to brachial systolic blood pressure and diastolic blood pressure, measured in millimeters of mercury; pulse pressure was calculated as SBP-DBP, and $\ln(\text{SBP} / \text{DBP})$ refers to the natural logarithm of the relative pressure (13, 26).

Statistical analysis

Statistical analysis was performed using SPSS software (Version 15.0, SPSS Chicago, USA). Continuous data were presented in median±IQR (interquartile range) or mean±standard deviation (SD). Comparisons of multiple mean values were carried out by student t test or Mann-Whitney U test. To test the distribution pattern, the Kolmogorov-Smirnov test was utilized. Categorical variables were summarized percentages and compared with the Chi-square test or Fisher's exact test. Correlations were sought by the Spearman's and Pearson correlation test. The multivariate linear regression analysis was performed to determine independent relationship between CFR and aortic stiffness and other potential confounding variables. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics

Demographic and clinical characteristics and laboratory results of the study population are summarized in Table 1. The mean age of the study population was 47.3 ± 6.47 years. Gender and mean age were similar between the groups ($p > 0.05$). As expected, the prevalence of HT was significantly higher in patients with MetS. The mean values for BMI and waist circumference were significantly higher in patients with MetS ($p < 0.05$ for all). The mean values hsCRP and FPG levels were significantly higher in patients with MetS than in controls. Patients with MetS had significantly higher LDL cholesterol and triglyceride concentrations, and lower HDL cholesterol levels ($p < 0.05$ for all). Twenty of MetS patients underwent coronary angiography and found normal coronary arteries within last 6 months. All patients in both groups had exercise stress test, which revealed as negative for all.

CFR and aortic distensibility

During adenosine infusion, no major adverse reactions were observed. The mean baseline diastolic peak velocity (DPV) value was similar in both groups (26.3 ± 1.5 cm/s vs. 26.6 ± 1.8 cm/s, $p = 0.430$) but the mean hyperemic DPV was significantly lower in patients with MetS compared with control subjects (60.1 ± 4.5 cm/s vs. 67.7 ± 5.2 cm/s, $p < 0.001$). When CFR was compared between groups, patients with MetS had significantly lower CFR values than did those without MetS (2.3 ± 0.2 vs. 2.7 ± 0.2 , $p < 0.001$).

There were no significant differences with regard to end-diastolic volume, end-systolic volume and ejection fraction bet-

Table 1. Comparison of clinical, laboratory and transthoracic and Doppler echocardiography findings

Variables	MetS (n=46)	Controls (n=44)	*p
Age, years	47.3±6.5	46.0±6.1	0.215
Men, n (%)	25 (54.3)	18 (40.9)	0.214
Smoker, n (%)	20 (43.5)	13 (29.5)	0.195
Hypertension, n (%)	29 (63.0)	0 (0)	<0.001
Diabetes mellitus, n (%)	3 (3.3)	0 (0)	0.242
BMI, kg/m ²	31.9±4.1	24.0±3.4	<0.001
Waist circumference, cm	107.1±8.7	84.9±8.7	<0.001
Fasting glucose, mg/dL	106.1±18.3	90.0±7.8	<0.001
Total cholesterol, mg/dL	213.1±33.2	186.2±33.1	<0.001
LDL cholesterol, mg/dL	127.7±35.7	114.2±26.6	0.046
HDL cholesterol, mg/dL	37.7±8.3	53.1±10.6	<0.001
Triglyceride, mg/dL	243.6±64.3	95.8±32.7	<0.001
hs-CRP, mg/L	3.6±3.0	2.1±2.1	0.008
Baseline PDV, cm/s	26.3±1.5	26.6±1.8	0.430
Hyperemic PDV, cm/s	60.1±4.5	67.7±5.2	<0.001
CFR	2.3±0.2	2.7±0.2	<0.001
LVMI, g/m ²	107.5±17.2	80.7±10.6	<0.001
LV EF, %	64.1±2.1	65.1±1.6	0.214

Data are presented as mean±SD and number (percentage)
 *Student's t-test and Chi-square test
 BMI - body mass index, CFR - coronary flow reserve, HDL - high-density lipoprotein, hs-high sensitive, hsCRP - high-sensitive C - reactive protein, LDL - low-density lipoprotein, LVEF - left ventricular ejection fraction, LVMI - left ventricular mass index, MetS - metabolic syndrome, PDV - peak diastolic velocity

ween the groups. LVMI was significantly higher in patients with MetS than in control subjects ($p < 0.001$). Aortic distensibility was significantly decreased, and aortic stiffness (AS) was increased significantly in patients with MetS compared to controls ($10.4 \pm 3.5 / 10^{-6} \cdot \text{cm}^{-2} \cdot \text{dyn}^{-1}$ vs. $12.7 \pm 3.4 / 10^{-6} \cdot \text{cm}^{-2} \cdot \text{dyn}^{-1}$, $p = 0.002$, 6.5 ± 2.0 vs. 3.2 ± 0.8 , $p < 0.001$) (Table 2).

Association of CFR with clinical and echocardiographic variables

In correlation analysis, CFR was significantly correlated with age ($r = -0.220$, $p < 0.0001$), systolic blood pressure ($r = -0.596$, $p < 0.001$), diastolic blood pressure ($r = -0.216$, $p = 0.042$), waist circumference ($r = -0.642$, $p < 0.001$), total cholesterol ($r = -0.251$, $p = 0.018$), HDL-cholesterol ($r = 0.514$, $p < 0.001$), triglyceride ($r = -0.507$, $p < 0.001$), fasting glucose ($r = -0.358$, $p < 0.001$), hsCRP ($r = -0.227$, $p = 0.033$), LVMI ($r = -0.396$, $p < 0.001$), and AS ($r = -0.604$, $p < 0.001$).

In multivariate linear regression analysis in which CFR was taken as a dependent variable and age, waist circumference, SBP, FPG, HDL-cholesterol, triglyceride, LVMI and AS were taken as independent variables, we found that AS ($\beta = -0.217$, $p = 0.047$), SBP ($\beta = 0.215$, $p = 0.050$) and waist circumference ($\beta = -0.272$, $p = 0.012$) have an independent association with impaired CFR (Table 3).

Table 2. Comparison of aortic elastic properties of the groups

Variables	Metabolic syndrome (n=46)	Controls (n=44)	*p
Systolic blood pressure, mmHg	131.4±15.3	110.0±10.6	<0.001
Diastolic blood pressure, mmHg	74.6±10.8	68.4±7.5	0.002
Aortic systolic diameter, cm	3.40±0.23	3.28±0.31	0.035
Aortic diastolic diameter, cm	3.12±0.23	2.90±0.31	<0.001
Aortic strain, %	10.5±2.9	12.1±5.1	0.08
Aortic distensibility, cm ² .dyn ⁻¹ .10 ⁻⁶	10.4±3.5	12.7±3.4	0.002
Aortic stiffness	6.5±2.0	3.2±0.8	<0.001
Data are presented as mean±SD *Unpaired Students' t-test			

Table 3. Independent relationship between CFR and confounding variables by multivariate linear regression analysis (r²=0.571, p<0.001)

Independent variables	Beta regression coefficient	p
Age	-0.067	0.413
Waist circumference	-0.272	0.012
Systolic blood pressure	-0.215	0.050
Fasting glucose	0.045	0.625
HDL-cholesterol	0.133	0.202
Triglyceride	-0.117	0.229
hsCRP	0.004	0.959
LVMi	-0.028	0.746
Aortic stiffness	-0.217	0.047
Multivariate linear regression analysis CFR - coronary flow reserve, HDL - high-density lipoprotein, hsCRP - high- sensitive C - reactive protein, LVMi - left ventricular mass index		

Discussion

This study demonstrated that coronary flow reserve is impaired in patients with MetS and there is an independent relationship between impaired CFR and increased aortic stiffness evaluated by echocardiography.

MetS is a group of risk factors including obesity, dyslipidemia, insulin resistance/impaired glucose tolerance, and/or hypertension and is accompanied by pro-inflammatory and thrombotic states (27). Since all components of MetS have unfavourable effects on the endothelium, endothelial dysfunction more prevalent in patients with MetS and could play a role in the increased risk for cardiovascular disease and type 2 DM in this population (28). Many reported studies have used several modalities to investigate the relationship MetS and coronary microvascular circulation. Turhan et al. (29) reported an impaired coronary blood flow using the Thrombolysis in Myocardial Infarction frame count method in MetS patients with angiographically normal coronary arteries. Pirat et al. (7), using transthoracic echocardiography, have reported an impaired vasodilatory response to pharmacologic agents in the LAD of coronary arte-

ries in patients with MetS. In present study, we also evaluated CFR, the magnitude of the increase in blood flow at maximal coronary vasodilation, by using transthoracic Doppler echocardiography as a reliable and reproducible way to assess CFR (30) and found that there is a coronary microvascular endothelial dysfunction in MetS patients.

MetS impairs the ability of the coronary circulation to regulate vascular resistance and balance myocardial oxygen supply and demand (9). All the components of MetS (hypertension, dysglycemia, dyslipidemia, and obesity) can individually impair microvascular function (10, 28, 31). Exact mechanisms underlying impaired pharmacologic coronary vasodilation in MetS have not been clearly defined, but are likely related to altered functional expression of receptors and ion channels, endothelial and vascular smooth muscle function, paracrine and neuroendocrine influences, structural remodeling of coronary arterioles and/or microvascular rarefaction (9). Coronary vasomotor dysfunction in the MetS is related to chronic activation of the renin-angiotensin and sympathetic nervous system that leads to augmented angiotensin II type 1 and alpha 1-adrenoceptor mediated coronary vasoconstriction (5, 32).

Aortic stiffness describes the elastic resistance that the aorta sets against its distension (11). Many methodologies, both invasive and non-invasive, have been applied to the assessment of arterial elasticity (33). To evaluate aortic stiffness, two important variables should be noted: the change in volume due to blood injection in the aorta, and the pressure change caused by this volume change (11). Noninvasive measures fall into three board groups: 1) measuring pulse wave velocity (PWV), 2) relating change in diameter (or area) of an artery to distending pressure, and 3) assessing arterial pressure waveforms (11, 34). PWV, which is defined as the velocity of the arterial pulse for moving along the vessel wall, plays an important clinical role in defining patients under high cardiovascular risk and it is inversely correlated with arterial elasticity and relative arterial compliance (35). Measurement of aortic stiffness by applanation tonometry with pulse-wave velocity has been the gold-standard method and is well validated in large populations as a strong predictor of adverse cardiovascular outcomes (34). Additionally, pulse wave velocity can also be assessed noninvasively by echocardiography with pulse wave Doppler. Although this method has not been as commonly used, it seems to have good correlation (r=0.83) with the applanation tonometry (36). The main advantage of ultrasound techniques is their wide availability, and the main limitation is the incomplete visualization of the aortic arch (34). To non-invasively quantify aortic stiffness measurement of systolic blood pressure, diastolic blood pressure and changes in aortic diameters are necessary. Aortic diameters can be measured noninvasively with echocardiography, computed tomography, and magnetic resonance imaging. Stefanadis et al. (13) demonstrated that the noninvasively evaluated aortic stiffness is comparable with invasive methods with a high degree of accuracy. There is growing evidence that large artery stiffness is a significant predictor of adverse cardiovas-

cular outcome (12). MetS causes an increase in arterial stiffness independently of other cardiovascular risk factors (14). Several components of the MetS, including high blood pressure, hyperglycemia, and abdominal fat, have been related to increased aortic stiffness (12, 15).

Relations between microvascular function and aortic stiffness have been reported (37, 38). In the Framingham Heart Study offspring cohort increased aortic stiffness was associated with higher forearm vascular resistance at baseline and during reactive hyperemia, and with blunted flow reserve during hyperemia (39). Aortic stiffening may cause an increase in aortic pulse pressure, left ventricular load, and ultimately, left ventricular hypertrophy (LVH). This LVH, together with the decreased diastolic transmural pressure gradient caused by the decrease in diastolic blood pressure, interacts with coronary flow and flow reserve (17, 40). Besides the aortocoronary hemodynamic relationship, aortic stiffness may be a marker of a more generalized vascular disease or coexists with microvascular disease (13). Another interpretation is that abnormalities in the microcirculation and, therefore, in peripheral vascular resistance, lead to the perturbations in aortic stiffness (41). The hypothesis that coronary flow may be influenced by aortic elastic properties was introduced by Bouvain et al. (42), and was confirmed by experimental studies (37, 38). In previous studies, significant correlations between CFR and aortic stiffness assessed by pulse wave velocity have been demonstrated in patients with hypertension and coronary artery disease (43, 44). Aortic stiffness has been described to reduce the improvement in hyperemic coronary blood flow after a successful percutaneous coronary intervention (45). Nemes et al. (46) described reduced CFR and increased indices of aortic stiffness [E(p) and E(s)] in patients with LAD coronary artery disease as compared with patients with normal epicardial coronary arteries. In addition to these findings in patients with coronary artery disease, Nemes et al. demonstrated significant correlations between CFR and aortic stiffness in patients without coronary artery disease, but with hypertension, aortic valve stenosis, type-2 diabetes and hypercholesterolemia (16-19). However, presence of an association between aortic stiffness and impaired CFR in MetS has never been evaluated.

Each of components of the MetS has been independently associated with vascular dysfunction (6, 47). In hypertension, the structure and function of the microcirculation are altered (48). As the vasoconstriction takes place with the decreases in vasodilatation, wall to lumen ratio of precapillary arterioles increases (41). The obese patients have similar alterations in microcirculation (49). Insulin resistance is also associated with impaired capillary recruitment and microvascular vasodilation (41). In addition, obesity is associated with insulin resistance and insulin resistance leads to endothelial dysfunction (31). Endothelial and microvascular dysfunction are present in obese subjects even in the absence of hypertension or hyperglycemia, and it is better correlated to waist/hip ratio than BMI (50). Additionally, endothelial dysfunction may lead to functional stiffening of large arteries as the reduced availability of nitric oxide and increased activity of

vasoconstrictors (51). Endothelial dysfunction may lead to smooth muscle cell proliferation and increased synthesis of structural proteins such as collagen. The insulin resistance of obesity is known to be associated with arterial stiffness (52). Our study revealed an independent relationship of decreased coronary flow reserve with increased aortic stiffness, waist circumference or systolic blood pressure.

Study limitations

Our study has several limitations. The most significant of all is the small number of patients in both groups. Another major concern is the measurement method of aortic stiffness, which was not performed with pulsed wave velocity analysis. Owing to the lack of clinical indications and the invasive nature of the procedure, we did not perform coronary angiography in all patients. Also we did not assess invasively CFR. However, transthoracic Doppler echocardiography with pharmacological stress for the assessment of CFR has been demonstrated to be a useful and highly reproducible tool to evaluate CFR (30). The cross-sectional design of this study, causation cannot be established. Although our data suggest that these echocardiographic properties are related to overall effect of MetS on the aorta and coronary arteries, confirmatory longitudinal work is necessary.

Conclusion

The cluster of metabolic and hemodynamic abnormalities present in metabolic syndrome is associated with impaired coronary flow reserve. Waist circumference, systolic blood pressure or aortic stiffness has an independent association with coronary microvascular dysfunction. These results can suggest the overall effect of MetS on the function and structure of the aorta and coronary arteries. Using a noninvasive and readily available tool, transthoracic Doppler echocardiography, aortic stiffness and coronary flow reserve can easily be simultaneously evaluated. However, future research is warranted to provide more robust information on direct evaluation of aortic stiffness and CFR in patients with MetS.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - D.T., N.B.; Design - D.T., K.Ç.; Supervision - K.Ç., O.T.; Resource - D.T., S.A.; Materials - Z.G., N.B.; Data collection&/or Processing - O.T., D.T., İ.K.; Analysis &/or interpretation - F.Ö., İ.K.; Literature search - D.T., Z.G.; Writing -D.T.; Critical review - S.A., F.Ö.

References

1. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433-8. [CrossRef]

2. Mottillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, et al. The metabolic syndrome and cardiovascular risk a systematic review and meta-analysis. *J Am Coll Cardiol* 2010; 56: 1113-32. [\[CrossRef\]](#)
3. Malik S, Wong ND, Franklin SS, Kamath TV, L'Italien GJ, Pio JR, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation* 2004; 110: 1245-50. [\[CrossRef\]](#)
4. Setty S, Sun W, Tune JD. Coronary blood flow regulation in the prediabetic metabolic syndrome. *Basic Res Cardiol* 2003; 98: 416-23. [\[CrossRef\]](#)
5. Zhang C, Knudson JD, Setty S, Araiza A, Dincer UD, Kuo L, et al. Coronary arteriolar vasoconstriction to angiotensin II is augmented in prediabetic metabolic syndrome via activation of AT1 receptors. *Am J Physiol Heart Circ Physiol* 2005; 288: 2154-62. [\[CrossRef\]](#)
6. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, et al. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. *J Am Coll Cardiol* 2006; 47: 1188-95. [\[CrossRef\]](#)
7. Pirat B, Bozbaş H, Şimşek V, Yıldırım A, Sade LE, Gürsoy Y, et al. Impaired coronary flow reserve in patients with metabolic syndrome. *Atherosclerosis* 2008; 201: 112-6. [\[CrossRef\]](#)
8. Teragawa H, Morita K, Shishido H, Otsuka N, Hirokawa Y, Chayama K, et al. Impaired myocardial blood flow reserve in subjects with metabolic syndrome analyzed using positron emission tomography and N-13 labeled ammonia. *Eur J Nucl Med Mol Imaging* 2010; 37: 368-76. [\[CrossRef\]](#)
9. Berwick ZC, Dick GM, Tune JD. Heart of the matter: coronary dysfunction in metabolic syndrome. *J Mol Cell Cardiol* 2012; 52: 848-56. [\[CrossRef\]](#)
10. Knudson JD, Dincer D, Bratz IA, Sturek M, Dick GM, Tune JD. Mechanism of coronary dysfunction in obesity and insulin resistance. *Microcirculation* 2007; 14: 317-38. [\[CrossRef\]](#)
11. Nemes A, Geleijnse ML, Forster T, Soliman OI, Ten Cate FJ, Csanády M, et al. Echocardiographic evaluation and clinical implications of aortic stiffness and coronary flow reserve and their relationship. *Clin Cardiol* 2008; 31: 304-9. [\[CrossRef\]](#)
12. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, et al. Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 2001; 37: 1236-41. [\[CrossRef\]](#)
13. Stefanadis C, Stratos C, Boudoulas H, Kourouklis C, Toutouzas P. Distensibility of the ascending aorta: comparison of invasive and non-invasive techniques in healthy men and in men with coronary artery disease. *Eur Heart J* 1990; 11: 990-6.
14. Sipilä K, Koivisto T, Moilanen L, Nieminen T, Reunanen A, Jula A, et al. Metabolic syndrome and arterial stiffness: the Health 2000 Survey. *Metabolism* 2007; 56: 320-6. [\[CrossRef\]](#)
15. Sutton Tyrrell K, Newman A, Simonsick EM, Havlik R, Pahor M, Lakatta E, et al. Aortic stiffness is associated with visceral adiposity in older adults enrolled in the study of health, aging and body composition. *Hypertension* 2001; 38: 429-33. [\[CrossRef\]](#)
16. Nemes A, Forster T, Csanady M. Decreased aortic distensibility and coronary flow velocity reserve in patients with significant aortic valve stenosis with normal epicardial coronary arteries. *J Heart Valve Dis* 2004; 13: 567-73.
17. Nemes A, Forster T, Csanady M. Simultaneous echocardiographic evaluation of coronary flow velocity reserve and aortic distensibility indices in hypertension. *Heart Vessels* 2007; 22: 73-8. [\[CrossRef\]](#)
18. Nemes A, Forster T, Lengyel C, Csanady M. Reduced aortic distensibility and coronary flow velocity reserve in diabetes mellitus patients with negative coronary angiogram. *Can J Cardiol* 2007; 23: 445-50. [\[CrossRef\]](#)
19. Nemes A, Forster T, Csanady M. Impaired coronary flow velocity reserve and aortic distensibility in patients with untreated hypercholesterolemia-an echocardiographic study. *Int J Cardiovasc Imaging* 2007; 23: 15-23. [\[CrossRef\]](#)
20. Grundy SM, Cleeman JJ, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005; 112: 2735-52. [\[CrossRef\]](#)
21. Lenfant C, Chobanian AV, Jones DW, Roccella EJ; Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7):resetting the hypertension sails. *Hypertension* 2003; 41: 1178-9. [\[CrossRef\]](#)
22. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997; 20: 1183-97.
23. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, et al. ACC/AHA guidelines for the Clinical Application Of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation* 1997; 95: 1686-744. [\[CrossRef\]](#)
24. Devereux RB, Reichek N. Echocardiographic determination of the left ventricular mass in man. Anatomic validation of the method. *Circulation* 1977; 55: 613-8. [\[CrossRef\]](#)
25. Korcarz CE, Stein JH. Noninvasive assessment of coronary flow reserve by echocardiography: technical considerations. *J Am Soc Echocardiogr* 2004; 17: 704-7. [\[CrossRef\]](#)
26. Stefanadis C, Stratos C, Vlachopoulos C, Marakas S, Boudoulas H, Kalikazaros I, et al. Pressure-diameter relation of the human aorta. A new method of determination by the application of a special ultrasonic dimension catheter. *Circulation* 1995; 92: 2210-9. [\[CrossRef\]](#)
27. Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008; 28: 629-36. [\[CrossRef\]](#)
28. Tziomalos K, Athyros VG, Karagiannis A, Mikhailidis DP. Endothelial dysfunction in metabolic syndrome: prevalence, pathogenesis and management. *Nutr Metab Cardiovasc Dis* 2010; 20: 140-6. [\[CrossRef\]](#)
29. Turhan H, Erbay AR, Yaşar AS, Biçer A, Şaşmaz H, Yetkin E. Impaired coronary blood flow in patients with metabolic syndrome: documented by Thrombolysis in Myocardial Infarction (TIMI) frame count method. *Am Heart J* 2004; 148: 789-94. [\[CrossRef\]](#)
30. Hozumi T, Yoshida K, Akasaka T, Asami Y, Ogata Y, Takagi T, et al. Noninvasive assessment of coronary flow velocity and coronary flow velocity reserve in the left anterior descending coronary artery by Doppler echocardiography: comparison with invasive technique. *J Am Coll Cardiol* 1998; 32: 1251-9. [\[CrossRef\]](#)
31. Eroğlu S, Sade LE, Bozbaş H, Müderrisoğlu H. Decreased coronary flow reserve in obese women. *Türk Kardiyol Dern Ars* 2009; 37: 391-6.
32. Dinçer UD, Araiza AG, Knudson JD, Molina PE, Tune JD. Sensitization of coronary alpha-adrenoceptor vasoconstriction in the prediabetic metabolic syndrome. *Microcirculation* 2006; 13: 587-95. [\[CrossRef\]](#)
33. Stehouwer CD, Henry RM, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. *Diabetologia* 2008; 51: 527-39. [\[CrossRef\]](#)

34. Cavalcante JL, Lima JA, Redheuil A, Al-Mallh MH. Aortic stiffness: current understanding and future directions. *J Am Coll Cardiol* 2011; 57: 1511-22. [\[CrossRef\]](#)
35. Yıldız M, Aykan AC, Hasdemir H. Assessment of arterial stiffness with pulse wave velocity or augmentation index: Which method is the best? *Scientific Letter. Türkiye Klinikleri J Med Sci* 2012; 32: 214-7. [\[CrossRef\]](#)
36. Jiang B, Liu B, McNeill KL, Chowienczyk PJ. Measurement of pulse wave velocity using pulse wave Doppler ultrasound: comparison with arterial tonometry. *Ultrasound Med Biol* 2008; 34: 509-12. [\[CrossRef\]](#)
37. Ohtsuka S, Kakiyama M, Watanabe H, Sugishita Y. Chronically decreased aortic distensibility causes deterioration of coronary perfusion during increased left ventricular contraction. *J Am Coll Cardiol* 1994; 24: 1406-14. [\[CrossRef\]](#)
38. Watanabe H, Ohtsuka S, Kakiyama M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. *J Am Coll Cardiol* 1993; 21: 1497-506. [\[CrossRef\]](#)
39. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 2005; 112: 3722-8. [\[CrossRef\]](#)
40. Eren M, Görgülü S, Uslu N, Çelik S, Dağdeviren B, Tezel T. Relation between aortic stiffness and left ventricular diastolic function in patients with hypertension, diabetes, or both. *Heart* 2004; 90: 37-43. [\[CrossRef\]](#)
41. Serne EH, de Jongh RT, Eringa EC, IJzerman RG, Stehouwer CD. Microvascular dysfunction: a potential pathophysiological role in the metabolic syndrome. *Hypertension* 2007; 50: 204-11. [\[CrossRef\]](#)
42. Bouvraïn Y, Levy B. 'Windkessel' and coronary debit. *Arch Mal Coeur Vaiss* 1981; 74: 635-9.
43. Wang GH, Hu DY. Effect of pulse wave velocity on coronary flow reserve in patients with essential hypertension. *Zhonghua Yi Xue Za Zhi* 2005; 85: 54-7.
44. Fukuda D, Yoshiyama M, Shimada K, Yamashita H, Ehara S, Nakamura Y, et al. Relation between aortic stiffness and coronary flow reserve in patients with coronary artery disease. *Heart* 2006; 92: 759-62. [\[CrossRef\]](#)
45. Leung MC, Meredith IT, Cameron JD. Aortic stiffness affects the coronary blood flow response to percutaneous coronary intervention. *Am J Physiol Heart Circ Physiol* 2006; 290: H624-H30. [\[CrossRef\]](#)
46. Nemes A, Forster T, Gruber N, Csanady M. Coronary flow velocity reserve and indices describing aortic distensibility in patients after coronary angiography. *Int J Cardiol* 2004; 96: 29-33. [\[CrossRef\]](#)
47. Di Carli MF, Charytan D, McMahon GT, Ganz P, Dorbala S, Schelbert HR. Coronary circulatory function in patients with the metabolic syndrome. *J Nucl Med* 2011; 52: 1369-77. [\[CrossRef\]](#)
48. Levy BI, Ambrosio G, Pries AR, Struijker-Boudier HA. Microcirculation in hypertension: a new target for treatment? *Circulation* 2001; 104: 735-40. [\[CrossRef\]](#)
49. de Jongh RT, Serne EH, IJzerman RG, de Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. *Circulation* 2004; 109: 2529-35. [\[CrossRef\]](#)
50. Weirnsperger N, Nivoit P, De Aguiar LG, Bouskela E. Microcirculation and the metabolic syndrome. *Microcirculation* 2007; 14: 403-38. [\[CrossRef\]](#)
51. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP, et al. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries in vivo. *Hypertension* 2001; 38: 1049-53. [\[CrossRef\]](#)
52. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR. Non-insulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes. The ARIC Study. Atherosclerosis Risk in Communities Study. *Circulation* 1995; 91: 1432-43. [\[CrossRef\]](#)

Relations between microvascular function and aortic stiffness in metabolic syndrome

Metabolik sendromda mikrovasküler fonksiyon ve aort sertliği arasındaki ilişki

The metabolic syndrome (MetS) is characterized by abdominal obesity, elevated blood pressure, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterolemia, and hyperglycemia (1). Vascular dysfunction caused by endothelial dysfunction is an early abnormality in the MetS that may contribute to premature atherosclerosis (2). Each of the components of the MetS has been independently associated with vascular dysfunction (3-5). Because there was the 2.6-fold increased risk of coronary death among those with the MetS (6), other mechanisms may contribute to the potential adverse effect of features of the MetS on vascular function and, in particular, endothelial function, thereby increasing the potential for atherothrombotic complications (7). Several studies demonstrated the relationship between MS and coronary microvascular circulation. MetS patients showed impaired response of myocardial blood flow to a cold press or test in by PET analysis (8), indicating the presence of coronary microvascular endothelial dysfunction. Similarly, MetS patients showed an impaired coronary blood flow in with angiographically normal coronary arteries by Thrombolysis in Myocardial Infarction frame count method (9). Moreover, patients with MetS showed an impaired vasodilatory response to pharmacologic agents in the left ascending of coronary artery by transthoracic echocardiography (10). Possible mechanisms for impaired coronary vasodilation in patients with MetS are insulin resistance which may induce endothelial dysfunction mediated by oxidative stress (11), reduced adiponectin which have a role in the phosphorylation of eNOS (12), release of pro-inflammatory cytokines (e.g., interleukin-6, tumor necrosis factor- α) by visceral adipose tissue (13). These mechanisms may solely and/or multifactorially contribute to coronary endothelial dysfunction in MetS patients (14).

The present study revealed that coronary flow reserve (CFR) is impaired in patients with MetS and there is an independent relationship between impaired CFR and increased aortic stiffness evaluated by echocardiography. This study demonstrates that CFR was significantly correlated with age, blood pressure, waist circumference, lipid profile, fasting glucose, high-sensitivity C-reactive protein, left ventricular (LV) mass index, and aor-

tic stiffness. The relationship between CFR and aortic stiffness persisted after adjusting for age and each components of MetS.

In this study, the evaluation of aortic stiffness was performed via relating change in diameter of aorta to distending pressure, not assessed by pulse wave velocity (PWV) (15). In previous studies, significant correlations between CFR and aortic stiffness assessed by PWV have been demonstrated in patients with hypertension and coronary artery disease. PWV is the gold standard of aortic stiffness and easily performed in clinical practice. To prove the efficacy of newly non-invasive method to detect the aortic stiffness, the description of the method is needed, but the authors did not describe the methodological review of aortic stiffness. Moreover, the hypothesis that coronary flow may be influenced by aortic elastic properties was not confirmed by simply demonstrating the relationship between CFR and aortic stiffness. Because increased left ventricular (LV) end diastolic pressure associated with LV hypertrophy and endothelial dysfunction may interacts with aortic stiffness and CFR in MetS, further evaluations such as LV filling pressure and brachial flow-mediated dilatation, which was associated with aortic stiffness in the Framingham Heart Study offspring cohort (16) are needed.

However, the finding of impaired coronary microvascular dysfunction is more prominent in MS patients may provide important information clarifying the pathogenesis of MetS-induced cardiovascular events. Moreover, further evidence is needed for the early presence of impaired endothelium-independent and endothelium-dependent coronary vasodilator function in patients with MetS and if these abnormalities in coronary vasodilator function are worsened by the combined presence of already-established cardiovascular risk factors (i.e., dyslipidemia, smoking, and CAD).

Tae Joon Cha, Kyoung Im Cho

**Division of Cardiology, Department of Internal Medicine,
Kosin University School of Medicine, Busan-South Korea**

Conflict of interest: None declared.

Address for Correspondence/Yazışma Adresi: Dr. Tae Joon Cha, Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Kosin University, 34 Amnam-Dong Seo-Ku, Busan 602-702-South Korea E-mail: chatjn@hanafos.com

Accepted Date/Kabul Tarihi: 11.01.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.069



References

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; 106: 3143-421.
2. Watarai T, Yamasaki Y, Ikeda M, Kubota M, Kodama M, Tsujino T, et al. Insulin resistance contributes to carotid arterial wall thickness in patients with non-insulin-dependent-diabetes mellitus. *Endocr J* 1999; 46: 629-38. [\[CrossRef\]](#)
3. Pitkänen OP, Nuutila P, Raitakari OT, Porkka K, Iida H, Nuotio I, et al. Coronary flow reserve in young men with familial combined hyperlipidemia. *Circulation* 1999; 99: 1678-84. [\[CrossRef\]](#)
4. Di Carli MF, Janisse J, Grunberger G, Ager J. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol* 2003; 41: 1387-93. [\[CrossRef\]](#)
5. Schindler TH, Cardenas J, Prior JO, Facta AD, Kreissl MC, Zhang XL, et al. Relationship between increasing body weight, insulin resistance, inflammation, adipocytokine leptin, and coronary circulatory function. *J Am Coll Cardiol* 2006; 47: 1188-95. [\[CrossRef\]](#)
6. Rewers M, Zaccaro D, D'Agostino R, Haffner S, Saad MF, Selby JV, et al. Insulin sensitivity, insulinemia, and coronary artery disease: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2004; 27: 781-7. [\[CrossRef\]](#)
7. Forgione MA, Leopold JA, Loscalzo J. Roles of endothelial dysfunction in coronary artery disease. *Curr Opin Cardiol* 2000; 15: 409-15. [\[CrossRef\]](#)
8. Quiñones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenez X, Hernandez G, et al. Coronary vasomotor abnormalities in insulin-resistant individuals. *Ann Intern Med* 2004; 140: 700-8.
9. Turhan H, Erbay AR, Yaşar AS, Biçer A, Şaşmaz H, Yetkin E. Impaired coronary blood flow in patients with metabolic syndrome: documented by Thrombolysis in Myocardial Infarction (TIMI) frame count method. *Am Heart J* 2004; 148: 789-94. [\[CrossRef\]](#)
10. Pirat B, Bozbaş H, Şimşek V, Yıldırım A, Sade LE, Gürsoy Y, et al. Impaired coronary flow reserve in patients with metabolic syndrome. *Atherosclerosis* 2008; 201: 112-6. [\[CrossRef\]](#)
11. Perticone F, Ceravolo R, Candigliota M, Ventura G, Iacopino S, Sinopoli F, et al. Obesity and body fat distribution induce endothelial dysfunction by oxidative stress: protective effect of vitamin C. *Diabetes* 2001; 50: 159-65. [\[CrossRef\]](#)
12. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003; 278: 45021-6. [\[CrossRef\]](#)
13. Malavazos AE, Ermetici F, Coman C, Corsi MM, Morricone L, Ambrosi B. Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. *Int J Cardiol* 2007; 121: 132-4. [\[CrossRef\]](#)
14. Teragawa H, Mitsuba N, Nishioka K, Ueda K, Kono S, Higashi Y, et al. Impaired coronary microvascular endothelial function in men with metabolic syndrome. *World J Cardiol* 2010; 7: 205-10. [\[CrossRef\]](#)
15. Tok D, Özcan F, Kadife İ, Turak O, Çağlı K, Başar N, et al. Impaired coronary flow reserve evaluated by using echocardiography is associated with increased aortic stiffness in patients with metabolic syndrome: an observational study. *Anadolu Kardiyol Derg* 2013; 13: 227-34.
16. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, et al. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. *Circulation* 2005; 112: 3722-8. [\[CrossRef\]](#)

Relationship between hospital volume and risk-adjusted mortality rate following percutaneous coronary intervention in Korea, 2003 to 2004

2003 ve 2004 yılları arasında Kore'de perkütan koroner girişim sonrası hastane hacmi ve risk-ayarlı mortalite arasındaki ilişki

Yong Hoon Kim, Ae-Young Her

Division of Cardiology, Department of Internal medicine, Kangwon National University School of Medicine, Chuncheon City-South Korea

ABSTRACT

Objective: There have been a large number of studies that have investigated the relationship between outcomes and provider volume for a wide variety of medical conditions and surgical conditions. The objective of this study was to explore the relation between hospital volume and risk-adjusted mortality following percutaneous coronary intervention between 2003 and 2004 in Korea.

Methods: This is a retrospective analysis of database in National Health Insurance Review & Assessment Service and Korean National Statistical Office. The study data set confined to the ICD-10 diagnosis and procedure codes that were recorded in the National Health Insurance Review Agency. Risk modeling was performed through logistic regression and validated with cross-validation. The statistical performance of the developed model was evaluated using c-statistics, R^2 , and Hosmer-Lemeshow statistic. Crude and risk-adjusted 30-day mortality was evaluated among patients who underwent Percutaneous Coronary Intervention (PCI) between 2003 and 2004 at low (less 200 cases/year), medium (200~399 cases/year), and high (400 cases or more/year) PCI volume hospitals.

Results: The final risk-adjustment model consisted of ten risk factors for 30-day mortality. These factors were found to have statistically significant effects on patient mortality. The c-statistic and Hosmer-Lemeshow χ^2 goodness-of-fit test and the model's performance were good [$R^2=0.147$, c-statistic 0.823, 4.1037 ($p=0.8476$)]. A total number of 60 low-volume hospitals (9.071 patients) and 27 medium-volume hospitals (15.623 patients) and 15 high-volume hospitals (19.669 patients) were included. Crude 30-day mortality rate was 1.4%, 1.1%, and 1.0% ($p=0.0106$) in each volume hospitals. But risk-adjusted mortality rate was not significantly different among three groups (1.3%, 1.0%, and 1.1% in each volume hospitals).

Conclusion: Although we found a significant different crude 30-day mortality rates according to hospital PCI volume, but did not find a relationship between hospital volume and 30-day risk-adjusted mortality rates following PCI in Korea. (*Anadolu Kardiyol Derg 2013; 13: 237-42*)

Key words: Percutaneous coronary intervention, volume, outcome, risk-adjustment, mortality, regression analysis

ÖZET

Amaç: Çok değişik tıbbi ve cerrahi durumlar için, hizmet sağlayanın volümü ile sonuçlar arasındaki ilişkiyi araştıran pek çok çalışma vardır. Bu çalışmanın amacı, 2003 ve 2004 yılları arasında Kore'de perkütan koroner girişim sonrası hastane hacmi ve risk-ayarlı mortalite arasındaki ilişkiyi ortaya çıkarmaktır.

Yöntemler: Bu çalışma Ulusal Sağlık Sigorta İnceleme ve Değerlendirme Servisi ve Kore Ulusal İstatistik Ofisi veritabanının retrospektif bir analizidir. Çalışmanın verileri Ulusal Sağlık Sigorta İnceleme Ajansı'nda kaydedilmiş ICD-10 tanı ve işlem kodlarını kapsar. Risk modelleme lojistik regresyon yoluyla yapıldı ve çapraz-doğrulama ile doğrulandı. Geliştirilen modelin istatistiksel performansı c-istatistikleri, R^2 , ve Hosmer-Lemeshow istatistiği kullanılarak değerlendirildi. Basit ve riske ayarlı 30 günlük mortalite, Perkütan Koroner Müdahale (PKM) yapılan hastalar

Address for Correspondence/Yazışma Adresi: Ae-Young Her, M.D. Ph.D., Division of Cardiology, Department of Internal Medicine, Kangwon National University School of Medicine 200-947, 17-1, Hyoja 3-dong, Chuncheon City, Kangwon Province-South Korea
Phone: 82-33-258-9167, 82-10-6375-3863 Fax: 82-33-258-2455 E-mail: hermartha@hanmail.net

Accepted Date/Kabul Tarihi: 31.10.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.070



2003 ve 2004 yılları arasında, düşük (200'den az olgu/yıl), orta (200~399 olgu / yıl) ve yüksek (400 olgularda veya fazla/yıl) PKM hacimli hastanelerde değerlendirildi.

Bulgular: Son risk düzeltme modeli 30-günlük mortalite için on risk faktöründen oluşuyordu. Bu faktörlerin, hasta mortalitesi üzerine anlamlı etkilerinin olduğu saptandı. C-istatistik ve Hosmer-Lemeshow χ^2 "goodness-of-fit" testi ve modelin performansı iyiydi [$R^2=0.147$, c-statistic 0.823, 4.1037 ($p=0.8476$)]. Altmış düşük-hacimli hastanenin (9.071 hasta) ve 27 orta-hacimli hastanenin (15.623 hasta) ve 15 yüksek-hacimli hastanenin (19.669 hasta) toplam sayısı dahil edildi. Basit 30-günlük mortalite oranı her bir hastane volümü için sıra ile %1.4, %1.1 ve her birimin hastanelerde oranı %1.0 ($p=0.0106$) idi. Buna karşılık, risk ayarlı ölüm oranı üç grup arasında anlamlı değildi (%1.3, %1.0, ve %1.1; her bir hasta-ne volümü için).

Sonuç: Kore'de hastane PCI hacmine göre, basit 30-günlük mortalite oranlarında önemli farklılık bulmamıza rağmen PKG sonrası 30 günlük risk-ayarlı ölüm oranları ile hastane hacmi arasında bir ilişki bulamadık. (*Anadolu Kardiyol Derg 2013; 13: 237-42*)

Anahtar kelimeler: Perkütan koroner girişim, hacim, sonuç, risk-ayarlı, ölüm, regresyon analizi

Introduction

In general, it is believed that technically challenging manual procedures will result in a better outcome if it is performed by skilled specialists at high-volume institutions. Previous studies also have demonstrated above suggestions in many surgical procedures, such as coronary artery bypass graft, pancreatic and thoracic surgery (1-3). In cardiology, the relationship between hospital percutaneous coronary intervention (PCI) volume and in-hospital mortality has been widely investigated (4, 5). There is some evidence that the disparity in outcomes of PCI between high-and low-volume hospitals has narrowed over time (6). But a recent meta-analysis reported this relationship has not attenuated over time (7). Most of the studies related with hospital volume and outcome originated from USA hospitals. The number of studies from outside the USA was too small to explore the similarity of the effect across countries. Only a couple of studies originated from Japan (8-10). In addition, it is unclear whether previous results can be generalized to other countries outside the USA. So we tried to evaluate the relationship between hospital volume and risk-adjusted mortality rate following PCI in Korea.

Methods

Database

We analyzed data from the Korea National Health Insurance Review & Assessment Service and Korean National Statistical Office between 2003 and 2004 for this study. We used American Agency for Healthcare Research and Quality (AHRQ) for guidance of our study (11). So we defined general patient information and all the International Statistical Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure codes. In the present study, PCI patients were defined as the ones who were diagnosed with such codes as M6551, M6552, M6561, M6562, M6563, M6564, M6571, and M6572. We excluded patients under the age of 18 and neonatal or obstetric admissions in order to restrict our evaluation to the use of PCI in a typical adult population. We consulted with five expert interventional cardiologists working in university hospitals to reduce selection bias of risk factors.

Hospital PCI volume groups

To assess the validity of the annual hospital PCI volume threshold of 400 cases recommended by ACC/AHA PCI guidelines (12) and by the Leapfrog Group (13) we divided above data into three groups. Hospitals with fewer than 400 annual cases were divided into those below 200 cases (hereafter referred to as low-volume) and 200 to 399 cases (medium-volume). Hospitals with above 400 annual cases were classified as high-volume hospitals.

Definition of death

Major cardiac adverse events frequently occurred within one month of PCI so we investigated 30 day mortality rates (14) and we compared the deceased patient's biological information with data from the Korean National Statistical Office. We included only patients expired in hospital and excluded expired out of hospital or unidentified death in our analysis.

Variables for analysis

Patient characteristics such as admission source (referral, emergency medical services or others), admission type (outpatient or emergency room) and presence of diabetes mellitus, hypertension, hyperlipidemia, congestive heart failure (CHF), cardiogenic shock, arrhythmia, chronic obstructive lung disease (COPD), renal disease, peripheral vascular disease, stroke, multivessel procedure, stent deployment and the type of coronary artery disease (stable angina, unstable angina, myocardial infarction) were analyzed.

Statistical analysis

The SAS 9.1 statistical software (SAS Institute Inc., Cary, NC, USA) was used to perform the statistical analysis of the data. Patients biological, admission and comorbidity information were compared across the three hospital PCI volume groups using global chi-square analyses for categorical variables and risk-adjustment model. We performed univariate logistic regression analysis to evaluate risk factors that influence 30-day mortality. Those variables that were significant predictors on univariate analysis were entered into the multivariate logistic regression model. We calculated adjusted mortality rate and compared relationship between severity determining risk factors and hos-

pital volume. The statistical performance of the developed model was evaluated using C-statistics, R^2 , and Hosmer-Lemeshow statistic.

$$\text{Adjusted Mortality Rate} = \frac{\text{Actual Number of Deaths}}{\text{Predicted Number of Deaths}} \times \text{Overall Mortality Rate}$$

Odds ratios with 95% confidence intervals were calculated for each covariate. Statistical significance was defined as p values <0.05.

Results

Our analysis involved 44.363 patients. The mean age of the patient population was 63.8 years. 64.9 % were men and 35.1% were women. Clinical characteristics and variables included in our study are presented in Table 1. There were 102 hospitals performing PCI during the study period. A total of 60, 27 and 15 hospitals were in low, medium and high-volume hospital groups. 9.071 (20.5%) patients were treated at high-volume hospitals, 15.623 (35.2%) at medium-volume hospital and 19.669 (44.3%) at low-volume hospital. Mean age, admission type, diabetes, hypertension, hyperlipidemia, unstable angina, acute myocardial infarction (AMI), congestive heart failure (CHF), arrhythmia, chronic obstructive lung disease (COPD), renal disease, peripheral vascular disease, stroke, multivessel procedure and stent deployment to be significant predictors for 30-day mortality (Table 2). These significant risk factors entered into the multivariate logistic regression analysis. The logistic-regression model revealed age, emergency visitors, AMI, CHF, arrhythmia, COPD, renal disease, stroke, multivessel procedure and stent deployment to be significant predictors (Table 3). Hosmer-Lemeshow χ^2 goodness-of-fit test showed a p value of 0.8476 and good-model quality. The Cochran-Armitage trend test ($p=0.0106$) showed crude 30-day mortality rates declined with increasing volume and rates were 1.4% in low, 1.1% in medium and 1.0% in high volume hospitals, $p<0.05$. When we considered crude 30-day mortality rates patients treated at low-volume hospitals had significantly higher mortality rates than those treated in medium-volume (1.4% vs. 1.1%, $p<0.05$) or high-volume hospitals (1.4% vs. 1.0%, $p<0.05$). But we could not find any relationship between hospital volume and 30-day risk-adjusted mortality rates (1.3% in low, 1.0% in medium and 1.1% in high volume hospitals) following PCI in Korea (Table 4).

Discussion

The use of administrative data to identify inpatient complications is technically feasible and inexpensive but unproven as a quality measure. Weingart et al. (15) suggested that screening administrative data may offer an efficient approach for identifying potentially problematic cases for physician review.

Table 1. Patient's characteristics

Variables	No. of patients	%
Sex		
Male	28.787	64.9
Female	15.576	35.1
Age, years*	63.8±10.2	
40~50	4.521	10.2
51~60	9.947	22.4
61~70	16.240	36.6
≥70	13.655	30.8
Admission source		
Referral	3.736	8.4
Emergency medical services	1.268	2.9
Others	39.336	88.7
Admission type		
Emergency room	17.617	39.7
Outpatient	26.723	60.3
Diabetes mellitus	7.116	16.8
Hypertension	20.952	47.2
Hyperlipidemia	4.542	10.2
Coronary artery disease		
Stable	2.035	4.6
Unstable	18.970	42.8
AMI	20.468	46.1
CHF	3.187	7.2
Cardiogenic shock	367	0.8
Arrhythmia	1.898	4.3
COPD	729	1.6
Renal disease	1.166	2.6
Peripheral vascular disease	1.519	3.4
Stroke	2.583	5.8
Multivessel procedure	210	0.5
Stent employed	27.008	60.9
Total	44.363	-
Data are presented as mean±SD, number and percentage AMI – acute myocardial infarction, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease		

Sundararajan et al. (16) said ICD-10 Charlson comorbidity coding algorithm had a good to excellent discrimination in their ability to predict mortality. So we used ICD-10 diagnosis and procedure codes. During the past 20 years researchers have focused on measuring and explaining the association between patient outcomes and the volume of health services provided by hospitals and physicians (17). Mant studies have documented that higher volume is associated with better outcomes. They suggested this results may be because physicians develop more

Table 2. Comparison of risk factors in 30-day mortality

Risk Factors		Live, n (%)	Death, n (%)	*p
No. of patients		43.872 (98.9)	491 (1.1)	-
Sex	Male	28.502 (99.1)	285 (0.9)	0.0014
	Female	15.370 (98.7)	206 (1.3)	
Mean age±SD		63.7±10.1	71.1±9.9	<.0001†
Admission source	Referral	3.708 (99.2)	28 (0.8)	0.0724
	EMS	1.251 (98.7)	17 (1.3)	
	Others	38.913 (98.8)	446 (1.2)	
Admission type	Emergency	17.313 (98.3)	304 (1.7)	<.0001
	Outpatient	26.559 (99.3)	187 (0.7)	
Diabetes	Yes	7.045 (94.3)	420 (5.6)	<.0001
	No	36.827 (99.8)	71 (0.2)	
Hypertension	Yes	20.778 (99.2)	174 (0.8)	<.0001
	No	23.094 (98.7)	317 (1.3)	
Hyperlipidemia	Yes	4.059 (89.4)	483 (10.6)	<.0001
	No	39.813 (99.9)	8 (0.1)	
Coronary artery disease				
Stable angina	Yes	2.023 (99.4)	12 (0.6)	0.0225
	No	41.849 (98.9)	479 (1.1)	
Unstable angina	Yes	18.892 (99.6)	78 (0.4)	<.0001
	No	24.980 (98.4)	4138 (1.6)	
AMI	Yes	20.045 (97.9)	423 (2.1)	<.0001
	No	23.827 (99.7)	68 (0.3)	
CHF	Yes	3.101 (97.3)	86 (2.7)	<.0001
	No	40.771 (99.0)	405 (1.0)	
Cardiogenic shock	Yes	363 (98.9)	4 (1.1)	0.1971††
	No	43.509 (98.9)	487 (1.1)	
Arrhythmia	Yes	1.829 (96.4)	69 (3.6)	<.0001
	No	42.043 (99.0)	422 (1.0)	
COPD	Yes	703 (96.4)	26 (3.6)	<.0001
	No	43.169 (98.9)	465 (1.1)	
Renal disease	Yes	1.142 (97.9)	24 (2.1)	0.0016
	No	42.730 (98.9)	467 (1.1)	
Peripheral vascular disease	Yes	1.493 (98.3)	26 (1.7)	0.0219
	No	42.379 (98.9)	465 (1.1)	
Stroke	Yes	2.531 (98.0)	52 (2.0)	<.0001
	No	41.341 (98.9)	439 (1.1)	
Multivessel procedure	Yes	193 (91.9)	17 (8.1)	<.0001††
	No	43.679 (99.0)	474 (1.0)	
Stent employed	Yes	26.544 (98.3)	464 (1.7)	<.0001
	No	17.328 (99.8)	27 (0.2)	
*Chi-square test †Student's t-test ††Fisher's exact test AMI - acute myocardial infarction, CHF - congestive heart failure, COPD - chronic obstructive pulmonary disease, EMS - emergency service				

Table 3. Multiple logistic regression analysis for 30-day mortality

Variables	OR (95% CI)	p
Hospital PCI volume		
<200	1.530(1.170-2.025)	0.0082
200-399	1.325(1.011-1.554)	
>400	1.0	
Sex		
Male	1.0	0.1313
Female	0.988 (0.816-1.196)	
Age	1.068 (1.058-1.079)	<.0001
Admission type		
Outpatient	1.0	<.0001
Emergency	1.585 (1.313-1.915)	
AMI	4.093 (2.984-5.615)	<.0001
CHF	1.583 (1.239-2.023)	0.0002
Arrhythmia	2.481 (1.899-3.240)	<.0001
COPD	1.765 (1.162-2.682)	0.0078
Renal disease	1.740 (1.134-2.670)	0.0112
Peripheral vascular disease	1.170 (0.773-1.771)	0.4579
Stroke	1.415 (1.050-1.906)	0.0224
Multivessel procedure	4.870 (2.836-8.364)	<.0001
Stent employed	2.370 (1.470-3.821)	0.0004
R ²	0.147	
C - statistic	0.823	
Hosmer-Lemeshow χ^2 goodness-of-fit test (p value)	4.1037 (0.8476)	
AMI - acute myocardial infarction, CHF - congestive heart failure, CI - confidence interval, COPD - chronic obstructive pulmonary disease, OR - odds ratio, , PCI - percutaneous coronary intervention		

effective skills if they treat more patients (practice makes perfect) and physicians and hospitals achieving better outcomes receive more referrals and thus accrue larger volumes (selective referral) (18, 19). That is patients treated at high-volume hospitals encounter a lower risk of mortality when compared with patients treated at low-volume hospitals. But Burton et al. (20) reported a result that 17, 417 PCIs performed in Scotland between 1997 and 2003 found no influence of the annual PCI volume of the participating hospitals on 30-day death rate. A Task Force of the German Society of Cardiology on quality assurance in invasive cardiology concluded that only a weak volume-outcome relation exists for contemporary PCI (21). Moscucci et al. (22) and Spaulding et al. (23) reinforced the volume-outcome relation with the limitation that it could be observed in high-risk patients. So there are some debates on volume-outcome result of PCI patients, especially from the cutoff point of annual PCI volume. In Korea, Korean Circulation Society started nationwide multicenter PCI registry since 2006. Before this year only one center registry data was valuable. So our volume-outcome relationship study is the first report in Korea. Although crude 30-day

Table 4. 30-day mortality rates of patients undergoing PCI at low-volume (<200 cases/year), medium-volume (200-399cases/year) and high-volume (>400 cases/year) hospitals

Variables	Low-volume hospitals	Medium-volume hospitals	High-volume hospitals	Total
No. of hospitals	60	27	15	102
No. of patients, n (%)	9.071 (20.5)	15.623 (35.2)	19.669 (44.3)	44.363 (100.0)
Total No. of patients deaths, n (%)	124 (25.3)	169 (34.4)	198 (40.3)	491 (100.0)
Crude mortality rates, %	1.4	1.1	1.0	1.1*
Risk-adjusted mortality rates, %	1.3	1.0	1.1	1.1**

mortality rates were significantly different among three groups [1.4%, 1.1%, and 1.0% ($p=0.0106$)], risk-adjusted mortality rates were not significantly different among these groups (1.3%, 1.0%, and 1.1% in each volume hospitals). The patients treated at hospitals that performed fewer than 200 PCI procedures annually may have a similar mortality rates in any other PCI volume group. Several concerns have been raised about attempts to assess the previous results be generalized to other countries outside the USA. Lin et al. (10) suggests that current ACC/AHA PCI hospital volume minimums may need to be reevaluated in non-Western countries such as Taiwan. Epstein et al. (4) suggested that there is narrowing difference in mortality rates between high-and medium-volume hospitals due to accumulating experience with PCI procedures among surgeons, especially those serving in medium-PCI volume hospitals. In our study, crude 30-day mortality rate was 1.1% (Table 2). Zahn et al. (24) reported an in-hospital mortality of 1.85% in hospitals belonging to the lowest PCI volume quartile and 1.21% in the highest quartile. But technological improvement of PCI, PCI instruments and new pharmacologic therapies in recent years it might have reduced mortality. We used risk-adjusted mortality rate in this study. This equation is composed of actual number of deaths, predicted number of deaths and overall mortality rate. The statistical performance of the developed model was evaluated using c-statistic, R^2 , Hosmer-Lemeshow statistic. They showed good model quality. Future studies of the PCI volume-outcome association will need to determine the process through which volume and outcomes are linked and to identify recent year's trends.

Study limitations

Our analysis used ICD-10 diagnosis and procedure codes data, and thus may not had captured the full clinical detail of a patient's risk profile. In particular, no data regarding target coronary vessel characteristics, stent types, left ventricular ejection fraction or Killip class, type of arrhythmias, type of peripheral vascular disease, and use of antiplatelet agents were precisely recorded which makes the analysis incomplete. We evaluated

in-hospital mortality alone and could not assess other patient's outcomes, including periprocedural complications, repeat revascularization rates, or longer-term outcomes. Another limitation is we did not track the experience of individual operators. So we cannot account for the influence of individual operator PCI volume on the association between hospital PCI volume and mortality. Although we had finely analyzed database of Korean National Statistical Office, we included only patients deceased in hospital and excluded deceased out of hospital or unidentified death in our analysis.

Conclusion

Although we could find significant relationship between different crude 30-day mortality rates according to hospital PCI volume, we could not find a relationship between hospital volume and 30-day risk-adjusted mortality rates following PCI in Korea.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - Y.H.K.; Design - A.Y.H.; Supervision - A.Y.H.; Resource - Y.H.K.; Materials - Y.H.K.; Data collection&/or Processing - A.Y.H.; Analysis &/or interpretation - Y.H.K.; Literature search - A.Y.H.; Writing - Y.H.K.; Critical review - A.Y.H.

References

1. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. *N Engl J Med* 1979; 301: 1364-9. [\[CrossRef\]](#)
2. Edwards EB, Roberts JP, McBride MA, Schulak JA, Hunsicker LG. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. *N Engl J Med* 1999; 341: 2049-53. [\[CrossRef\]](#)
3. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al. Hospital volume and operative mortality in the United States. *N Eng J Med* 2002; 346: 1128-37. [\[CrossRef\]](#)
4. Epstein AJ, Rathore SS, Volpp KGM, Krumboltz HM. Hospital percutaneous coronary intervention volume and patient mortality, 1998 to 2000: does the evidence support current procedure volume minimums? *J Am Coll Cardiol* 2004; 43: 1755-62. [\[CrossRef\]](#)
5. McGrath PD, Wennberg DE, Dickens JD Jr, Siewers AE, Lucas FL, Malenka DJ, et al. Relation between operator and hospital volume and outcomes following percutaneous coronary interventions in the era of coronary stent. *JAMA* 2000; 284: 3139-44. [\[CrossRef\]](#)
6. Ho V. Evolution of the volume-outcome relation for hospitals performing coronary angioplasty. *Circulation* 2000; 101: 1806-11. [\[CrossRef\]](#)
7. Post PN, Kuijpers M, Ebels T, Zijlstra F. The relation between volume and outcome of coronary interventions: a systematic review and meta-analysis. *Eur Heart J* 2010; 31: 1985-92. [\[CrossRef\]](#)
8. Tsuchihashi M, Tsutsui H, Tada H, Shihara M, Takeshita A, Kono S, et al. Volume-outcome relation for hospitals performing angioplasty

- for acute myocardial infarction; results from the Nationwide Japanese Registry. *Cir J* 2004; 68: 887-91. [\[CrossRef\]](#)
9. Shiraishi J, Kohno Y, Sawada T, Arihara M, Hyogo M, Yagi T, et al. Effects of hospital volume of primary percutaneous coronary interventions on angiographic results and in-hospital outcomes for acute myocardial infarction. *Cir J* 2008; 72: 1041-6. [\[CrossRef\]](#)
 10. Lin HC, Lee HC, Chu CH. The volume-outcome relationship of percutaneous coronary intervention: can current procedure volume minimums be applied to a developing country? *Am Heart J* 2008; 155: 547-52. [\[CrossRef\]](#)
 11. AHRQ Quality Indicators-Guide to Inpatient Quality Indicators: Quality of Care in Hospital-Volume, Mortality, and Utilization. Rockville: Agency for Healthcare Research and Quality, 2002, AHRQ Pub. No.02-R0204.
 12. Smith SC Jr, Dove JT, Jacobs AK, Kennedy JW, Kereiakes D, Kern MJ, et al. ACC/AHA guidelines for percutaneous coronary interventions (revision of the 1993 PTCA guidelines)-executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). *J Am Coll Cardiol* 2001; 37: 2215-39. [\[CrossRef\]](#)
 13. Milstein A, Galvin RS, Delbanco SF, Salber P, Buck CR Jr. Improving the safety of health care: the leap frog initiative. *Eff Clin Pract* 2000; 6: 313-6.
 14. Lindsay J Jr, Pinnow EE, Pichard AD. Frequency of major adverse cardiac events within one month of coronary angioplasty: useful measure of operator performance. *J Am Coll Cardiol* 1999; 34: 1916-23. [\[CrossRef\]](#)
 15. Weingart SN, Iezzoni LI, Davis RB, Palmer RH, Cahalane M, Hamel MB, et al. Use of administrative data to find substandard care: validation of the complications screening program. *Med Care* 2000;38:796-806. [\[CrossRef\]](#)
 16. Sundararajan V, Quan H, Halfon P, Fushimi K, Luthi JC, Burnand B, et al. Cross-national comparative performance of three versions of the ICD-10 Charlson index. *Med Care* 2007; 45: 1210-5. [\[CrossRef\]](#)
 17. Luft HS. The relation between surgical volume and mortality: an exploration of causal factors and alternative models. *Med Care* 1980; 18: 940-59. [\[CrossRef\]](#)
 18. Luft HS, Hunt SS, Maerki SC. The volume-outcome relationship: practice-makes-perfect or selective-referral patterns? *Health Serv Res* 1987; 22: 157-82.
 19. Flood AB, Scott WR, Ewy W. Does practice make perfect? Part II: The relation between volume and outcomes and other hospital characteristics. *Med Care* 1984; 22: 115-25. [\[CrossRef\]](#)
 20. Burton KR, Slack P, Oldroyd KG, Pell AD, Flapan AD, Starkey IR, et al. Hospital volume of throughput and periprocedural and medium-term adverse events after percutaneous coronary intervention: retrospective cohort study of all 17,417 procedures undertaken in Scotland, 1997-2003. *Heart* 2006; 92: 1667-72. [\[CrossRef\]](#)
 21. Vogt A, Strasser RH. Position document on quality assurance in invasive cardiology. Are minimum numbers in percutaneous coronary angioplasty evidence based? *Z Kardiol* 2004; 93: 829-33. [\[CrossRef\]](#)
 22. Moscucci M, Share D, Smith D, O'Donnell MJ, Riba A, McNamara R, et al. Relationship between operator volume and adverse outcome in contemporary percutaneous coronary intervention practice: an analysis of quality-controlled multicenter percutaneous coronary intervention clinical database. *J Am Coll Cardiol* 2005; 46: 625-32. [\[CrossRef\]](#)
 23. Spaulding C, Morice MC, Lancelin B, El Haddad S, Lepage E, Bataille S, et al. Is the volume-outcome relation still an issue in the era of PCI with systematic stenting? Results of the greater Paris area PCI registry. *Eur Heart J* 2006; 27: 1054-60. [\[CrossRef\]](#)
 24. Zahn R, Gottwik M, Hochadel M, Senges J, Zeymer U, Vogt A, et al. Volume-outcome relation for contemporary percutaneous coronary interventions (PCI) in daily clinical practice: is it limited to high-risk patients? Results from the Registry of Percutaneous Coronary Interventions of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte(ALKK). *Heart* 2008; 94: 329-35. [\[CrossRef\]](#)

Hospital volume and mortality relation in PCI - Is there a need for modification of ACC/AHA percutaneous coronary intervention guidelines in Asia?

PKG'lerde hastane vaka sayıları ile mortalite ilişkisi-ACC/AHA'nın perkütan koroner girişim kılavuzlarında Asya ülkeleri için değişikliğe gerek var mı?

The relationship between hospital volume and outcome relation in percutaneous coronary intervention (PCI) is important for patients, policy makers and referring physicians. Hospital volume is the explicit criterion for health care purchasers recommended by Leapfrog group. In accordance with current American College of Cardiology/American Heart Association (ACC/AHA) percutaneous coronary intervention (PCI) clinical practice guidelines, Leapfrog has established a minimum institutional volume requirement of 400 cases per year for hospitals offering PCI (1, 2). For these reason, centralization of PCI cases in core facilities has been advocated. This volume threshold is mainly based on studies originating from USA in the 1980s and 1990s which showed increased PCI mortality for patients treated at hospitals with annual volumes <400 cases (3, 4). However, there have been many changes in recent years in PCI practice by widespread use of low profile balloons, stents, glycoprotein IIb/IIIa inhibitors and intra-aortic balloon pumps. These changes and widespread PCI education opportunities increased interventional cardiologists' abilities and self-confidence, which raise the possibility that currently recommended hospital PCI volume threshold of 400 cases may no longer be appropriate.

Turkish Society of Cardiology published a national guideline for competency in interventional cardiology in 2004 and stated that 150 PCI cases/year is enough for a hospital to perform PCI. Recommended physician volume is 50 PCI cases/year. They stated that higher volume is better but setting an unrealistically high volume would deter hospitals and physicians from establishing PCI programs and restrict patient access to life saving therapies (5). Currently volume mortality statistics for PCI are not available for Turkey but they will be valuable to determine whether suggested guidelines are appropriate and can be generalized to other Asian countries.

A study representing contemporary PCI in clinical practice showed a small but significant volume-outcome relation for in-hospital mortality. However, this relation was only apparent in high-risk subgroups, such as patients presenting with acute myo-

cardial infarction (6). It is unclear whether this minimum value standard applies to non-Western countries. A Japanese study enrolling 401 acute myocardial infarction patients from 11 hospitals between years 2004-2006 did not find an obvious relationship between hospital PCI volume and in-hospital outcomes (7). In a study from Taiwan, adjusted odds of 30-day mortality for patients undergoing PCI at medium-volume hospitals (200-399 cases/year) was not significantly different from those of patients treated at high-volume hospitals (>400 cases/year). This suggests that current ACC/AHA PCI hospital volume minimums may need to be re-evaluated in non-Western countries such as Taiwan (8).

Another western study of 362.748 patients found no evidence of higher in-hospital mortality in patients undergoing PCI at medium-volume hospitals (200-399 cases/year) compared with patients treated at hospitals with annual PCI volumes of 400 cases or more suggesting current ACC/AHA PCI hospital volume minimums might merit reevaluation (9).

In this issue of Anatolian Journal of Cardiology Kim et al. (10) found a significant different crude 30-day mortality rates according to hospital PCI volume, but did not find a relationship between hospital volume and 30-day risk-adjusted mortality rates following PCI in Korea. Their large study analyzing patient statistics between year 2003-2004 and involving 102 hospitals and 44.363 patients is valuable to show mortality trends which are not thoroughly published in Asian countries like in Europe and USA. Their study will lead to more detailed studies to define characteristics of low volume hospitals and operators which make them as successful as high volume centers when risk adjusted mortalities are compared. Their mortality values will set a benchmark and stimulate other Asian countries to determine their volume-mortality relations and implement guidelines according to the local resources, needs and physician qualifications. Although regionalizing care for less common, elective surgeries may be practical, regionalizing acute care, particularly for common medical conditions like acute myocardial infarction, seems both clinically and politically infeasible and may disrupt

Address for Correspondence/Yazışma Adresi: Dr. Ayhan Olcay, İstanbul Medipol Üniversitesi, Kardiyoloji Bölümü, Bağcılar, İstanbul-Türkiye Phone: +90 212 460 77 77 Fax: +90 212 460 70 70 E-mail: drayhanolcay@gmail.com

Accepted Date/Kabul Tarihi: 11.01.2013 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.071



care for patient. More detailed studies should be done giving physician education and volume characteristics, stent usage, antiplatelet and anticoagulant use in Asian countries. Establishing common education goals and short courses for interventional cardiologists in Asian countries can be very useful. Those joint efforts can establish an "Asian alumni", improve cooperation between people with similar culture and local problems.

Ayhan Olçay

**Department of Cardiology, Faculty of Medicine, İstanbul
Medipol University, İstanbul-Turkey**

Conflict of interest: None declared.

References

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation* 2011; 124: 2574-609. [\[CrossRef\]](#)
2. The Leapfrog Group. 2002. [Accessed October 2]. Evidence-based hospital referral: the Leapfrog Group. Available at http://www.leapfroggroup.org/FactSheets/EHR_FactSheet.PDF
3. Jollis JG, Peterson ED, DeLong ER, Mark DB, Collins SR, Muhlbaier LH, et al. The relation between the volume of coronary angioplasty procedures at hospitals treating Medicare beneficiaries and short-term mortality. *N Engl J Med* 1994; 331: 1625-9. [\[CrossRef\]](#)
4. Kimmel SE, Berlin JA, Laskey WK. The relationship between coronary angioplasty procedure volume and major complications. *JAMA* 1995; 274: 1137-42. [\[CrossRef\]](#)
5. Türk Kardiyoloji Derneği Girişimsel Kardiyolojide Yetkinlik Kılavuzu. *Türk Kardiyol Dern Arş* 2005; 33: 0.
6. Zahn R, Gottwik M, Hochadel M, Senges J, Zeymer U, Vogt A, et al. Volume-outcome relation for contemporary percutaneous coronary interventions (PCI) in daily clinical practice: is it limited to high-risk patients? Results from the Registry of Percutaneous Coronary Interventions of the Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK). *Heart* 2008; 94: 329-35. [\[CrossRef\]](#)
7. Ohtsuka Machino T, Toyama M, Obara K, Takeyasu N, Watanabe S, Aonuma K, et al. Effect of hospital case volume on treatment and in-hospital outcomes in patients undergoing percutaneous coronary intervention for acute myocardial infarction. Results from the Ibaraki Coronary Artery Disease Study (ICAS) Registry. *Int Heart J* 2008; 49: 249-60. [\[CrossRef\]](#)
8. Lin HC, Lee HC, Chu CH. The volume-outcome relationship of percutaneous coronary intervention: can current procedure volume minimums be applied to a developing country? *Am Heart J* 2008; 155: 547-52. [\[CrossRef\]](#)
9. Epstein AJ, Rathore SS, Volpp KG, Krumholz HM. Hospital percutaneous coronary intervention volume and patient mortality, 1998 to 2000: does the evidence support current procedure volume minimums? *J Am Coll Cardiol* 2004; 43: 1755-62. [\[CrossRef\]](#)
10. Kim YH, Her AY. Relationship between hospital volume and risk-adjusted mortality rate following percutaneous coronary intervention in Korea, 2003 to 2004. *Anadolu Kardiyol Derg* 2013; 13: 237-42.

The effects of chronic usage of enzyme inhibitors and angiotensin receptor blockers on contrast-induced nephropathy in low-risk patients

Düşük riskli hastalarda anjiyotensin dönüştürücü enzim inhibitörleri ve anjiyotensin reseptör blokerlerinin kronik kullanımının kontrast madde nefropatisi üzerine etkileri

Nezihi Barış, Ebru Özpelit, Nazile Bilgin Doğan, Hande Kangül, Sefa Gül, Bahri Akdeniz, Sema Güneri

Department of Cardiology, Faculty of Medicine, Dokuz Eylül University, İzmir-Turkey

ABSTRACT

Objective: There is conflicting data about the role of renin- angiotensin- aldosterone system (RAAS) blockers in contrast-induced nephropathy (CIN) pathophysiology. In this study, we aimed to investigate the effects of chronic usage of RAAS blocker drugs on development of CIN in low risk patients.

Methods: Study was designed as a prospective cohort study. A total of 295 patients were enrolled in the study. Study population was consisted of three subgroups according to prior usage of RAAS blockers: no RAAS blocker group (n=95), angiotensin-converting enzyme inhibitor (ACEI) group (n=106), angiotensin receptor blocker (ARB) group (n=94). CIN was defined as an increase of $\geq 25\%$ in creatinine over the baseline value or 0.5 mg/dL rise within 48-72 h of angiography. Mehran score was calculated for each patient. Baseline variables and percentage of CIN were compared with ANOVA, Mann-Whitney U, Kruskal-Wallis and Pearson Chi-square tests between groups. In order to determine the independent predictors of CIN, binary logistic regression analyses were performed.

Results: CIN occurred in 18 patients (17.0%) in the ACEI group, 17 patients (18.1%) in ARB group and 7 patients (7.4%) in the no RAAS group. CIN occurrence was significantly higher in RAAS than no RAAS group (17.5% vs. 7.4%, $p=0.01$). Chronic RAAS blocker administration was an independent predictor of CIN (OR=2.69; 95% CI: 1.025-7.067; $p=0.04$). Mehran score was the only other independent predictor for CIN (OR=1.15; 95% CI: 1.019-1.310; $p=0.02$).

Conclusion: In patients with near normal renal functions who are undergoing elective coronary procedure, chronic usage of ACEI and ARB increases the risk of CIN. (*Anadolu Kardiyol Derg 2013; 13: 245-50*)

Key words: Contrast-induced nephropathy, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, regression analysis

ÖZET

Amaç: Kontrast madde nefropatisi (KMN) koroner girişim yapılan hastalarda önemli bir sorundur. Renin- anjiyotensin-aldosteron sistemi (RAAS) blokerlerinin KMN gelişimindeki rolüne ait veriler çelişkilidir. Bu çalışmada düşük riskli hastalarda kronik RAAS blokeri ilaç kullanımının KMN gelişimi üzerine olan etkisinin araştırılması amaçlanmıştır.

Yöntemler: Prospektif kohort olarak dizayn edilen çalışmaya elektif koroner girişim yapılan 295 hasta alındı. RAAS blokeri kullanımına göre hastalar 3 ayrı gruptan oluşturuldu: RAAS blokeri kullanmayanlar (n=95), anjiyotensin dönüştürücü enzim inhibitörü (ADEİ) kullananlar (n=106), anjiyotensin reseptör blokeri (ARB) kullananlar (n=94). KMN koroner girişim sonrası 48-72 saat içinde bazal kreatinin değerinde $\geq 25\%$ ve üzeri veya 0.5 mg/dL artış olması şeklinde tanımlandı. Her hasta için Mehran skoru hesaplandı. Gruplar arasındaki bazal veriler ve KMN gelişimi ANOVA, Mann-Whitney U, Kruskal-Wallis ve Pearson Ki-kare testleri ile karşılaştırıldı. KMN için bağımsız öngördürücülerin bulunabilmesi için binary lojistik regresyon analizi yapıldı.

Bulgular: ADEİ grubunda 18 (%17.0), ARB grubunda 17 (%18.1), RAAS blokeri kullanmayan grupta 7 (%7.4) hastada KMN gelişti. RAAS blokeri alan grupta KMN gelişimi almayan gruba göre anlamlı olarak fazlaydı (sırasıyla %17.5 - %7.4, $p=0.01$). Kronik RAAS blokeri kullanımı (OR=2.69; %95 GA: 1.025-7.067; $p=0.04$) ve Mehran skoru (OR=1.15; %95 GA: 1.019-1.310; $p=0.02$) KMN için bağımsız öngördürücüler olarak bulundu.

Address for Correspondence/Yazışma Adresi: Dr. Nezihi Barış, Dokuz Eylül Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, 35340 İnciraltı, İzmir-Türkiye Phone: +90 232 412 41 03 Fax: +90 232 279 25 65 E-mail: nezihi.baris@deu.edu.tr

Accepted Date/Kabul Tarihi: 07.12.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 21.12.2012

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.050



Sonuç: Elektif koroner girişim yapılan, normal veya normale yakın böbrek fonksiyonları olan hastalarda kronik ADEİ ve ARB kullanımı KMN gelişimi riskini arttırmaktadır. (*Anadolu Kardiyol Derg 2013; 13: 245-50*)

Anahtar kelimeler: Kontrast madde nefropatisi, anjiyotensin dönüştürücü enzim inhibitörü, anjiyotensin reseptör blokleri, regresyon analizi

Introduction

Contrast-induced nephropathy (CIN) is characterized by acute deterioration of renal functions that occurs after parenteral administration of contrast media in the absence of other possible causes of renal impairment. Its incidence varies widely due to usage of different definitions, and also different population characteristics. The most commonly used definition is an increase in serum creatinine by 25% or by 0.5 mg/dL from a baseline value by 48-72 h post contrast administration (1). In patients with normal renal functions, CIN has been reported as occurring in 3.3-14.5% of patients (2). Factors that have been identified to be associated with CIN include: diabetes mellitus, congestive heart failure, recent acute myocardial infarction, cardiogenic shock, and pre-existing renal impairment. CIN is associated with renal failure, prolonged hospitalization, increased mortality and morbidity (3). As there is no specific therapy for CIN, the main focus is on preventive strategies. Some preventive measures are well defined such as optimal hydration of the patients, avoidance of concomitant nephrotoxic drug usage and minimizing the amount of contrast media. However the role of renin-angiotensin-aldosterone system (RAAS) blocking agents, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) in the pathophysiology of CIN remains controversial, as the available literature is conflicted and discordant. Some reports have implicated these RAAS blocking agents as nephrotoxic and exacerbating renal failure with CIN whereas other reports have touted the use of these same RAAS blocking agents to protect the kidneys from the effects of CIN (4-8).

Previous studies on this topic generally focused on the patients with chronic kidney disease, hemodynamic insufficiency and acute myocardial infarction (5-8). In the majority of these studies the role of continuing or withdrawing of ACEI and ARB on development of CIN were examined. However the knowledge about chronic usage of these drugs in stable patients who underwent elective cardiac angiography and intervention is limited.

In this study we aimed to investigate the effects of chronic usage of RAAS blocker drugs on development of CIN and to establish the predictors of CIN in stabile patients who underwent elective coronary angiography and intervention.

Methods

Study design

A prospective cohort study was designed.

Study population and study protocol

Study was performed in patients 18 years of age and older who were referred to our cardiology department for non-emergent coronary angiography between May 2010 and July 2012.

Study population was designed as 3 subgroups; group 1 with no RAAS blockers; group 2 patients on chronic use of ACEI and group 3; patients on chronic use of ARB. Enrolling 100 consecutive patients for each group was planned.

The patients who underwent emergent or early invasive coronary procedures (coronary procedures within initial 48 hours of acute coronary syndromes), who had hemodynamic instability, who had severe chronic renal disease (glomerular filtration rate <30 mL/min) were excluded from the study. Usage of aldosterone antagonists and other nephrotoxic drugs were also defined as exclusion criteria.

Contrast-induced nephropathy was our primary end-point and the secondary end-point was change of creatinine (delta Cre) after procedure compared to baseline value.

All of the participants gave written informed consent and the local research ethics committee had previously approved the study protocol. The patients were followed for 48-72 hours after the procedure for the assessment of renal functions. After exclusion of 33 patients who did not complete the post procedural follow-up, a total of 295 patients were enrolled in the study. Among these, 95 were in group 1 (no RAAS blocker), 106 were in group 2 (patients on ACEI) and 94 were in group 3 (patients on ARB).

Study variables and definitions

The presence of hypertension, diabetes mellitus, hyperlipidemia and history of coronary artery disease were assessed via patients' medical questioning. Blood pressure was measured according to recommendations.

Chronic RAAS blocker usage was defined as the use of the drug for a minimum of one month. No RAAS blocker group consisted of patients who did not use any RAAS blockers more than one month. Baseline and follow-up glomerular filtration rate (eGFR) were estimated using the Cockcroft-Gault formula: $(140 - \text{age}) * \text{weight (kg)} / \text{serum creatinine (mg/dL)} * 72 (*0.85 \text{ in female})$ (9). Mehran score was calculated according to assessment of the associated risk factors, including dose of contrast media, baseline eGFR, age, presence of hypotension, heart failure, anemia, and diabetes mellitus (10). As long as the study population was consisted of stabile patients, some parameters of Mehran score such as hypotension and usage of intra-aortic balloon pump were ignored. CIN defined as an increase of serum creatinine 25% over the baseline value or 0.5 mg/dL rise within 48-72 h of coronary angiography procedure (1).

Laboratory analysis

A blood sample for serum creatinine, blood urea nitrogen (BUN), glucose, albumin, total cholesterol, sodium, and hemoglobin was drawn before the angiography after an 8-hour overnight fast and follow-up serum creatinine and BUN were measured

48-72 h after angiography. Serum creatinine was determined using an auto-analyzer, enzymatically and using the Jaffé method.

Angiography and contrast media

Type and amount of contrast media used were recorded for each patient. Three types of contrast agents (ioxaglate, iodixanol and iopromide) were used for coronary procedure. According to ethical rules, the patients whose baseline creatinine was ≥ 1.2 mg/dL, received preventive treatment including 0.9% isotonic infusion (1 mL/kg/h, upper limit 100 mL/h) and N-acetylcysteine 600 mg twice daily as our previous study (11). The usage of N-acetylcysteine with fluid infusion was recommended in guideline as a class II recommendation but only N-acetylcysteine administration was not recommended (12).

Statistical analysis

The SPSS statistical software (SPSS for Windows15.0, Inc., Chicago, IL, USA) was used for all statistical calculations. Continuous variables were given as mean $\pm$ standard deviation (SD), and categorical variables were defined as percentage. Continuous variables were analyzed with Kolmogorov-Smirnov for testing normal distribution. Differences between groups were tested using one-way analysis of variance (ANOVA), Mann-Whitney U, Kruskal-Wallis and Chi-square test when appropriate. Paired t-test and Wilcoxon signed ranks test were used to compare differences within groups following an intervention. We performed binary logistic regression with the presence of CIN as the dependent variable and the following as potential covariates: age, eGFR, contrast amount, serum creatinine, left ventricular ejection fraction, Mehran score, presence of hypertension, diabetes mellitus, RAAS blocker use, female gender, hyperlipidemia and history of coronary artery disease. Variables that were statistically significant in univariate analysis were included in the final multivariate model to identify predictors of CIN. A two-sided 95% confidence interval (CI) was constructed around the point estimate of the odds ratio (OR). All tests were two-sided, and a p value of less than 0.05 was considered for statistical significance.

Statistical power of this study was calculated for CIN, it was found as 98.6%.

Results

Demographic and baseline characteristics

Baseline characteristics were comparable for 3 groups except hypertension. Prevalence of hypertension was significantly higher ($p<0.05$) in RAAS blocker group (ACEI and ARB) than no RAAS blocker group as expected. Contrast agent's type and volume were comparable for 3 groups (Table 1).

Primary and secondary end-point outcome

When we compared ARB and no RAAS blocker group, CIN was significantly higher in ARB than no RAAS blocker group [17 (18.1%) vs. 7 (7.4%) respectively, $p=0.04$]. Although CIN was

Table 1. Baseline characteristics of study patients

Variables	All groups (n=295)	No RAAS (n=95)	ACEI (n=106)	ARB (n=94)	*p
Age, years	63.8 $\pm$ 12.7	61.9 $\pm$ 12.9	64.1 $\pm$ 12.0	65.4 $\pm$ 13.1	0.16
Female, %	28.5	28.4	23.6	34.0	0.26
Hypertension, %	60.7	27.4	75.5	77.7	<0.001
SBP, mmHg	126.7 $\pm$ 14.5	124.4 $\pm$ 11.0	127.7 $\pm$ 14.6	128.0 $\pm$ 17.2	0.21
DBP, mmHg	78.2 $\pm$ 10.9	76.4 $\pm$ 9.5	79.2 $\pm$ 10.5	78.9 $\pm$ 12.6	0.10
Diabetes mellitus	34.6	33.7	34.0	36.2	0.92
Hyperlipidemia	52.5	54.7	50.9	52.1	0.86
History of CAD	23.7	17.9	23.6	29.8	0.40
eGFR (baseline), mL/min	87.0 $\pm$ 35.1	87.9 $\pm$ 34.6	89.3 $\pm$ 37.1	83.5 $\pm$ 33.3	0.49
Creatinine, mg/dL	0.98 $\pm$ 0.31	1.00 $\pm$ 0.32	0.97 $\pm$ 0.33	0.97 $\pm$ 0.26	0.77
LVEF, %	47.9 $\pm$ 12.8	46.9 $\pm$ 13.7	48.5 $\pm$ 12.5	48.4 $\pm$ 12.3	0.73
Contrast volume, mL	111.0 $\pm$ 34.4	110.0 $\pm$ 25.8	111.7 $\pm$ 38.6	111.1 $\pm$ 37.1	0.37
Iodixanol, %	21.4	18.9	23.6	21.3	0.53
Ioxaglate, %	40.7	46.3	40.6	35.1	0.53
Iopromide, %	38.0	34.7	35.8	43.6	0.53
Mehran score	4.64 $\pm$ 3.78	4.51 $\pm$ 3.72	4.55 $\pm$ 3.86	4.86 $\pm$ 3.78	0.81
Preventive treatment, %	20.3	21.1	16.0	24.5	0.32
Patients with (30 $\leq$ eGFR baseline <60), n (%)	76 (25.8)	26 (27.4)	26 (24.5)	24 (25.5)	0.89

Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as percentage
 *ANOVA, Kruskal-Wallis and Chi-square tests
 ACEI - angiotensin-converting enzyme inhibitor, ARB - angiotensin receptor blocker, CAD - coronary artery disease, DBP - diastolic blood pressure, eGFR - estimated glomerular filtration rate, LVEF - left ventricular ejection fraction, RAAS - renin angiotensin aldosterone system, SBP - systolic blood pressure.

higher in ACEI than no RAAS blocker group, p value did not reach significance [18 (17.0%) vs. 7 (7.4%) respectively, $p=0.06$]. CIN rate was significantly higher in ACEI and ARB (RAAS blocker group) than no RAAS blocker group [35 (17.5%) vs. 7 (7.4%) respectively, $p=0.01$] (Fig. 1). Our secondary end-point delta Cre was comparable for ACEI, ARB and no RAAS blocker groups (0.08 $\pm$ 0.2, 0.12 $\pm$ 0.3 and 0.09 $\pm$ 0.3 mg/dL, respectively, $p=0.25$).

When the subgroup of patients with eGFR 30-60 mL/min was analyzed, there was no statistical significant difference for CIN between ACEI, ARB and no RAAS blocker groups (30.8%, 25.0% and 11.5%, respectively, $p=0.23$).

CIN predictors

When the patients with and without CIN were compared, percentage of hypertension, Mehran score, age and baseline serum creatinine were significantly higher, baseline eGFR was significantly lower in patients with CIN (Table 2). When we per-

form multivariate analysis, we found Mehran score and RAAS blocker usage as independent predictors for CIN (Table 3).

All study population analyzed for serum creatinine and eGFR. After contrast administration, serum creatinine significantly increased (0.98 ± 0.31 vs. 1.08 ± 0.47 mg/dL, $p < 0.05$) and eGFR significantly decreased (87.0 ± 35.1 vs. 82.4 ± 36.0 mL/min, $p < 0.05$).

Discussion

The main finding of our study was significantly higher incidence of CIN in chronic RAAS blocker users compared to patients with no RAAS blocker treatment. In the baseline characteristics, only hypertension was significantly higher in our RAAS blocker

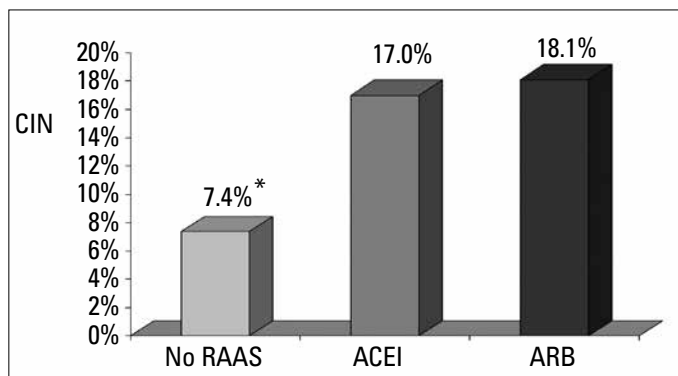


Figure 1. Comparison of CIN percentage between groups

Chi-square test

* $p = 0.04$ for No RAAS and ARB groups, $p = 0.02$ for No RAAS and RAAS (ACEI+ARB) groups, $p = 0.06$ for No RAAS and ACEI groups

Table 2. Clinical variables in patients with and without CIN

Variables	CIN (+) (n=42)	CIN (-) (n=253)	*p
Age, years	68.8±10.0	63.0±12.9	0.006
Hypertension, %	76.2	58.1	<0.001
Mehran score	7.0 (0-16)	4.0 (0-14)	<0.001
eGFR (baseline), mL/min	70.1±27.2	89.8±35.5	0.001
Creatinine (baseline), mg/dL	0.9 (0.5-2.38)	1.0 (0.57-2.30)	0.013

Variables are presented as mean±SD and as percentage
*t-test for independent samples, Mann-Whitney U test and Chi-square test
CIN - contrast-induced nephropathy, eGFR - estimated glomerular filtration rate

Table 3. Independent predictors of CIN according to binary logistic regression analyses

Variables	Odds Ratio	95% CI	p
Age	0.993	0.947-1.042	0.78
eGFR (baseline)	0.994	0.974-1.015	0.58
Cre (baseline)	1.433	0.344-5.966	0.62
Hypertension	0.898	0.373-2.164	0.81
Mehran score	1.15	1.019-1.310	0.02
RAAS blocker	2.69	1.025-7.067	0.04

Cre - creatinine, CI - confidence interval, eGFR - estimated glomerular filtration rate, RAAS - renin angiotensin aldosterone system

group. It is actually associated with our selection bias. This factor could indeed affect the primary endpoint of CIN development, as hypertension is a well-known risk factor for nephrosclerosis. However, considering the similar baseline values of eGFR, systolic and diastolic blood pressures in 3 subgroups, we thought that the effect of hypertension on CIN could be ignored. Multivariate analysis also confirmed this assumption, presenting chronic RAAS blocker usage as an independent predictor of CIN development. The second main finding was Mehran score which was the only other independent predictor of CIN even in our low-risk study population. Mehran risk score is an important parameter which can predict the risk of CIN in patients with elective coronary procedures and also with acute coronary syndromes. Recently it has been shown that Mehran risk score was also successful in predicting long-term major adverse cardiac event and mortality in acute myocardial infarction patients treated with percutaneous coronary intervention (13).

In our study, mean creatinine of all study population was 0.98 ± 0.31 (0.50-2.38) mg/dL which indicates a relatively good baseline kidney function compared to the other similar studies in literature. The mean eGFR of the total study population was 87.0 ± 35.1 mL/min and the percentage of the patients whose eGFR below 60 was only 25.8%. Average Mehran score of our group was also relatively low. These findings were related to our inclusion criteria as we had excluded the patients with unstable clinical conditions. As a result, we can say that, our study group consisted of low risk, stable patients with nearly normal renal functions who underwent elective intervention. In daily clinical practice, vast majority of patients who underwent coronary angiography are similar to our study population. As mentioned previously, reports regarding the effects of RAAS blockers on CIN development are mostly focused on patients with mild to moderate renal impairment. At this point this study is the first showing the effects of chronic RAAS blocker usage on CIN development in patients with normal renal functions.

Controversial results for relation of ACEI, ARB and CIN were reported in literature. Some studies reported RAAS blockers were preventive for CIN (6, 7). A study by Gupta et al. (7) in India randomized patients to captopril 25 mg TID for three days (starting 1 h prior to contrast administration) and found a 79 % risk reduction in developing CIN compared to controls who received no therapy. It has been speculated that ACEIs may confer protection against CIN by counteracting afferent arteriolar vasoconstriction and subsequent medullary ischemia caused by angiotensin II activation after contrast administration. On the contrary, the vast majority of the studies reported that RAAS blocker cause deterioration of renal functions. In a recent study Hölscher et al. (14) prospectively assess predictors of CIN and long-term outcomes of affected patients. Utilizing the data from the 412 patients studied in the Dialysis-Versus-Diuresis (DVD) trial, post-procedural hemodialysis, left ventricular ejection fraction <35%, serum phosphate, and ACEI use were found to be independently associated with increased incidence of CIN. ACEI

intake was associated with a six-fold increase in the incidence of CIN post-procedure (OR 6.16, 95% CI 2.01-18.93) (14). ACE inhibitors prevent the conversion of angiotensin I-II, thus releasing the vasoconstriction of the efferent glomerular arterioles, with a subsequent decrease in the glomerular hydrostatic pressure. With a lower glomerular hydrostatic pressure, there is less glomerular filtration (15). It has been suggested that this decrease in eGFR may predispose to the development of CIN in patients taking ACEI and ARB (4, 5). Most of the studies investigated the effect of continuation or acute withdrawing of RAAS blockers. Rosenstock et al. (16) investigated the patients with chronic kidney disease (Stage 3-4) who are on chronic ACEI-ARB therapy (16). They continued or discontinued the drug 24 h before coronary angiography. Additionally, they had a no RAAS blocker group. The authors found no statistically significant differences between the groups in the incidence of CIN: continuation group 6.2%, discontinuation group 3.7%, and no RAAS blocker group 6.3% ($p=.66$). Rosenstock et al. (16) concluded that ACEIs do not increase the incidence of CIN. They recommended not withholding ACEIs prior to contrast exposure. However a recent report from Mayo clinic suggests withdrawal of RAAS blocker usage 24-48 hour before elective interventions, relying on their own clinical experience and also an earlier literature data (17, 18). Chronic ACEI administration was investigated by Cirit et al. (5). They found that chronic ACEI administration was a risk indicator of CIN. CIN occurred in 17 patients in the ACEI group and 7 patients in the control group (15.6% vs. 5.8%, $p=0.015$). In this study, the study population was also consisted of patients with mild to moderate renal insufficiency. Recently a review has been published by Patel et al. (19). This review focused on the role of ACEIs in CIN. In this review, the results of 5 randomized clinical trials and 678 patient were analyzed. Based on these data they concluded that there is no definite correlation between ACEIs and the occurrence of CIN in the cardiac catheterization laboratory and withholding ACEIs prior to catheterization does not probably decrease the incidence of CIN and is not recommended. They also stated that starting ACEIs before the procedure for the sole purpose of lowering the risk of CIN cannot be recommended based on the current evidence (19).

The presence of different conclusions can result from significant differences in methodology, study populations, interventions. The possible consideration of potential factors contributing to ACE inhibitors in prevention of contrast-induced nephropathy included baseline Cr levels, volume of contrast media, age, diabetes mellitus, dose, and the structure of ACEIs. Besides, the definition of contrast-induced nephropathy was also variable among the studies.

Renin-angiotensin-aldosterone system blockers constitute a major treatment modality for cardiovascular and renal diseases, and the use of ACEIs is very common among patients undergoing coronary angiography. Currently, it is not known whether withholding ACEIs before angiography is a potential preventive

measure for CIN. However chronic usage of RAAS blockers seems to be a risk factor for CIN development. Previously this was proven in patients with mild to moderate renal insufficiency. In this study, it is shown that chronic RAAS blocker usage is also a risk factor for CIN development in patients with near normal renal functions. This study is also the important in regard of results related to ARB. Angiotensin receptor blockers were found to increase the CIN development significantly. This association was even stronger in ARB group compared to ACEI group. In a recent study, impact of ACEI and ARB on the frequency of CIN was evaluated through a post hoc analysis from the DVD trial (20). This study showed that patients receiving ACEI or ARB while undergoing cardiac catheterization significantly more often developed CIN within 72 h after coronary procedure. However, in this study, patients receiving ACEI or ARB were not evaluated separately. Moreover only 12% of the patients with RAAS treatment, were ARB users, that the impact of ARB on CIN development was not analyzed in a separate manner.

Study limitations

Our study has some limitations. First of all, it has a single-center design that the results could better be generalized if they will be repeated in other future trials. Second, the dose and the structure of the ACEI and ARB were not homogeneous among the groups. Although we had data about the structure of the drugs, we did not further analyze as the patient numbers in subgroups would be too small for interpreting the data.

Conclusion

The results of the present study show that in patients with near normal renal functions who are undergoing elective coronary procedure, chronic use of ACEI and ARB increase the risk of CIN. In daily practice, considering this finding could be particularly important in the pre-procedural risk assessment of the patients.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - N.B.; Design - N.B., E.Ö.; Supervision - S.G., N.B.; Resource - S.G., N.B., E.Ö., B.A.; Materials - N.B.D., H.K.; Data Collection&/or Processing - N.B.D., H.K., S.G.; Analysis&/or Interpretation - N.B., B.A.; Literature Search - N.B., E.Ö.; Writing - N.B., E.Ö.; Critical Reviews - S.G., B.A.

References

1. Pucelikova T, Dargas G, Mehran R. Contrast-induced nephropathy. *Catheter Cardiovasc Interv* 2008; 71: 62-72. [CrossRef]
2. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; 105: 2259-64. [CrossRef]

3. McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; 103: 368-75. [\[CrossRef\]](#)
4. Toprak O, Cirit M, Bayata S, Yeşil M, Aslan SL. The effect of pre-procedural captopril on contrast-induced nephropathy in patients who underwent coronary angiography. *Anadolu Kardiyol Derg* 2003; 3: 98-103.
5. Cirit M, Toprak O, Yeşil M, Bayata S, Postacı N, Pupim L, et al. Angiotensin-converting enzyme inhibitors as a risk factor for contrast-induced nephropathy. *Nephron Clin Pract* 2006; 104: 20-7. [\[CrossRef\]](#)
6. Komenda P, Zalunardo N, Burnett S, Love J, Buller C, Taylor P, et al. Conservative outpatient renoprotective protocol in patients with low GFR undergoing contrast angiography: a case series. *Clin Exp Nephrol* 2007; 11: 209-13. [\[CrossRef\]](#)
7. Gupta RK, Kapoor A, Tewari S, Sinha N, Sharma RK. Captopril for prevention of contrast-induced nephropathy in diabetic patients; a randomized study. *Indian Heart J* 1999; 51: 521-6.
8. Dangas G, Iakovou I, Nikolsky E, Aymong ED, Mintz GS, Kipshidze NN, et al. Contrast-induced nephropathy after percutaneous coronary interventions in relation to chronic kidney disease and hemodynamic variables. *Am J Cardiol* 2005; 95: 13-9. [\[CrossRef\]](#)
9. Gault MH, Longerich LL, Harnett JD, Wesolowski C. Predicting glomerular function from adjusted serum creatinine. *Nephron* 1992; 62: 249-56. [\[CrossRef\]](#)
10. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, et al. A simple risk score for prediction of contrast induced nephropathy after coronary intervention: development and initial validation. *J Am Coll Cardiol* 2004; 44: 1393-9. [\[CrossRef\]](#)
11. Özcan EE, Güneri S, Akdeniz B, Akyıldız İZ, Şenaslan O, Barış N, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J* 2007; 154: 539-44. [\[CrossRef\]](#)
12. The ad-hoc working group of ERBP: Fliser D, Laville M, Covic A, Fouque D, Vanholder R, Juillard L, et al. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines on Acute Kidney Injury: Part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 2012; 27: 4263-72.
13. Wi J, Ko YG, Shin DH, Kim JS, Kim BK, Choi D, et al. Prediction of contrast-induced nephropathy with persistent renal dysfunction and adverse long-term outcomes in patients with acute myocardial infarction using the mehran risk score. *Clin Cardiol* 2012 Oct 1. doi: 10.1002/clc.22060. [\[CrossRef\]](#)
14. Hölscher B, Heitmeyer C, Fobker M, Breithardt G, Schaefer RM, Reinecke H. Predictors for contrast-induced nephropathy and longterm survival: prospectively assessed data from the Dialysis-Versus-Diuresis (DVD) trial. *Can J Cardiol* 2008; 24: 845-50. [\[CrossRef\]](#)
15. Schoolwerth AC, Sica DA, Ballermann BJ, Wilcox CS. Renal considerations in angiotensin-converting enzyme inhibitor therapy: a statement for healthcare professionals from the Council on the Kidney in Cardiovascular Disease and the Council for High Blood Pressure Research of the American Heart Association. *Circulation* 2001; 104: 1985-91. [\[CrossRef\]](#)
16. Rosenstock JL, Bruno R, Kim JK, Lubarsky L, Schaller R, Panagopoulos G, et al. The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *Int Urol Nephrol* 2008; 40: 749-55. [\[CrossRef\]](#)
17. Onuigbo MAC, Onuigbo NTC. Does renin-angiotensin aldosterone system blockade exacerbate contrast-induced nephropathy in patients with chronic kidney disease? A prospective 50-month Mayo Clinic study. *Renal Failure* 2008; 30: 67-72. [\[CrossRef\]](#)
18. Louis BM, Hoch BS, Hernandez C, Namboodiri N, Neiderman G, Nissenbaum A, et al. Protection from the nephrotoxicity of contrast dye. *Renal Failure* 1996; 18: 639-46. [\[CrossRef\]](#)
19. Patel K, King CA, Jovin IS. Angiotensin-converting enzyme inhibitors and their effects on contrast-induced nephropathy after cardiac catheterization or percutaneous coronary intervention. *Cardiovasc Revasc Med* 2011; 12: 90-3. [\[CrossRef\]](#)
20. Kiski D, Stepper W, Brand E, Breithardt G, Reinecke H. Impact of renin-angiotensin-aldosterone blockade by angiotensin-converting enzyme inhibitors or AT-1 blockers on frequency of contrast medium-induced nephropathy: a post-hoc analysis from the Dialysis-Versus-Diuresis (DVD) trial. *Nephrol Dial Transplant* 2010; 25: 759-64. [\[CrossRef\]](#)

Evaluation of right ventricular functions in patients with nasal polyposis: an observational study

Nazal polipozisli hastalarda sağ ventrikül fonksiyonlarının değerlendirilmesi: Gözlemsel bir çalışma

Eda Şimşek, Ziya Şimşek*, M. Hakan Taş*, Cüneyt Kucur, Ersin Günay¹, Harun Üçüncü**

Clinic of Ear, Nose and Throat, Erzurum Region Education and Research Hospital, Erzurum-Turkey
Departments of *Cardiology and **Ear, Nose and Throat, Faculty of Medicine, Atatürk University, Erzurum-Turkey
¹Department of Thoracic Disease, Faculty of Medicine, Afyon Kocatepe University, Afyon-Turkey

ABSTRACT

Objective: The aim of this study was to assess the right ventricular functions in patients with nasal polyposis using the strain (S) and strain rate (SR) echocardiography.

Methods: A prospective, cross-sectional observational study was performed. The study included 40 patients with nasal polyposis (NP) (Group 1), and 25 healthy controls (Group 2). The study comprised patients with Stage 2 and Stage 3 nasal obstruction and no symptoms that could be associated with right ventricular heart failure. Longitudinal peak systolic strain (PSS) and peak systolic strain rate (PSSR) were measured from the basal-mid and apical segments of the right ventricle free wall. Student's t-test, Pearson's correlation analysis and Bland-Altman test were used for statistical analysis.

Results: Pulmonary arterial systolic pressure was significantly higher in group 1 than group 2 (31.2 ± 5.8 , 19.7 ± 4.3 , respectively, $p < 0.001$). PSS and PSSR values at the basal, mid and apical segments of the right ventricular lateral wall of the group I were significantly lower compared to the control group ($p < 0.001$, $p = 0.002$ and $p = 0.002$ for PSS, $p = 0.003$, $p < 0.001$ and $p < 0.001$ for PSSR, respectively). The comparison of Stage 2 and Stage 3 NP patients revealed a significant difference only in the SR measurement of the right ventricular mid segment ($p = 0.002$). There was a significant correlation between the systolic pulmonary arterial pressure (sPAP) and right ventricular S and SR values ($p < 0.001$).

Conclusion: In this study, S/SR echocardiography showed a subclinical deficit of the right ventricular longitudinal functions in patients with NP who are considered to have normal right ventricular functions. (*Anadolu Kardiyol Derg 2013; 13: 251-6*)

Key words: Nasal polyposis, right ventricular functions, strain/strain rate

ÖZET

Amaç: Bu çalışmada amaç nazal polipozisi olan hastalarda sağ ventrikül fonksiyonlarını gerilme/gerilme hızı ekokardiyografi metodları ile değerlendirmektir.

Yöntemler: Çalışma enine kesitli gözlemsel prospektif olarak planlandı. Çalışmaya nazal polipozisli (NP) 40 hasta (Grup 1) ve sağlıklı 25 kontrol grubu (Grup 2) birey alındı. Hasta grubu nazal obstrüksiyonun seviyesi evre 2 ve evre 3 olan ve sağ kalp yetersizliğine bağlı olabilecek herhangi bir semptomu olmayan hastalardan oluşturuldu. Sağ ventrikül serbest duvarının bazal-mid ve apikal segmentlerinden longitudinal pik sistolik strain (PSS) ve pik sistolik strain rate (PSSR) değerleri ölçüldü. İstatistiksel analizde Student-t test, Pearson korelasyon analizi ve Bland-Altman testi kullanıldı.

Bulgular: Pulmoner arter sistolik basınç Grup 1'de oldukça anlamlı düzeyde daha yüksek bulundu (31.2 ± 5.8 , 19.7 ± 4.3 , $p < 0.001$). PSS ve PSSR değerleri NP grubunda sağ ventrikül lateral duvarının bazal, mid ve apikal tüm segmentlerinde kontrol grubuna göre oldukça anlamlı derecede düşük bulundu (PSS için sırasıyla; $p < 0.001$, $p = 0.002$ ve $p = 0.002$, PSSR için sırasıyla; $p = 0.003$, $p < 0.001$ ve $p < 0.001$). Evre 2 ve evre 3 NP'li hastalar kendi aralarında karşılaştırıldığında ise; yalnızca sağ ventrikül mid-segmenti SR değerinde anlamlı farklılık gözlemlendi ($p = 0.02$). Sistolik pulmoner arteriyel basınç (sPAP) yüksekliği ile sağ ventrikül S ve SR değerleri arasında oldukça anlamlı düzeyde bir korelasyon olduğu görüldü.

Sonuç: Çalışmamız, sağ ventrikül (SV) fonksiyonları normal olarak kabul edilen NP'li hastalarda S/SR ekokardiyografi ile SV longitudinal fonksiyonlarında subklinik düzeyde bozulma olduğunu göstermiştir. (*Anadolu Kardiyol Derg 2013; 13: 251-6*)

Anahtar kelimeler: Nazal polipozis, sağ ventrikül fonksiyonları, gerilme/gerilme hızı

Address for Correspondence/Yazışma Adresi: Dr. Eda Şimşek, Osman Gazi Mah. Gökdemir Sitesi A Blok, Kat: 6 Daire No: 29 25100 Erzurum- Türkiye Phone: +90 505 884 15 96 Fax: +90 442 316 63 40 E-mail: hekimed@hotmial.com

Accepted Date/Kabul Tarihi: 09.11.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

© Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

© Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.072



Introduction

Nasal polyposis (NP) is a chronic inflammatory disorder of nasal and sinus mucosa with prominent nature of eosinophilia. This chronic inflammation results in a mass formation originating from mucosa of the sinus and prolapsing mostly through the lumen at the nasal mucosal surface (1). These mass formations leading to nasal obstruction are responsible from the clinical picture. This obstruction may also result in pulmonary hypertension (PH) and cor pulmonale (2). Nasopharyngeal muscles relax during sleep in patients with nasal obstruction. This relaxation increases the upper airway resistance during inspiration, leads to paralaryngeal collapse and hypoventilation, which end up with hypoxia and hypercapnia (3, 4). Chronic hypoxia and hypercapnia cause pulmonary arterial vasoconstriction and PH. If left untreated, this condition may lead to overloading, hypertrophy and dilatation of the right ventricle due to already increased pulmonary vascular resistance and pulmonary arterial pressure, which consequently causes right ventricular (RV) insufficiency and death (5, 6). Thus, early detection and treatment of myocardial disease are essential in such patients to prevent cardiopulmonary complications.

Tissue Doppler Imaging (TDI) is a technique, which is based on the demonstration of the movement of myocardial tissue with the low-frequency and high amplitude by filtering the movements of blood components with high-frequency (7). Strain (S) and strain rate (SR) echocardiography, which have been derived from myocardial colored TDI technique are clinically significant parameters and measure the global and regional myocardial functions rapidly and accurately (8). Studies on S/SR echocardiography techniques to investigate the RV functions have shown that these imaging techniques are convenient and effective in displaying the RV functions (9). They have suggested that S/SR echocardiography detects patients who are missed with conventional echocardiography, at an early subclinical stage.

We thought that, because of the hypoxia, hypoventilation and hypercapnia, right ventricular functions in patients with nasal polyposis could be affected in myocardial tissue level. To our knowledge, this hypothesis has not been confirmed before in the literature.

The aim of this study was to assess the right ventricular functions using S/SR echocardiography parameters in patients with nasal obstruction due to NP for at least one year.

Methods

Study design

A cross-sectional prospective observational trial was performed at Department of Ear, Nose and Throat, in Atatürk University, School of Medicine, Erzurum, Turkey between June 2009 and July 2010.

Patient selection

Consecutive 40 patients (Group 1) who presented with diagnosis of NP and 25 healthy controls (Group 2) were enrolled in

the study. The patients younger than 18 years and older than 45 years, those with a nasal pathology obstructing the nasal passage, diabetes mellitus, hypertension, chronic obstructive lung disease, asthma and known coronary artery disease were excluded. Age- and gender-matched controls were recruited from among healthy patients attending the same hospital during the same study period.

Informed consent was received from all patients. The study protocol was approved by the Ethics Committee Atatürk University School of Medicine, Erzurum, Turkey.

Endoscopic examination

Nasal obstruction and NP diagnosis were based on history, symptoms, anterior rhinoscopy findings and endoscopic examination. NP was staged according to endoscopic findings (10) such as Stage 0: No polyps, Stage 1: Mild polyposis, Stage 2: Intermediate polyposis, and Stage 3: Severe polyposis.

For endoscopic examination, 4 mm rigid 0 and 30-degree endoscope (Karl-Storz® GmbH&Co. Tuttlingen, Germany) were used. The study group comprised patients with Stage 2 or 3 nasal obstructions and without any symptoms that could be attributed to right heart failure.

Echocardiography

Echocardiographic measurements of the patients were done in the left lateral position with Vingmed ultrasound system (Vingmed System 7, General Electric, Horten, Norway) using a 2.5 MHz transducer, under single lead electrocardiography monitoring. The measurements were performed, independently, by two cardiologists unaware of the groups. Parasternal long axis and apical four chamber images were recorded according to the recommendations of the American Society for Echocardiography. Parasternal long axis images were used for left ventricular end-diastolic diameter (LVED), left ventricular end systolic diameter (LVES) and left atrial diameter (LA) measurements. Following this left ventricular ejection fraction (LVEF) was calculated using the Teicholz method. Right atrial (RA) and right ventricular diastolic (RV) diameters were measured based on apical four chamber images (11). Systolic pulmonary arterial pressure (sPAP) was calculated with the simplified Bernoulli equation, by adding the right atrial pressure value (10 mmHg) to the value calculated using the tricuspid flow velocity, considering the diameter of vena cava inferior and the level of its collapse resultant from respiration. In the apical four -chamber imaging, pulse wave Doppler sampling volume was placed on the interception point of the right ventricle lateral wall with the tricuspid annulus and the peak systolic myocardial velocity (Sm), diastolic early (Em) and late (Am) wave-lengths were recorded (Fig. 1).

Strain/Strain rate imaging

First, the RV free wall was visualized parallel to the transducer in 2-dimensional imaging and the tissue velocity imaging (TVI) function frame rate was considered >100/s. Images were

obtained with the minimum possible angle and maximum frame rate, only including the RV free wall. Images including three consecutive sinus beats at end of the expiratory stage were digitally recorded. The colored Doppler myocardial images were analyzed offline using software (EchoPC, GE Vingmed, Horten, Norway). Longitudinal peak systolic strain (PSS) (Fig. 2) and peak systolic strain rate (PSSR) (Fig. 3) were measured at the RV free wall basal-mid and apical segments (12). Distance between the two measured points was chosen as 10 mm. Three segments were analyzed for each individual in both groups. Measurements were performed two times on separate days, and average values were taken. Weak images and segments with an angular difference >30 degrees were excluded from the study.

Statistical analyses

Data were analyzed with SPSS 11.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate whether the variables were normally distributed. The continuous variables were expressed as mean±standard deviation; categorical data were expressed as percent (%). Student's t-test was used to compare parametric variables between the patient and control groups, Chi-square test - categorical variables, and Pearson's correlation analysis was used to assess the correlation between pulmonary arterial systolic pressure and S and SR parameters. Inter-observer and intra-observer agreements were assessed by Bland-Altman analysis. A p value <0.05 was considered statistically significant.

Results

Age, gender, body mass index (BMI), and systolic and diastolic blood pressures were similar in both groups. In echocardiographic examination, LVED dimension, interventricular septum (IVS) thickness, LA, RA and RV diameters were similar in both groups. LVEF displayed no difference between the two groups whereas LVED dimension was significantly higher in Group 1 than Group 2; on the other hand, PAPs was significantly higher in Group 1 (p<0.001). The demographic and echocardiographic data for groups were listed in Table 1. TDI findings from the right ventricular lateral wall tricuspid annulus revealed that Sm, Em and Am velocities were similar in both groups (Table 2).

Assessment of strain rate and strain values

PSS and PSSR values from the RV lateral wall basal, mid and apical segments were significantly lower in the NP group compared to the control group. The total rate of segments that could not be examined in patient and control groups was 3% for S and 7% for SR. Moreover, intra-observer and inter-observer variables were computed 5% and 7.2%, respectively. PSS and PSSR values for all segments and their statistical comparisons were demonstrated in Table 3.

Comparison of Stage 2 and Stage 3 NP patients revealed that only the SR value for the RV mid-segment was significantly different (p=0.02); other segments did not show a significant difference in S and SR values (Table 4).

Table 1. Demographic and echocardiographic data of nasal polyposis patients and control subjects

Variables	Group 1 (n=40)	Group 2 (n=25)	*p
Age, years	36±9	38±6	0.41
Gender, M/F	25/15	16/9	0.91
BMI, kg/m ²	25.29±2.4	24.75±2.0	0.35
SBP, mmHg	116±12.9	112.6±11.2	0.28
DBP, mmHg	74.0±7.5	70.8±7.7	0.10
LVDD, mm	46.6±3.9	44.0±4.1	0.01
LVSD, mm	30.2±3.1	28.8±3.5	0.09
IVS, mm	9.43±1.4	9.40±1.3	0.94
LVEF, %	63.2±4.0	64.3±4.6	0.28
LA, mm	34.4±2.7	33.0±2.9	0.09
RA, mm	34.5±4.0	34.8±2.9	0.78
RV, mm	34.6±4.6	35.0±2.7	0.71
sPAP, mmHg	31.2±5.8	19.7±4.3	<0.001

Results are shown as mean±standard deviation and numbers
*Unpaired Students' t-test and Chi-square test
BMI - body mass index, DBP - diastolic blood pressure, F - female, IVS - interventricular septum, LA - left atrium, LVDD - left ventricular diastolic diameter, LVEF - left ventricular ejection fraction, LVSD - left ventricular systolic diameter, M - male, RA - right atrium, RV - right ventricle, SBP - systolic blood pressure, sPAP - systolic pulmonary artery pressure

Table 2. Tissue Doppler findings of the RV lateral wall tricuspid annulus

Variables	Group 1 (n=40)	Group 2 (n=25)	*p
Sm, cm/s	13.1±1.6	13.2±1.6	0.98
Em, cm/s	12.9±3.4	13.1±3.0	0.77
Am, cm/s	12.3±2.5	13.2±2.1	0.05

Results are shown as mean±standard deviation
*Unpaired Students' t-test
Am - late diastolic myocardial velocity, Em - early diastolic myocardial velocity, RV - right ventricular, Sm - systolic myocardial velocity

Pulmonary arterial pressure level was inversely correlated with RV S and SR values in all segments (Table 5).

Discussion

This study showed a subclinical level of impairment on right ventricular functions with S/SR echocardiographic methods in patients with NP.

Cardiovascular complications of NP are attributed to the chronic upper airway obstruction. Chronic alveolar hypoxia may lead to hypoxemic pulmonary vasoconstriction within time, which may result in hypertension and right ventricular heart failure (6, 13, 14). Chronic upper airway obstruction will increase the pressure load of the right ventricle and this in turn will lead to hypertrophy and subendocardial ischemia by increasing the RV wall tension, which eventually ends up with RV dysfunction (15). Pulmonary hypertension may not be an early sign. Fuster et al. (16) reported that the mean time from initial symptoms to diagnosis was 1.9 years in patients with PH. Thus, early diagnosis is of utmost importance in such patients.

Table 3. Peak systolic strain and strain rate values of the right ventricular lateral wall

	Peak systolic strain (%)			Peak systolic strain rate (/s)		
	Group 1 (n=40)	Group 2 (n=25)	*p	Group 1 (n=40)	Group 2 (n=25)	*p
Basal	-19.6±3.0	-22.9±2.60	<0.001	-2.16±0.32	-2.44±0.40	0.003
Mid	-22.0±2.90	-24.2±2.30	0.002	-2.12±0.33	-2.44±0.35	<0.001
Apical	-20.7±3.50	-23.4±2.80	0.002	-2.11±0.38	-2.51±0.32	<0.001

Results are shown as mean±standard deviation
*Unpaired Students' t-test

Table 4. Peak systolic strain and strain rate values of the right ventricular lateral wall in Stage 2 and Stage 3 nasal polyposis patients

	Peak systolic strain (%)		*p	Peak systolic strain rate (/s)		*p
	Stage 2 (n=25)			Stage 3 (n=15)		
Basal	-20.4±3.90	-18.9±2.0	0.12	-2.26±0.36	-2.09±0.27	0.1
Mid	-22.8±2.90	-21.3±2.70	0.1	-2.25±0.33	-2.09±0.27	0.019
Apical	-21.0±3.20	-20.4±3.80	0.58	-2.16±0.42	-2.07±0.36	0.46

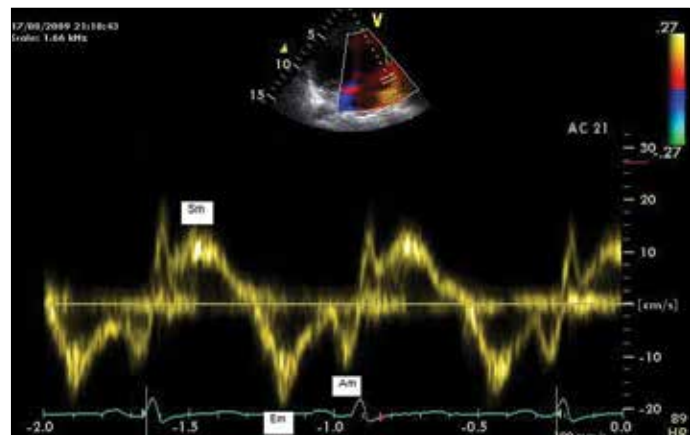
Results are shown as mean±standard deviation
*Unpaired Students' t-test

Table 5. Correlation between pulmonary arterial pressure and right ventricular lateral wall peak systolic strain and peak systolic strain rate

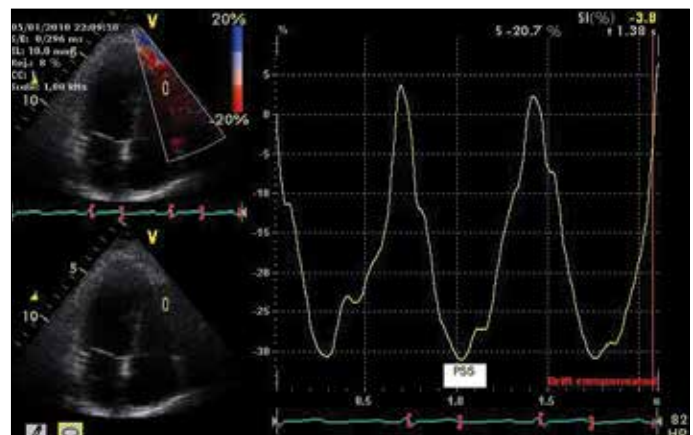
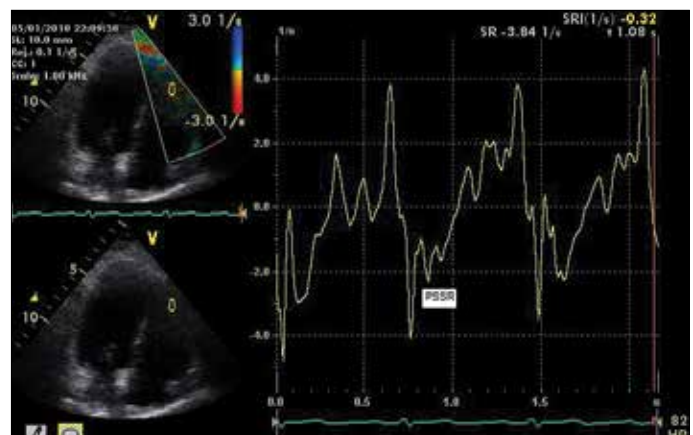
Pulmonary arterial pressure	*R	*p
Basal RV PSS	-0.55	<0.001
Mid RV PSS	-0.45	<0.001
Apical RV PSS	-0.40	0.001
Basal RV PSSR	-0.49	<0.001
Mid RV PSSR	-0.55	<0.001
Apical RV PSSR	-0.49	<0.001

*Pearson's correlation analysis
PSS - peak systolic strain, PSSR - peak systolic strain rate, RV - right ventricle

Echocardiography is the method of choice to assess RV functions in daily practice. Studies assessing RV functions have shown that the TDI technique is practical and handy, and has potential value (17, 18). However, TDI has some limitations such as the negative effect on velocity of the increasing distance between the heart and the probe due to the elongation of the myocardium, transfer of active and passive deformation in neighboring segments and respiration (8). S and SR techniques have been developed from tissue Doppler velocities to overcome those problems. Recent studies have suggested that S/SR echocardiography methods are superior to tissue Doppler velocities in assessing myocardial functions (19-21). The assessment of RV longitudinal functions in our study revealed that while the Sm, Em and Am values did not display a significant difference between the patient and the control groups in the tissue Doppler arm, S/SR parameters revealed that the RV functions were significantly decreased in the patient group compared to the control patients.

**Figure 1. Tissue Doppler imaging of the right ventricular lateral wall tricuspid annulus in a patient with nasal polyposis**

Am - late diastolic myocardial velocity. Em - early diastolic myocardial velocity, Sm - systolic myocardial velocity

**Figure 2. Peak systolic strain (PSS) measurement of the right ventricular lateral wall mid segment in a patient with nasal polyposis****Figure 3. Peak systolic strain rate (PSSR) measurement of the right ventricular lateral wall mid segment in a patient with nasal polyposis**

Although the PAPs values of the patients were intermediately increased (31.2 ± 5.8) in our study group, they had no symptom attributable to RV insufficiency. Moreover, RA and RV diameters were within normal range in conventional echocardiography (34.6 ± 4.6 mm and 34.5 ± 4.0 mm respectively). Our patient and

control groups had similar clinical and conventional echocardiographic findings. However, examination with S/SR echocardiography revealed a subclinical dysfunction in the patient group. Moreover, there was a significant negative correlation between the PAPs and S/SR values in the RV basal-mid and apical segments. In other words, S/SR values decreased as the PAPs increased. Early detection of such findings may be fundamental for the treatment of patients with NP.

Studies about the value of S/SR echocardiography techniques to assess RV functions have reported that these methods are practical and effective to show RV functions. Vitarelli et al. (22) categorized patients with obstructive lung disease and PH according to their PAPs values as Group 1 (<35 mmHg) and Group 2 (>35 mmHg) and compared them with healthy controls. They found that the decrease in RV S/SR values were correlated with the extent of PAPs and pulmonary function test results and they suggested that S/SR values might be clinical prognostic markers of RV insufficiency. Lopez-Candales et al. (23) reported that the RV longitudinal free wall S values were significantly decreased in patients with a high mean pulmonary arterial pressure (78 ± 24 mmHg) compared to healthy individuals. A review by Gondi et al. (9) on the clinical usefulness of RV TDI suggested that all data obtained by comparing various patient populations revealed that TDI was an acceptable, reproducible and practical additional echocardiographic parameter in assessing RV systolic and diastolic functions. However, they suggested that such patients had subclinical conditions that could not be detected with conventional echocardiography.

Study limitations

Similar to previous studies, the major limitation in our study was angle dependence and artifacts. The angle difference increases from the basis to the apical part of the heart. The amount of deformation increases when the angle difference exceeds 30 degrees. We took care to keep the tissue direction less than 30 degrees and parallel to ultrasound waves. Besides, we tried to keep the frame rates high to decrease the margin of error. Lack of magnetic resonance imaging and/or invasive techniques, which are considered the gold standard in the assessment of RV functions, is another major limitation. However, studies have shown that S/SR parameters correlate well with invasive hemodynamic parameters. Other limitation is relatively small number of patients included in this study.

Conclusion

The results of our study suggest that NP patients who are clinically asymptomatic and have normal RV functions with conventional echocardiography have subclinical RV longitudinal dysfunction with S/SR echocardiography. S/SR echocardiography may be used as a reliable determinant of RV systolic functions in patients with no right heart failure findings.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - E.Ş., Z.Ş.; Design - Z.Ş.; Supervision - Z.Ş.; Resource - C.K., H.Ü., E.Ş.; Materials - M.H.T.; Data collection&/or Processing - M.H.T., E.Ş.; Analysis &/or interpretation - M.H.T., E.Ş.; Literature search - C.K., E.G.; Writing - Z.Ş., E.G.; Critical review - E.G., H.Ü.; Other - C.K.

References

1. Pawankar R. Nasal polyposis: An update. *Curr Opin Allergy Clin Immunol* 2003; 3: 1-6. [\[CrossRef\]](#)
2. Fidan V, Aksakal E. Effects of endoscopic sinus surgery on pulmonary artery pressure in patients with extensive nasal polyposis. *J Craniofac Surg* 2011; 22: 592-3. [\[CrossRef\]](#)
3. Rappai M, Collop N, Kemp S, DeShazo R. The nose and sleep related disordered. *Chest* 2003; 124: 2309-23. [\[CrossRef\]](#)
4. Guilleminault C, Korobkin R, Winkle R. A review of 50 children with obstructive sleep apnea syndrome. *Lung* 1981; 159: 275-87. [\[CrossRef\]](#)
5. Naiboğlu B, Deveci S, Duman D, Kaya KS, Toros S, Kinis V, et al. Effect of upper airway obstruction on pulmonary arterial pressure in children. *Int J Pediatr Otorhinolaryngol* 2008; 72: 1425-9. [\[CrossRef\]](#)
6. Duman D, Naiboğlu B, Esen HS, Toros SZ, Demirtunç R. Impaired right ventricular function in adenotonsillar hypertrophy. *Int J Cardiovasc Imaging* 2008; 24: 261-7. [\[CrossRef\]](#)
7. Nikitin NP, Witte K. Application of tissue Doppler imaging in cardiology. *Cardiology* 2004; 101: 170-84. [\[CrossRef\]](#)
8. Voight JU, Flachskampf EA. Strain and strain rate, new and clinically relevant echo parameters of regional myocardial function. *Z. Kardiol* 2004; 93: 249-58.
9. Gondi S, Dokainish H. Right ventricular tissue Doppler and strain imaging: Ready for clinical use? *Echocardiography* 2007; 24: 522-32. [\[CrossRef\]](#)
10. Johansen LV, Illum P, Kristensen S, Winther L, Vang Petersen S, Synnerstad B. The effect of budesonide (Rhinocort) in the treatment of small and medium sized nasal polyps. *Clin Otolaryngol* 1993; 18: 524-7. [\[CrossRef\]](#)
11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on standards, subcommittee on quantitation of two-dimensional echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358-7.
12. Gilman G, Khandheria BK, Hagen ME, Abraham TP, Seward JB, Belohlavek M. Strain rate and strain: a step-by-step approach to image and data acquisition. *J Am Soc Echocardiogr* 2004; 17: 1011-20. [\[CrossRef\]](#)
13. Abd El-Moneim ES, Badawy BS, Atya M. The effect of adenoidectomy on right ventricular performance in children. *Int J Pediatr Otorhinolaryngol* 2009; 73: 1584-8. [\[CrossRef\]](#)
14. Menashe VD, Farrehi C, Miller M. Hypoventilation and cor pulmonale due to chronic upper airways obstruction. *J Pediatr* 1965; 67: 198-203. [\[CrossRef\]](#)
15. Chaudry KR, Ogawa S, Pauletto FJ. Biplane measurement of left and right ventricular volumes using wide-angle cross sectional echocardiography. *Am J Cardiol* 1978; 4: 391-404. [\[CrossRef\]](#)

16. Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL. Primary pulmoner hypertension: natural history and the importance of thrombosis. Circulation 1984; 70: 580-7. [\[CrossRef\]](#)
17. Moustapha A, Lim M, Saikia S, Kaushik V, Kang SH, Barasch E. Interrogation of the tricuspid annulus by Doppler tissue imaging in patients with chronic pulmonary hypertension: implications for the assessment of right ventricular systolic and diastolic function. Cardiology 2001; 95: 101-4. [\[CrossRef\]](#)
18. Rajdev S, Nanda NC, Patel V, Singh A, Mehmood F, Vengala S, et al. Tissue Doppler assessment of longitudinal right and left ventricular strain and strain rate in pulmonary artery hypertension. Echocardiography 2006; 23: 872-9. [\[CrossRef\]](#)
19. Hashimoto I, Li X, Hejmadi Bhat A, Jones M, Zetts AD, Sahn DJ. Myocardial strain rate is a superior method for evaluation of left ventricular subendocardial function compared with tissue Doppler imaging. J Am Coll Cardiol 2003; 42: 1574-83. [\[CrossRef\]](#)
20. Artis NJ, Oxborough DL, Williams G, Pepper CB, Tan LB. Two-dimensional strain imaging: a new echocardiographic advance with research and clinical applications. Int J Cardiol 2008; 123: 240-8. [\[CrossRef\]](#)
21. Greenberg NL, Firstenberg MS, Castro PL, Main M, Travaglini A, Odabashian JA, et al. Doppler-derived myocardial systolic strain rate is a strong index of left ventricular contractility. Circulation 2002; 105: 99-105. [\[CrossRef\]](#)
22. Vitarelli A, Conde Y, Cimino E, Stellato S, D'Orazio S, D'Angeli I, et al. Assessment of right ventricular function by strain rate imaging in chronic obstructive pulmonary disease. Eur Respir J 2006; 27: 268-75. [\[CrossRef\]](#)
23. Lopez-Candales A, Dohi K, Bazaz R, Edelman K. Relation of right ventricular free wall mechanical delay to right ventricular dysfunction as determined by tissue Doppler imaging. Am J Cardiol 2005; 96: 602-6. [\[CrossRef\]](#)

*Kalbi mecruha haber verme sakın yaresini
Koyuver çirpına dursun arasın çaresini
Bozma gel! hasta ile hastalığın aresini
Belki Allah yaratır çaresizin çaresini.*

*Na ümit etme tabip hastayı dermanından
İhtiraz üzre bulun his eyle iz'anından
Kesmez ümidini kul rabbinin ihsanından
Belki Allah yaratır çaresizin çaresini.*

Dr. Ali Paşa

Value of stress echocardiography in mitral stenosis

Mitral darlığının değerlendirilmesinde stres ekokardiyografinin değeri

Kadriye Orta Kılıçkesmez, Serdar Küçükoglu

Department of Cardiology, Institute of Cardiology, İstanbul University, İstanbul-Turkey

ABSTRACT

Mitral stenosis (MS) is a common disease that causes substantial morbidity. Timely recognition and treatment of the mitral stenotic lesion is very important. Stress echocardiography plays an important role in evaluating asymptomatic patients with significant mitral stenosis and symptomatic patients with only mild disease at rest. In patients with mitral stenosis, stress echocardiography protocols assess for the change in the mean transmitral pressure gradient and a peak pulmonary artery systolic pressure during exercise. In this review, clinical use of stress echocardiography in patients with mitral stenosis is summarized. (*Anadolu Kardiyol Derg 2013; 13: 257-60*)

Key words: Mitral stenosis, stress echocardiography, exercise test, dipyridamole, dobutamine, pulmonary artery systolic pressure

ÖZET

Mitral darlığı önemli morbiditeye neden olan bir hastalıktır. Mitral darlığının zamanında tanınması ve tedavi edilmesi önemlidir. Stres ekokardiyografi ileri düzeyde mitral darlığı olan semptomsuz ve orta düzeyde mitral darlığı olup semptomlu olan hastaların değerlendirilmesinde önemli rol oynar. Stres ekokardiyografi protokolü ile ortalama mitral kapak gradyanı ve pulmoner arter sistolik basıncında egzersiz ile oluşan değişiklik saptanır. Bu derlemede, mitral darlığı olan hastalarda stres ekokardiyografinin yeri özetlenmiştir. (*Anadolu Kardiyol Derg 2013; 13: 257-60*)

Anahtar kelimeler: Mitral darlık, stres ekokardiyografi, egzersiz testi, dipiridamol, dobutamin, pulmoner arter sistolik basıncı

Introduction

Several diseases have been accepted as pathological causes for mitral valve stenosis (MS), especially rheumatic valvular disease is still a prevalent in underdeveloped and developing countries (1). The main features are leaflet thickening, nodularity, and commissural fusion, all of which result in narrowing of the valve to the shape of a fish mouth. The leaflets might be calcified. Chordal fusion and shortening adds a further resistance to blood flow (2). Timely recognition and treatment of the underlying mitral stenotic lesion can prevent development of irreversible pulmonary hypertension, ventricular dysfunction and other complications (3). Patient management involves monitoring for clinical symptoms or functional deterioration assessed

by echocardiography and Doppler examination. While resting values of mitral gradients and pulmonary arterial pressures do not always reflect the severity of the disease, stress echocardiography may provide the necessary clues to determine the clinical and hemodynamic impact of MS (4).

This review evaluates whether the use of stress echocardiography to assess disease severity and to determine the optimal time for either surgical or percutaneous intervention of mitral stenosis.

Clinical importance

Stress echocardiography plays very important role in evaluating patients with mitral stenosis. Hence, guidelines of both the American College of Cardiology/American Heart Association

Address for Correspondence/Yazışma Adresi: Dr. Kadriye Orta Kılıçkesmez, İstanbul Üniversitesi Kardiyoloji Enstitüsü, Kardiyoloji Anabilim Dalı, Haseki, İstanbul-Türkiye Phone: +90 212 459 20 00 Fax: +90 212 459 20 33 E-mail: kadriye11@yahoo.com

Accepted Date/Kabul Tarihi: 16.08.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.074



(ACC/AHA) and European Society of Cardiology (ESC) have placed emphasis on the role of exercise testing to provide objective evidence of exercise capacity, symptom status and echocardiographic parameter (1, 5). Advances in diagnosis and risk stratification, progress in percutaneous balloon valvuloplasty, surgical options including closed or open valvotomy and valve replacement have led to improved outcomes of patients with valvular heart disease in the past 5 decades (1). The most important indication for intervention in patients with significant valve disease (mitral valve area $<1.5 \text{ cm}^2$) is the development of symptoms, as emphasized in recent ACC/AHA and ESC guidelines (1, 5). Although Doppler echocardiographic examination at rest is now the preferred imaging modality for the evaluation of patients with cardiac valvular disease, the current ACC/AHA guidelines have given a class I recommendation for stress echocardiography in patients with mitral stenosis and discordance between symptoms and stenosis severity (1).

Stress echocardiography

Stress echocardiography for mitral valve disease is performed via both exercise and pharmacologic protocols. The measurement of pulmonary artery pressures and mean transmitral pressure gradient during stress echocardiography can help to distinguish those who could benefit from valvuloplasty or valve replacement from those who should be maintained on medical therapy (6-8).

General test protocol

Stress echocardiography for mitral stenosis is performed with either exercise or pharmacologic stress. Exercise echocardiography is usually preferred over pharmacological stress because it provides information about exertional symptoms and blood pressure response (6).

Exercise test: Exercise echocardiography is often used to assess functional capacity and the hemodynamic response in patients with mitral stenosis (9). Exercise echocardiography can be performed using either a treadmill or a bicycle protocol. Treadmill exercise can be performed with Bruce or modified Bruce protocols, and bicycle exercise echocardiography is performed during either an upright or a recumbent posture. Workload is gradually increased until the patient achieves target heart rate or develops symptoms of fatigue or shortness of breath. Images were obtained at baseline during rest and immediately after discontinuation of exercise. The most important advantage of bicycle exercise is the chance to obtain images during the various levels of exercise. When a treadmill test is performed, scanning during exercise is not feasible, most protocols rely on immediate post exercise imaging. Therefore, the patient is moved immediately from the treadmill to an imaging bed and that imaging may be completed within 1-2 min (9). The advantage of treadmill exercise echocardiography is that it is the most commonly practiced protocol, and patients usually achieve higher workloads in exercise (10). On the other hand, the disadvantage

is that the data acquisition is restricted to images at baseline and post-maximal exercise, and rapid position changes after exercise are required. The collection of echocardiographic data should be performed within the 1-2 minutes of the maximal exercise. The advantage of bicycle exercise echocardiography is the chance to obtain images during the various level of exercise, but elderly patients may not exercise well in this position (9).

Dobutamine: If pharmacologic stress is necessary, the standard dobutamine protocol using continuous intravenous infusion is used (3, 11, 12). Dobutamine echocardiography was performed using three-min stages and starting at 5 mcg/kg/minute , followed by 10, 20, 30, and $40 \text{ } \mu\text{g/kg per min}$. Atropine (total dose $\leq 2 \text{ mg}$) was administered at the start of the $40 \text{ } \mu\text{g/kg per min}$ stage if needed to augment heart rate (9).

Dobutamine stress echocardiography is a good alternative if the patient cannot exercise (6).

Dipyridamole: The standard dipyridamole protocol consists of an intravenous infusion of 0.84 mg/kg over 10 min, in two separate infusions. If no endpoint is reached, atropine is added. Aminophylline (240 mg iv) should be available for immediate use in case an adverse dipyridamole-related event occurs (9).

Adenosine: Adenosine can be used, infused at a maximum dose of $140 \text{ } \mu\text{g/kg/min}$ over 6 min (9).

Pacing: Pacing is started at 100bpm and increased every 2 min by 10 bpm until the target heart rate is achieved or until other standard endpoints are reached (9).

Accordingly, we can identify two groups of patients whose symptoms do not correlate with the resting mitral valve area and gradient. The first group, who lead a sedentary life style and do not complain of symptoms, but have significant mitral stenosis. The second group, whose severe symptomatology appears to be out of proportion to their resting mitral valve area ($>1.5 \text{ cm}^2$). An increase in the mitral valve area without significant changes in the transmitral gradient and pulmonary artery pressure during exercise will point less severe disease in second group from the first group (3).

The threshold values proposed by the ACC/AHA guidelines for consideration for intervention are a mean transmitral pressure gradient $>15 \text{ mmHg}$ or a peak pulmonary artery systolic pressure $>60 \text{ mmHg}$ during stress. In patients with pulmonary artery pressures or valve gradients above these values, percutaneous balloon valvotomy or surgical intervention is recommended, even for patients with apparently moderate mitral stenosis at rest (1, 9).

In patients who have predominantly mitral stenosis peak exercise pulmonary artery systolic pressure is inversely related to exercise capacity (13). The transmitral mean pressure gradient commonly increases during exercise, regardless of the severity of stenosis, in accordance with exercise duration and exercise induced changes in cardiac output (7, 12). Symptoms like dyspnea and fatigue that most of these patients developed during the test can be attributed to the elevated left atrial pressure caused by flow-dependent increases in gradients across

the stenotic mitral valve. Tunick et al. (4) have shown that patients with mitral stenosis who were limited by dyspnea developed a greater increase in pulmonary artery pressure during stress testing than those who were limited by fatigue. In addition, Brochet et al. (14) investigated the role of values recorded during the first stage of exercise Doppler echocardiography in asymptomatic patients. Mitral stenosis severity and rest and peak systolic pulmonary artery pressures were not different between patients who did and did not develop dyspnea. Progressions of mean gradient and relative peak systolic pulmonary artery pressure (sPAP) (ratio of sPAP/baseline sPAP) were significantly greater in patients who developed dyspnea compared with those who did not, whereas no difference was observed for absolute systolic pulmonary artery pressure progression. Onset of dyspnea was associated with a high increase of relative peak systolic pulmonary artery pressure, but not with the 60 mmHg peak systolic pulmonary artery pressure threshold. Grimaldi et al. (8) reported, predictors of adaptation to exercise were age, mean pulmonary gradient and systolic pulmonary pressure, according to multivariate analysis, best predictor was resting mean pressure gradient.

Previous studies of MS have reported an association between the echocardiographic findings and functional class and increase in plasma levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) (15). Tanboğa et al. (16) showed BNP level and sPAP better correlated with mitral valve (MV) resistance than mitral valve area (MVA) and mean MV gradient. Uçar et al. (17) found elevated plasma BNP levels in pure MS in sinus rhythm and plasma BNP levels correlated with disease severity, such as transmitral gradient, sPAP, functional capacity, left ventricular end -systolic diameter.

In a recent study by our group, we investigated whether elevated NT pro-BNP predicts pulmonary artery systolic pressure increase on exercise stress echocardiography in asymptomatic or mildly symptomatic patients with moderate to severe mitral stenosis. We demonstrated, NT pro-BNP levels correlate with functional class and echocardiographic findings in patients with mitral stenosis and indicate exercise induced augmentation of peak pulmonary artery systolic pressure >60 mmHg (18). Exercise echocardiographic methods have certain limitations the results may be affected by the person who performs the echocardiography, this point that the measurement of NT pro-BNP appears to be the method to be employed in the assessment of the severity of MS, for its features as shortness, simplicity, objectivity, and being noninvasive. Results of these studies suggest that natriuretic peptide testing may be an addition to the information obtained by echocardiography in the assessment of MS in clinical practice.

New stress echocardiographic techniques

3D echocardiography

3D echocardiography enables visualization from both left ventricular and left atrial side perspectives. Evaluation of the mitral apparatus using 3D echocardiography is most useful defining the

extent and location of pathology, severity of valvular dysfunction. Three -dimensional stress echocardiography has been performed with exercise, dobutamine and dipyridamole. Multislice views from 3D echocardiography stress studies should be interpreted in a similar 2D stress studies evaluating stress-induced wall motion and thickening abnormalities (19, 20).

2D Strain echocardiography

Tissue Doppler imaging and derived strain and strain rate measurement have offered alternatives for quantification of regional contraction at rest or during stress. Strain, describes myocardial deformation, that is, the fractional change in the myocardial segment. Strain rate, is the rate of change in strain and usually expressed as 1/sec or sec⁻¹. These techniques provide incremental information in clinical settings. For both techniques, the accuracy of measurement, however, depends on image quality and the accuracy of tracking. In expert hands, strain and strain rate parameters can improve accuracy and prognostic value of stress test echocardiogram (21).

Future clinical trials, especially in mitral stenosis patients, needs include standardization and acquisition.

Conclusion

The role of stress echocardiography in assessing mitral stenosis is evolving. In mitral stenosis a patient whose symptom complex is discordant to resting hemodynamic data, stress echocardiography has been successful in clarifying the extent of valvular involvement. Together with exercise capacity and symptomatic responses to exercise, it provides the clinician with diagnostic and prognostic information that can contribute to subsequent clinical decisions. Furthermore, with a better understanding of its utility, there is an expected increase in the use of exercise echocardiography to help management decisions in patients with mitral stenosis.

All of the above-mentioned considerations clinical trials should be designed and developed on the basis of a thorough knowledge of physio-pathological, prognostic, and technical characteristics of stress echo-Doppler techniques and parameters, choosing the most performable and reproducible.

Conflict of interest: None declared.

Peer-Review: Internally peer-reviewed.

Authorship contributions: Concept - K.O.K., S.K.; Design - K.O.K., S.K.; Supervision - S.K.; Analysis &/or interpretation - K.O.K., S.K.; Literature search - K.O.K.; Writing - K.O.K.; Critical review - S.K.

References

1. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al. 2006 Writing Committee Members; American

- College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2008; 118: 523-661. [\[CrossRef\]](#)
2. Chandrashekar Y, Westaby S, Narula J. Mitral stenosis. *Lancet* 2009; 374: 1271-83. [\[CrossRef\]](#)
 3. Wu WC, Aziz GF, Sadaniantz A. The use of stress echocardiography in the assessment of mitral valvular disease. *Echocardiography* 2004; 21: 451-8. [\[CrossRef\]](#)
 4. Tunick PA, Freedberg RS, Gargiulo A, Kronzon I. Exercise Doppler echocardiography as an aid to clinical decision making in mitral valve disease. *J Am Soc Echocardiogr* 1992; 5: 225-30.
 5. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al. Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007; 28: 230-68.
 6. Hecker SL, Zabalgoitia M, Ashline P, Oneschuk L, O'Rourke RA, Herrera CJ. Comparison of exercise and dobutamine stress echocardiography in assessing mitral stenosis. *Am J Cardiol* 1997; 80: 1374-7. [\[CrossRef\]](#)
 7. Schwammenthal E, Vered Z, Agranat O, Kaplinsky E, Rabinowitz B, Feinberg MS. Impact of atrioventricular compliance on pulmonary artery pressure in mitral stenosis: an exercise echocardiographic study. *Circulation* 2000; 102: 2378-84. [\[CrossRef\]](#)
 8. Grimaldi A, Olivetto I, Figini F, Pappalardo F, Capritti E, Ammirati E, et al. Dynamic assessment of 'valvular reserve capacity' in patients with rheumatic mitral stenosis. *Eur Heart J Cardiovasc Imaging* 2012; 13: 476-82. [\[CrossRef\]](#)
 9. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur J Echocardiogr* 2008; 9: 415-37. [\[CrossRef\]](#)
 10. Cheriex EC, Pieters FA, Janssen JH, de Swart H, Palmans-Meulemans A. Value of exercise Doppler-echocardiography in patients with mitral stenosis. *Int J Cardiol* 1994; 45: 219-26. [\[CrossRef\]](#)
 11. Sagar KB, Wann LS, Paulson WJ, Lewis S. Role of exercise Doppler echocardiography in isolated mitral stenosis. *Chest* 1987; 92: 27-30. [\[CrossRef\]](#)
 12. Braverman AC, Thomas JD, Lee RT. Doppler echocardiographic estimation of mitral valve area during changing hemodynamic conditions. *Am J Cardiol* 1991; 68: 1485-90. [\[CrossRef\]](#)
 13. Song JK, Kang DH, Lee CW, Lee SG, Cheong SS, Hong MK, et al. Factors determining the exercise capacity in mitral stenosis. *Am J Cardiol* 1996; 78: 1060-2. [\[CrossRef\]](#)
 14. Brochet E, Détaint D, Fondard O, Tazi-Mezalek A, Messika-Zeitoun D, lung B, et al. Early hemodynamic changes versus peak values: what is more useful to predict occurrence of dyspnea during stress echocardiography in patients with asymptomatic mitral stenosis? *J Am Soc Echocardiogr* 2011; 24: 392-8. [\[CrossRef\]](#)
 15. Selçuk MT, Selçuk H, Maden O, Erbay AR, Temizhan A, Aksu T, et al. The effect of percutaneous balloon mitral valvuloplasty on N-terminal- pro B- type natriuretic peptide plasma levels in mitral stenosis. *Int Heart J* 2007; 48: 579-90. [\[CrossRef\]](#)
 16. Tanboğa IH, Kurt M, Ekinci M, Işık T, Kaya A, Bilen E, et al. Hemodynamic assessment of mitral stenosis: mitral valve resistance as an echocardiographic index. *J Heart Valve Dis* 2012; 21: 203-7.
 17. Uçar O, Bayar N, Karagöz A, Aydoğdu S. Valvular heart disease: plasma B-type natriuretic peptide levels in patients with pure rheumatic mitral stenosis. *Acta Cardiol* 2012; 67: 59-64.
 18. Kılıçkesmez KO, Özkan AA, Abacı O, Çamlıca H, Koças C, Kaya A, et al. Serum N-terminal brain natriuretic peptide indicates exercise induced augmentation of pulmonary artery pressure in patients with mitral stenosis. *Echocardiography* 2011; 28: 8-14.
 19. Hien MD, Rauch H, Lichtenberg A, De Simone R, Weimer M, Ponta OA, et al. Real-time three-dimensional transesophageal echocardiography: Improvements in Intraoperative Mitral Valve Imaging. *Anesth Analg* 2012 Jul 13. [Epub ahead of print]
 20. Little SH. Three-dimensional echocardiography to quantify mitral valve regurgitation. *Curr Opin Cardiol* 2012; 27: 477-84. [\[CrossRef\]](#)
 21. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G, et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. *Eur J Echocardiogr* 2011; 12: 167-205. [\[CrossRef\]](#)

Epicardial adipose tissue: a review of physiology, pathophysiology, and clinical applications

Epikardiyal yağ dokusu: Fizyoloji, patofizyoloji ve klinik uygulamalar hakkında bir derleme

Cihan Şengül, Olcay Özveren¹

Division of Cardiology, Gaziosmanpaşa Hospital, İstanbul-Turkey

¹Department of Cardiology, Faculty of Medicine, Yeditepe University, İstanbul-Turkey

ABSTRACT

Visceral fat tissue is an important predictor of cardio-metabolic diseases, carrying more risk than general fat accumulation. Epicardial fat, a particular form of visceral fat deposited around the heart, is considered an important cardiovascular risk predictor, in view of producing and releasing several adipo-cytokines. There is growing evidence about the physiological and metabolic importance of epicardial fat. Epicardial fat thickness and volume have both strong correlation between obesity, impaired fasting glucose, insulin resistance, metabolic syndrome, hypertension, diabetes mellitus, and atherosclerosis. Epicardial fat can be assessed by transthoracic echocardiography, cardiac magnetic resonance imaging, and computed tomography. In this article, we reviewed the anatomy, physiology, function, and the methods of assessment of epicardial fat tissue. We also have tried to discuss its relationship to metabolic syndrome and coronary atherosclerosis in the lights of recent findings. (*Anadolu Kardiyol Derg 2013; 13: 261-5*)

Key words: Epicardial fat, visceral fat, cardiac imaging, cardiometabolic risk

ÖZET

Kardiyo-metabolik hastalıkların önemli bir belirteci olan visseral yağ dokusu genel yağ birikiminden daha fazla risk oluşturmaktadır. Visseral yağın kalp etrafında depolanan özel bir şekli olan epikardiyal yağ, çok sayıda adipo-sitokin üretme ve salma yeteneği sayesinde önemli bir kardiyovasküler risk belirteci olarak düşünülmektedir. Epikardiyal yağın fizyolojik ve metabolik önemine dair artan deliller mevcuttur. Epikardiyal yağ kalınlığı ve hacminin her ikisinin de obezite, bozulmuş glikoz intoleransı, metabolik sendrom, hipertansiyon, diyabet ve ateroskleroz ile güçlü korelasyonları mevcuttur. Epikardiyal yağ transtorasik ekokardiyografi, kardiyak manyetik rezonans ve bilgisayarlı tomografi ile değerlendirilebilir. Bu yazıda epikardiyal yağ dokusunun anatomisini, fizyolojisini, fonksiyonunu ve değerlendirme metotlarını gözden geçirdik. Aynı zamanda metabolik sendrom ve koroner ateroskleroz ile ilişkisini son bilgiler ışığında tartışmaya çalıştık. (*Anadolu Kardiyol Derg 2013; 13: 261-5*)

Anahtar kelimeler: Epikardiyal yağ, visseral yağ, kardiyak görüntüleme, kardiyometabolik risk

Introduction

Anatomy and physiology of EAT

Cardiac fat tissue resides in three locations: epicardium, pericardium, and intracellular fat. Epicardial adipose tissue (EAT) is present on the surface of the heart between the myocardium and visceral pericardium and covers more than three quarters of the surface of the heart (1). EAT is concentrated in the atrioventricular and interventricular grooves, along the

major branches of the coronary arteries, around the atria, over the free wall of the right ventricle (RV) and over the apex of the left ventricle (LV) (2) in the normal adult population. EAT is supplied by side-branches of the coronary arteries similar to the microcirculation of the myocardium. Therefore, EAT can locally modulate both myocardium and coronary arteries (3, 4). There are sufficient data suggesting that there are differences between EAT and other visceral adipose tissue of the body. Microscopically EAT is composed of adipocytes which are smaller than those in cutaneous and other visceral fat depots, and inflammatory, stro-

Address for Correspondence/Yazışma Adresi: Dr. Cihan Şengül, Koşuyolu Mahallesi Huzur Apt. 158 Kadıköy, İstanbul-Türkiye
Phone: +90 505 335 05 96 Fax: +90 212 615 38 49 E-mail: drcsengul@yahoo.com

Accepted Date/Kabul Tarihi: 19.09.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 06.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.075



movascular and immune cells (5), but interestingly the number of adipocytes per gram of tissue is greatest in EAT. As fatty acid synthesis is greater in EAT, the rate of fatty acid breakdown is significantly higher than other fat depots of the body.

Both adipocytes and tissue macrophages have secretory properties in EAT and they are capable of producing adipokines and cytokines as in omental and mesenteric visceral adipose tissue. These adipokines and cytokines influence the myocardium and coronary arteries via two mechanisms (i.e. paracrine and vasocrine). Paracrine release of cytokines from EAT can traverse the coronary wall by diffusion from outside-to-inside and interact with cells in each layers of the vessel wall (6). On the other hand, in vasocrine signaling adipokines and free fatty acids might be released from EAT directly into *vasa vasorum* and be transported downstream into the coronary wall (7). Both of these mechanisms may be associated with atherogenesis.

Another function of EAT is the maintenance of fatty acid homeostasis. It may buffer the heart against excessively high circulating levels of fatty acids by its ability to rapidly take up and incorporate fatty acids. Furthermore, this fat depot serves as a local energy source for cardiac muscle in times of high demand (8). EAT might function similar to brown fat in order to defend the myocardium and coronary arteries against hypothermia (9). Finally, it is also proposed to buffer the coronary artery against the torsion induced by the arterial pulse wave and cardiac contraction (10).

EAT has cardioprotective properties through local secretion of anti-inflammatory and anti-atherogenic adipokines such as adiponectin and adrenomedullin. Recently, Iacobellis et al. (11) have demonstrated that chronic coronary artery disease (CAD) down regulated these adipokines. The Framingham offspring cohort revealed that EAT is greater in men than in women (12). However, some of echocardiographic studies disagree with the findings of Framingham cohort (13). There is also controversy whether age influences the amount of EAT. Smith et al. (14) demonstrated that there was no relationship between age and EAT in their autopsy study. Echocardiographic examination measuring the thickness of the EAT has supported their findings in a small subgroup (15). The Framingham offspring cohort demonstrated significant correlation between age and EAT (12).

Imaging techniques

Epicardial adipose tissue can easily be measured by transthoracic 2D-echocardiography. Echocardiograms can be obtained during cardiac cycles as the subject is the left lateral decubitus position. The investigators usually choose to measure epicardial fat on the free wall of the RV since it is accessible from both parasternal long and short axis views and includes the highest absolute epicardial fat layer thickness. Echo free space can be measured with optimal cursor orientation in each view. Iacobellis et al. (16) reported maximum EAT values at any site over the free wall of the RV is 1.8- 16.5 mm in healthy subjects. Echocardiographic epicardial fat thickness (EFT) reflects visceral adiposity rather than general obesity. Although Abbbara et al. (17) demonstrated

that echocardiography cannot give adequate window of all cardiac segments especially in obese subjects and is highly dependent on acoustic windows, the study demonstrated a good reproducibility with a coefficient of variation between two echocardiographers of only 3%. Echocardiography calculation of EFT on the free wall of the RV is in good reliability with EAT measurements with MRI ($r=0.91$, $p=0.001$) (16). EAT measurement with echocardiography in both clinical and research scenarios have several advantages, including its low cost, easy accessibility, rapid applicability and good reproducibility (18). Quantification of EAT with multislice computed tomography (CT) scanning can also easily be obtained. Measurement of the EAT volume on CT is usually performed by tracing the regions of interest on short axis views (19). EAT volume is obtained by adding up the traced areas which are measured from the apex of the heart to the center of the left atrium taking into account of the slice thickness. Automated computer assisted methods for quantification can also be used. In general, multidetector CT measurements of volumetric EAT are considered more reproducible than multidetector CT measurements of EAT. However, EAT is easier to perform and less time-consuming compared to the work for measurements of volumetric EAT; and therefore more suitable for research purposes. CT imaging of EAT can be done with high spatial resolution and atherosclerotic burden can also be measured in the same session. Disadvantages of CT are radiation exposition and high costs, which make it less practical for routine use.

MRI allows an accurate but more expensive and cumbersome measurement of EAT. Maximum EFT at the right ventricular free wall can be measured in different views: in a transversal 4-chamber view and in consecutive short-axis views covering the whole ventricle. In addition, mean EFT can be calculated by averaging results from the long-axis and short-axis measurements. MRI also allows quantitative assessment of the amount of EAT at the end diastole in the short-axis views covering the entire left and right ventricle by using the modified Simpson's rule with integration over the image slices (20).

Cardiometabolic risk and EAT

Metabolic syndrome

Metabolic syndrome (MS) is a cluster of several cardiovascular risk factors, which are found to be associated with two fold increase in risk of cardiovascular disease (CVD), mortality and stroke, and a 1.5-fold increase in risk of all-cause mortality (21). Insulin resistance and central obesity are the key components of MS, leading to glucose intolerance and dyslipidemia. The identification of predictors for premature atherosclerosis is crucial because subclinical atherosclerosis develops years before the clinical manifestations of CVD. EAT in MS influences on oxidative stress, endothelial dysfunction and vascular remodeling by adipokines. Recent findings suggest that EAT as a kind of visceral adipose tissue is associated with various components of metabolic syndrome as well as MS itself (22). Gorter et al. (19) docu-

mented in a CT study that patients with high body mass index (>27 kg/m²) have more EAT volume than those with a BMI <27 kg/m². Both MRI and echocardiographic studies support that EAT strongly and independently reflect intra-abdominal visceral fat (18-20).

Interestingly epicardial fat decreases after a very low calorie diet (6-month long weight loss program mean 20 kg by adhering to 900 kcal/day), bariatric surgery induced weight loss (average weight loss of 40 kg), or moderate aerobic exercise (23). The decrease in epicardial fat during weight loss is quicker and larger than the decrease in common indices of body fatness. This might be used for therapeutic target during weight-loss interventions including exercise or pharmaceutical treatments (24).

Glucose metabolism contributes to the development of atherosclerosis and relationship of EAT with it has been recently addressed. There is a strong correlation exists between fasting plasma glucose and EAT measured with echocardiography and CT (22). Recent studies demonstrated that both glucose transporter -4 and retinol binding protein levels affect local unfavorable glucose profile in EAT (25). Additionally, the relationship between epicardial fat and plasma insulin and mRNA expression of resistin which is a molecule linked with insulin resistance has been documented (16). Therefore, EAT seems to contribute to the development of insulin resistance. Iacobellis et al. (26) showed that cut-off value of EFT was 9.5 mm when insulin resistance was considered separately. In this study, highest values of EFT were found in patients with extremely high intra-abdominal fat and insulin resistance. In a recent study, an association has been found with the EAT volume and presence and extent of CAD in diabetic or non-diabetic patients (27).

Excess visceral fat is associated with increased blood pressure presumably through the renin-angiotensin system. The association of epicardial fat with hypertension has been demonstrated in some recent studies (28). We have demonstrated that EAT quantity increases in the non-hypertensive healthy patients with exaggerated blood pressure response to exercise stress testing. All these individuals were in risk for future hypertension (29). Echocardiographic EFT was found to be increased in untreated hypertensive patients with non-dipper blood pressure pattern (30). Increased EFT is also associated with changes in LV and RV mass and diastolic function (31). LV hypertrophy is related to a proportionate increase in EAT independent from obesity and age. Mechanical and biomolecular mechanisms could explain these associations (32).

Atherosclerosis

An increase of the quantity of EAT is associated with incident CAD and with major adverse cardiac events (33). Associations are independent from body mass index and other traditional risk factors. EAT is actually one of the factors contributing to CAD compared with other visceral adipose tissue (34). A recent meta-analysis of 2872 patients, Xu et al. (35) concluded that EFT and EAT volume are significantly increased in the CAD group compared to the non-CAD group. Patients in the higher

EAT tertile (≥ 100 mL) were more likely to have CAD compared with those in the lower EAT tertile (<100 mL) (risk ratio 0.69, 95% CI: 0.52, 0.92, $p=0.01$). The authors pointed that patients with coronary plaque had increased EAT volume compared with patients without coronary plaque. Another study demonstrated that EAT had significant correlation between both non-stenotic lesions and non-calcified plaque. Higher EAT volume was found in patients with noncalcified plaques than in patients with calcified plaques (36). This may be relevant for the development of acute coronary syndromes as non-calcified parts of a plaque contribute to plaque vulnerability (37). Furthermore, EAT volume is a strong and independent determinant of the presence of total coronary occlusions (38). EAT might affect the coronary microvascular function. Sade et al. (39) found that EFT was an independent predictor of diminished coronary flow reserve in women with angiographically normal coronary arteries.

EAT might also be used for screening the patients with intermediate risk of CAD. Bachar et al. (40) noted a strong positive correlation between EFT and coronary atherosclerosis quantified by the CT calcium score in 190 asymptomatic subjects with >1 cardiovascular risk factors. Therefore, EFT with low dose or without injection of contrast medium may be used as a coronary risk screening examination (40). A recent study has demonstrated an independent relationship between EFT and arterial stiffness, suggesting that echocardiographic EFT measurement could be an easy-to-measure tool for early detection of subclinical target organ damage (41).

EAT mediates the inflammatory process within the atherosclerotic plaque (42). The paracrine or vasocrine secretion of epicardial inflammatory adipokines, such as tumor necrosis factor alpha, plasminogen activator inhibitor-1, interleukin-6, interleukin -1b, monocyte chemo-attractant protein-1, and resistin contribute to the metabolic and inflammatory milieu that promotes atherogenesis (43). Whether the atherogenic effect of EAT occurs through vasocrine or paracrine pathway is unknown. Two longitudinal studies have reported results that supported the hypothesis of 'outside to inside signaling' as a cause of atherosclerosis. Oxidative stress also plays a role in the development of atherosclerosis. EAT exhibits higher reactive oxygen species and includes lower catalase activities compared with subcutaneous fat tissue (44). However, the relation of epicardial fat and oxidative stress is more complex and involves other cytokines and vasoactive factors such as leptin and angiotensin II (36). Besides, all these other inflammatory mediators and soluble intercellular adhesion molecules participate in several stages of the atherosclerotic process including chemotaxis, smooth-muscle cell proliferation, foam-cell development and migration, and plaque destabilization (45).

EAT may contribute to atherosclerosis not only through the secretion of bioactive molecules but also through specific mechanical effects. For instance, atherosclerotic plaque in coronary arteries leads to an asymmetric expansion of the vessel wall named positive remodeling (46). Because of its intrinsic compressibility, epicardial fat has been suggested to play a per-

missive role in vessel expansion. Coronary lesions, which are surrounded by the epicardial fat undergo expansion more easily than those lesions surrounded by the myocardium since the myocardium is relatively incompressible. This hypothesis is demonstrated in postmortem studies as well as in studies using CT by absence of atherosclerosis in coronary artery segments with myocardial bridges (47).

Conclusion

EAT is a unique fat depot in the body in terms of the size of its adipocytes, biochemical composition, and metabolic activity. EAT has significantly higher rates of lipolysis and lipogenesis compared to other visceral fat depots. Given its anatomical proximity to the heart, it interacts locally with the coronary arteries and the myocardium through paracrine or vasocrine pathways. EAT has strong correlation with visceral obesity, MS, diabetes mellitus, and CVD. It can be easily detected and measured by imaging modalities such as echo, CT and MRI. Understanding the role of epicardial fat in atherosclerosis is still unclear. Future clinical and experimental studies should aim to elucidate the function of epicardial fat in different physiological conditions.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept - C.Ş.; O.Ö.; Design - C.Ş.; Supervision - C.Ş.; O.Ö.; Analysis &/or interpretation - C.Ş.; Literature search - O.Ö.; Writing - C.Ş.; Critical review - O.Ö.

References

1. Roy PE. Lipid droplets in the heart interstitium: concentration and distribution. *Recent Adv Stud Cardiac Struct Metab* 1975; 10: 17-27.
2. Wheeler GL, Shi R, Beck SR, Langefeld CD, Lenchik L, Wagenknecht LE, et al. Pericardial and visceral adipose tissue measured volumetrically with computed tomography are highly associated in type 2 diabetic families. *Invest Radiol* 2005; 40: 97-101. [\[CrossRef\]](#)
3. Bambace C, Telesca M, Zoico E, Sepe A, Oliosio D, Rossi A, et al. Adiponectin gene expression and adipocyte diameter: a comparison between epicardial and subcutaneous adipose tissue in men. *Cardiovasc Pathol* 2011; 20: 153-6. [\[CrossRef\]](#)
4. Iacobellis G, Bianco AC. Epicardial adipose tissue: emerging physiological, pathophysiological and clinical features. *Trends Endocrinol Metab* 2011; 22: 450-7. [\[CrossRef\]](#)
5. Mazurek T, Zhang L, Zalewski A, Mannion JD, Diehl JT, Arafat H, et al. Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460-6. [\[CrossRef\]](#)
6. Kwon HM, Sangiorgi G, Ritman EL, McKenna C, Holmes DR Jr, Schwartz RS, et al. Enhanced coronary vasa vasorum neovascularisation in experimental hypercholesterolemia. *J Clin Invest* 1998; 101: 1551-6. [\[CrossRef\]](#)
7. Yudkin JS, Eringa E, Stehouwer CD. Vasocrine signaling from perivascular fat: a mechanism linking insulin resistance to vascular disease. *Lancet* 2005; 365: 1817-20. [\[CrossRef\]](#)
8. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, fetal development and biochemical properties. *Comp Biochem Physiol B* 1989; 94: 225-32. [\[CrossRef\]](#)
9. Sacks HS, Fain JN, Holman B, Cheema P, Chary A, Parks F, et al. Uncoupling protein-1 and related messenger ribonucleic acids in human epicardial and other adipose tissues: epicardial fat functioning as brown fat. *J Clin Endocrinol Metab* 2009; 94: 3611-5. [\[CrossRef\]](#)
10. Keegan J, Gatehouse PD, Yang GZ, Firmin DN. Spiral phase velocity mapping of left and right coronary artery blood flow: correlation for through-plane motion using selective fat-only excitation. *J Magn Reson Imaging* 2004; 20: 953-60. [\[CrossRef\]](#)
11. Iacobellis G, di Gioia CR, Cotesta D, Petramala L, Travaglini C, De Santis V, et al. Epicardial adipose tissue adiponectin expression is related to intracoronary adiponectin levels. *Horm Metab Res* 2009; 41: 227-31. [\[CrossRef\]](#)
12. Fox CS, Gona P, Hoffmann U, Porter SA, Salton CJ, Massaro JM, et al. Pericardial fat, intrathoracic fat, and measures of left ventricular structure and function: the Framingham Heart Study. *Circulation* 2009; 119: 1586-91. [\[CrossRef\]](#)
13. Iacobellis G, Assael F, Ribaudo MC, Zappaterreno A, Alessi G, Di Mario U, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. *Obes Res* 2003; 11: 304-10. [\[CrossRef\]](#)
14. Smith HL, Willius FA. Adiposity of the heart. A clinical and pathologic study of one hundred and thirty size obese patients. *Arch Intern Med* 1933; 52: 911-31. [\[CrossRef\]](#)
15. Reiner L, Mazzoleni A, Rodriguez FL, Freudenthal RR. The weight of the human heart. I. Normal cases. *AMA Arch Pathol* 1959; 68: 58-73.
16. Iacobellis G, Ribaudo MC, Assael F, Vecchi E, Tiberti C, Zappaterreno A, et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. *J Clin Endocrinol Metab* 2003; 88: 5163-8. [\[CrossRef\]](#)
17. Abbata S, Desai JC, Cury RC, Butler J, Nieman K, Reddy V. Mapping epicardial fat with multidetector computed tomography to facilitate percutaneous transepical arrhythmia ablation. *Eur J Radiol* 2006; 57: 417-22. [\[CrossRef\]](#)
18. Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr* 2009; 22: 1311-9. [\[CrossRef\]](#)
19. Gorter PM, van Lindert AS, de Vos AM, Meijis MF, van der Graaf Y, Doevendans PA, et al. Quantification of epicardial and pericoronary fat using cardiac computed tomography; reproducibility and relation with obesity and metabolic syndrome in patients suspected of coronary artery disease. *Atherosclerosis* 2008; 197: 896-903. [\[CrossRef\]](#)
20. Flüchter S, Haghi D, Dinter D, Heberlein W, Kühl HP, Neff W, et al. Volumetric assessment of epicardial adipose tissue with cardiovascular magnetic resonance imaging. *Obesity* 2007; 15: 870-8. [\[CrossRef\]](#)
21. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006; 119: 812-9. [\[CrossRef\]](#)
22. Wang TD, Lee WJ, Shih FY, Huang CH, Chang YC, Chen WJ, et al. Relations of epicardial adipose tissue measured by multidetector computed tomography to components of the metabolic syndrome are region-specific and independent of anthropometric indexes and

- intraabdominal visceral fat. *J Clin Endocrinol Metab* 2009; 94: 662-9. [\[CrossRef\]](#)
23. Nakazato R, Rajani R, Cheng VY, Shmilovich H, Nakanishi R, Otaki Y, et al. Weight change modulates epicardial fat burden: A 4-year serial study with non-contrast computed tomography. *Atherosclerosis* 2012; 220: 139-44. [\[CrossRef\]](#)
24. Sacks HS, Fain JN, Cheema P, Bahouth SW, Garrett E, Wolf RY, et al. Inflammatory genes in epicardial fat contiguous with coronary atherosclerosis in the metabolic syndrome and type 2 diabetes: changes associated with pioglitazone. *Diabetes Care* 2011; 34: 730-3. [\[CrossRef\]](#)
25. Salgado-Somoza A, Teijeira-Fernández E, Rubio J, Couso E, González-Juanatey JR, Eiras S. Coronary artery disease is associated with higher epicardial renin binding protein 4 (RBP4) and lower glucose transporter (GLUT) 4 levels in epicardial and subcutaneous adipose tissue. *Clin Endocrinol* 2012; 76: 51-8. [\[CrossRef\]](#)
26. Iacobellis G, Willens HJ, Barbaro G, Sharma AM. Threshold values of high-risk echocardiographic epicardial fat thickness. *Obesity (Silver Spring)* 2008; 16: 887-92. [\[CrossRef\]](#)
27. Versteylen MO, Takx RA, Joosen IA, Nelemans PJ, Das M, Crijns HJ, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. *Eur Heart J Cardiovasc Imaging* 2012; 13: 517-23. [\[CrossRef\]](#)
28. Sironi AM, Pingitore A, Ghione S, De Marchi D, Scattini B, Positano V, et al. Early hypertension is associated with reduced regional cardiac function, insulin resistance, epicardial, and visceral fat. *Hypertension* 2008; 51: 282-8. [\[CrossRef\]](#)
29. Şengül C, Özveren O, Duman D, Eroğlu E, Oduncu V, Tanboğa Hİ, et al. Echocardiographic epicardial fat thickness is related to altered blood pressure responses to exercise stress testing. *Blood Press* 2011; 20: 303-8. [\[CrossRef\]](#)
30. Şengül C, Çevik C, Özveren O, Duman D, Eroğlu E, Oduncu V, et al. Epicardial fat thickness is associated with non-dipper blood pressure pattern in patients with essential hypertension. *Clin Exp Hypertens* 2012; 34: 165-70. [\[CrossRef\]](#)
31. Iacobellis G, Ribaudo MC, Zappaterreno A, Iannucci CV, Leonetti F. Relation between epicardial adipose tissue and left ventricular mass. *Am J Cardiol* 2004; 94: 1084-7. [\[CrossRef\]](#)
32. Shin SY, Yong HS, Lim HE, Na JO, Choi CU, Choi JI, et al. Total and interatrial epicardial adipose tissues are independently associated with left atrial remodeling in patients with atrial fibrillation. *J Cardiovasc Electrophysiol* 2011; 22: 647-55. [\[CrossRef\]](#)
33. Verhagen SN, Visseren FL. Perivascular adipose tissue: as a cause of atherosclerosis. *Atherosclerosis* 2011; 214: 3-10. [\[CrossRef\]](#)
34. Ding J, Hsu FC, Harris TB, Liu Y, Kritchevsky SB, Szklo M, et al. The association of pericardial fat with incident coronary heart disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* 2009; 90: 499-504. [\[CrossRef\]](#)
35. Xu Y, Cheng X, Hong K, Huang C, Wan L. How to interpret epicardial adipose tissue as a cause of coronary artery disease: a meta-analysis. *Coron Artery Dis* 2012; 23: 227-33. [\[CrossRef\]](#)
36. Rodríguez A, Fortuño A, Gómez-Ambrosi J, Zalba G, Díez J, Frühbeck G. The inhibitory effect of leptin on angiotensin II-induced vasoconstriction in vascular smooth muscle cells is mediated via a nitric oxide-dependent mechanism. *Endocrinology* 2007; 148: 324-31. [\[CrossRef\]](#)
37. Konishi M, Sugiyama S, Sugamura K, Nozaki T, Ohba K, Matsubara J, et al. Association of pericardial fat accumulation rather than abdominal obesity with coronary atherosclerotic plaque formation in patients with suspected coronary artery disease. *Atherosclerosis* 2010; 209: 573-8. [\[CrossRef\]](#)
38. Ueno K, Anzai T, Jinzaki M, Yamada M, Jo Y, Maekawa Y, et al. Increased epicardial fat volume quantified by 64-multidetector computed tomography is associated with coronary atherosclerosis and totally occlusive lesions. *Circ J* 2009; 73: 1927-33. [\[CrossRef\]](#)
39. Sade LE, Eroğlu S, Bozbaş H, Özbiçer S, Hayran M, Haberal A, et al. Relation between epicardial fat thickness and coronary flow reserve in women with chest pain and angiographically normal coronary arteries. *Atherosclerosis* 2009; 204: 580-5. [\[CrossRef\]](#)
40. Bachar GN, Dicker D, Kornowski R, Atar E. Epicardial adipose tissue as a predictor of coronary artery disease in asymptomatic subjects. *Am J Cardiol* 2012; 110: 534-8. [\[CrossRef\]](#)
41. Kim BJ, Kim BS, Kang JH. Echocardiographic epicardial fat thickness is associated with arterial stiffness. *Int J Cardiol* 2012 Jun 21. [Epub ahead of print] [\[CrossRef\]](#)
42. Cheng VY, Dey D, Tamarappoo B, Nakazato R, Gransar H, Miranda-Peats R, et al. Pericardial fat burden on ECG-gated noncontrast CT in asymptomatic patients who subsequently experience adverse cardiovascular events. *JACC Cardiovasc Imaging* 2010; 3: 352-60. [\[CrossRef\]](#)
43. Rabkin SW. Epicardial fat: properties, function and relationship to obesity. *Obes Rev* 2007; 8: 253-61. [\[CrossRef\]](#)
44. Salgado-Somoza A, Teijeira-Fernández E, Fernández AL, González-Juanatey JR, Eiras S. Proteomic analysis of epicardial and subcutaneous adipose tissue reveals differences in proteins involved in oxidative stress. *Am J Physiol Heart Circ Physiol* 2010; 299: 202-9. [\[CrossRef\]](#)
45. Karastergiou K, Evans I, Ogston N, Miheisi N, Nair D, Kaski JC, et al. Epicardial adipokines in obesity and CAD induce atherogenic changes in monocytes and endothelial cells. *Arterioscler Thromb Vasc Biol* 2010; 30: 1340-6. [\[CrossRef\]](#)
46. Prati F, Arbustini E, Labellarte A, Sommariva L, Pawlowski T, Manzoli A, et al. Eccentric atherosclerotic plaques with positive remodelling have a pericardial distribution: a permissive role of epicardial fat? A three-dimensional intravascular ultrasound study of left anterior descending artery lesions. *Eur Heart J* 2003; 24: 329-36. [\[CrossRef\]](#)
47. Ishii T, Asuwa N, Masuda S, Ishikawa Y. The effects of a myocardial bridge on coronary atherosclerosis and ischaemia. *J Pathol* 1998; 185: 4-9. [\[CrossRef\]](#)

Kalp yetersizliği tedavisinde yeni açılımlar: Şimdi ve gelecek

Recent and future innovations in the treatment of heart failure

Alper Kepez, Bülent Mutlu

Marmara Üniversitesi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul-Türkiye

ÖZET

Kalp yetersizliği, tedavide sağlanan tüm gelişmelere karşın halen önemli bir halk sağlığı problemi olmayı sürdürmektedir. Kalp yetersizliği ile daha etkin mücadele edilebilmesi için pek çok alanda yeni tedavi stratejileri geliştirilmekte ve test edilmektedir. Klinik çalışmalarda etkinliği kanıtlanan tedavi stratejileri ise klinik uygulamaya girmektedir. Bu yazıda kalp yetersizliği tedavisinde klinik uygulamaya eklenen son tedavi stratejileri özetlenecek ve halen araştırma safhasında olan klinik uygulamaya girmeye aday stratejilere göz atılacaktır.

(*Anadolu Kardiyol Derg 2013; 13: 266-74*)

Anahtar kelimeler: Kalp yetersizliği, klinik çalışma, kılavuzlar

ABSTRACT

Heart failure is still an important public health problem despite important advances regarding its treatment. Several new treatment strategies are being investigated in order to contend with this disease. Strategies proved to be safe and effective in clinical trials are being adapted to clinical practice. In this review, we will first focus on most recent treatment strategies that are recommended to be used in clinical practice and then try to mention novel strategies which are still being explored in preclinical studies.

(*Anadolu Kardiyol Derg 2013; 13: 266-74*)

Key words: Heart failure, clinical trials, guidelines

Giriş

Kalp yetersizliği, tedavide elde edilen önemli gelişmelere karşın yüksek mortalite ve morbidite nedeni olan bir halk sağlığı problemi olmayı sürdürmektedir. 'Heart Failure Prevalence and Predictors in Turkey (HAPPY)' çalışması verilerine göre ülkemizdeki erişkin kalp yetersizliği ve asemptomatik sol ventrikül disfonksiyonu prevalanslarının mutlak değerleri sırasıyla %2.9 ve %4.8; tahmini değerleri ise sırasıyla %6.9 ve %7.9'dur (1). Klinik çalışmalarda, kalp yetersizliği olan hastalarda mortalitenin yıllık %8-12 arasında olduğu bildirilmiştir (2). Günümüzde kalp yetersizliği tedavisinde öncelikle ilaç dışı uygun tedavi stratejileri (tuz kısıtlaması, egzersiz, alkolün kesilmesi) ve farmakolojik tedavi

uygulanmaktadır. Son yıllarda intrakardiyak defibrilatör (IKD) ve/veya kardiyak resenkronizasyon tedavisi (KRT) gibi cihaz tedavileri ile mortalite ve morbiditede ek kazanımlar sağlanmıştır. Son evre hastalarda ventriküler yardımcı cihazlar ('asist device') ve kardiyak transplantasyon da kullanılabilinecek tedavi seçenekleri arasındadır.

Kalp yetersizliği ile mücadelenin daha etkin sürdürülebilmesi için pek çok araştırma yapılmakta, yeni tedavi stratejileri ve farmakolojik ajanlar test edilmektedir. Kontrollü, randomize klinik çalışmalarda etkinliği ispatlanan tedavi yöntemleri günlük kullanıma girmekte ve düzenli aralıklarla kılavuzlar yenilenmektedir.

Bu yazıda son çalışmalar ve kılavuzlar ışığında kalp yetersizliği tedavisindeki yenilikler ve gelecekte uygulanması öngörülen tedavi stratejileri özetlenmiştir.

Yazışma Adresi/Address for Correspondence: Dr. Alper Kepez, Marmara Üniversitesi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Pendik, İstanbul-Türkiye Tel: +90 532 220 18 99 Faks: +90 216 657 06 95 E-posta: alperkepez@yahoo.com

Kabul Tarihi/Accepted Date: 09.10.2012 **Çevrimiçi Yayın Tarihi/Available Online Date:** 06.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.076



Kalp yetersizliği tanısında yenilikler

Natriüretik peptidler

Avrupa Kardiyoloji Cemiyeti (AKC) 2008 yılı kılavuzunda serum 'beyin natriüretik peptid (BNP)' değerinin 100 pg/mL ve serum 'N-Terminal-proBNP (NT-proBNP)' değerinin 400 pg/mL değerinin altında olduğu olgularda kalp yetersizliği tanısının yüksek olasılıkla dışlanabileceği belirtilmiştir (3). Aynı kılavuzda serum BNP değerinin 400 pg/mL ve serum NT-proBNP değerinin 2000 pg/mL değerinin üzerinde olduğu olgularda ise kalp yetersizliği tanısının yüksek olasılıkla konulabileceği söylenmiştir.

Avrupa Kardiyoloji Cemiyeti (AKC) 2012 yılı kılavuzunda ise serum BNP ve NT-proBNP ölçümlerinin özellikle kalp yetersizliği tanısının dışlanması için kullanılması önerilmiştir (4). Bununla birlikte kalp yetersizliği tanısının dışlanmasında kullanılması önerilen serum BNP ve NT-proBNP eşik değerlerinde değişiklikler yapılmıştır. Buna göre akut semptomlarla başvuran hastalarda BNP için tanıyı dışlayıcı eşik değeri 100 pg/mL, NT-proBNP için ise 300 pg/mL kabul edilmiştir. Akut semptomlarla başvurmayan olgular için ise tanıyı dışlayıcı eşik değerleri BNP için 35 pg/mL, NT-proBNP için ise 125 pg/mL olarak belirtilmiştir. 2008 yılındaki kılavuzun aksine BNP ve NT-proBNP için tanısal eşik değer belirtilmemiştir.

Yakın zamanda yapılmış geniş çaplı randomize klinik çalışmalarda kalp yetersizliğinde kullanılan ilaç tedavisinin serum natriüretik peptid seviyesine göre titre edilmesi stratejisi, standart stratejiyle karşılaştırılmıştır. Yakın zamanda yayımlanan meta-analizlerde, düşük ejeksiyon fraksiyonlu (EF) kalp yetersizliği hastalarında tedavinin natriüretik peptid düzeyine göre titre edilmesi ile tüm nedenlere bağlı mortalitede önemli azalma sağlandığı ancak tüm nedenlere bağlı hastaneye yatış oranlarında değişiklik olmadığı bildirilmiştir (5). Bu bilgiler ışığında natriüretik peptid rehberliğinde tedavi titrasyonunun yalnızca standart tedavi ile yeteri kadar yanıt alınamamış sol ventrikül sistolik disfonksiyonu olan kalp yetersizliği hastalarına sınırlandırılması önerilmektedir (5).

Kalp yetersizliğinde non-farmakolojik tedavide yenilikler

Fiziksel aktivite ve rehabilitasyon

Pek çok sistemik derleme ve küçük çalışmaların meta analizlerinde düzenli fizik egzersiz ile kalp yetersizliği hastalarında fiziksel kondisyonda iyileşme sağlandığı, semptomlarda ve nöro-hormonal anormalliklerde düzelme izlendiği, hastaneye yatış oranlarında ise azalma gözlemlendiği bildirilmiştir (4).

Yakın zamanlarda yayımlanan ve konu ile ilgili tek geniş çaplı randomize çalışma olan 'Heart Failure. A Controlled Trial Investigating Outcomes of Exercise Training (HF- ACTION)' çalışmasında aerobik egzersizin EF değeri %35'in altında olan kalp yetersizliği hastalarında yaşam kalitesini arttırdığı görülmüştür (6). Çok değişkenli analizde düzenli egzersizin tüm

nedenlere bağlı mortalite ve tüm nedenlere bağlı hastaneye yatış oranlarını içeren klinik sonuçların mortalitelerinde anlamlı düzelme sağladığı saptanmıştır.

Bu sonuçlar ışığında sistolik kalp yetersizliği hastalarına özel fizik tedavi programları önerilmektedir. Buna karşın çalışmalarda yeteri kadar temsil edilmedikleri için yaşlı kalp yetersizliği popülasyonunda fizik aktivitenin etkileri net değildir. Benzer şekilde sol ventrikül sistolik fonksiyonları korunmuş kalp yetersizliği hastalarında da konu ile ilgili belirsizlik devam etmektedir (5).

Kalp yetersizliğinde farmakolojik tedavide yenilikler

Anjiyotensin II reseptör blokerleri

Anjiyotensin II reseptör blokerleri (ARB), anjiyotensin dönüştürücü enzim (ADE) inhibitörlerini tolere edemeyen hastalarda alternatif ilaç olarak kullanılabilirler. Önceki AKC kılavuzunda ADE inhibitörü ve beta-blokeri içeren optimal tedaviye rağmen semptomatik olan EF değeri %40'ın altındaki kalp yetersizliği hastalarında tedaviye ARB eklenmesi önerilmiştir (3). Buna karşın son AKC kılavuzunda bu hastalarda tedaviye ARB eklenmesi, mortalite yararı olmadığı gerekçesi ile artık önerilmemektedir (4).

'Heart Failure Endpoint Evaluation of Angiotensin II Antagonist Losartan (HEAAL)' çalışmasında ADE inhibitörünü tolere edemeyen sistolik kalp yetersizliği hastalarında 150 mg dozunda uygulanan losartan tedavisinin 50 mg'a göre mortaliteyi ve hastaneye başvuru oranlarını azaltmada daha üstün olduğu gösterilmiştir (7). Bu gözlem kalp yetersizliği hastalarında renin anjiyotensin sisteminin maksimum dozlarda bloke edilmesinin önemini göstermektedir.

Aldosteron antagonistleri

Önceki kılavuzlarda 'The Randomized Aldactone Evaluation Study (RALES)' çalışması ışığında optimal tedavi altında 'New York Kalp Cemiyeti Sınıflamasına (NYHA)' göre sınıf 3 ve 4 semptomları olan kalp yetersizliği hastalarına spiranolakton eklenmesi önerilmiştir (3, 8).

Aldosteron antagonistlerinin "remodelling" üzerine etkisini araştırmak için düzenlenen 'Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS)' çalışmasında selektif bir aldosteron antagonisti olan eplerenonun miyokart enfarktüsü sonrası diyabetik hastalarda veya sol ventrikül disfonksiyonu gelişen hastalarda (EF $\leq$ %40) etkileri araştırılmıştır (9). Eplerenon tedavisi alan grupta 16 aylık takip sonunda %15 mortalite azalması bildirilmiştir. Kalp yetersizliğine bağlı hospitalizasyonda da %15'lik azalma saptanmıştır (9).

Yakın zamanda yayımlanan 'Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)' çalışmasında mineralokortikoid antagonistlerinin sol ventrikül sistolik disfonksiyonu olup optimal tedavi altında sınıf 2 semptomları olan hastalarda mortalite ve morbidite üzerine etkileri araştırılmıştır (10). Bu hastalarda eplerenon tedavisi ile kardiyovasküler ölüm ve kalp yetersizliğine bağlı hospitalizasyon

için %37'lik relatif risk azalması sağlandığı görülmüştür. Bu çalışmada ışığında son AKC kılavuzunda ADE inhibitörü (veya ARB) ve beta bloker tedavi altında semptomları devam eden tüm sistolik kalp yetersizliği hastalarına, kontrendikasyon yoksa mineralokortikoid reseptör antagonisti başlanması önerilmiştir (4).

Ivabradin

Ivabradin sinüs nodunda I_f kanallarını bloke eden bir ilaçtır. Bu ilacın bilinen tek farmakolojik etkisi sinüs ritmindeki hastalarda kalp hızının azaltılmasıdır (AF hastalarında ventrikül hızını azaltmazlar) (4).

Geçmiş dönemlerde yapılmış olan geniş çaplı epidemiyolojik çalışmalarda (Chicago ve Framingham çalışmaları) genel popülasyonda kalp hızı ile kardiyovasküler ve total mortalite arasında önemli ilişki olduğu saptanmıştır (11, 12). Paris prospektif çalışmasında 5713 asemptomatik erkek birey 23 yıl boyunca takip edilmiş ve istirahat kalp hızının miyokart enfarktüsüne bağlı ani ölümün bağımsız öngördürücüsü olduğu saptanmıştır (13). FINRISK çalışmasında ise bireyler kalp hızlarına göre 5 gruba ayrılmış, kalp hızı yüksek olan gruplarda toplam mortalitenin daha yüksek olduğu görülmüştür (14). Bu çalışmada istirahat kalp hızı ve total mortalite arasındaki ilişkinin erkeklerde daha güçlü olduğu saptanmıştır.

'International Verapamil-SR/trandolapril Study (INVEST)' çalışmasında koroner arter hastalığı ve hipertansiyon hastalarında başlangıçtaki ve takiplerdeki istirahat kalp hızının artan ölüm, non-fatal miyokart enfarktüsü ve non-fatal inme ile ilişkili olduğu görülmüştür (15).

Kalp yetersizliği hastalarında beta blokerlerin (β -bloker) kullanımını inceleyen 23 çalışmanın meta-regresyon analizinde (n=19209), uygulanan beta bloker dozundan çok kalp hızında sağlanan azalmanın kardiyovasküler olay gelişimini engellediği görülmüştür (16).

'The Systolic Heart Failure with the I_f Inhibitor Ivabradine Trial (SHIFT)' çalışmasında kalp hızı 70/dk ve üzerinde olup fonksiyonel kapasitesi NYHA sınıf 3 ve 4 olan sinüs ritmindeki 6588 kalp yetersizliği hastası üzerinde ivabradinin etkileri araştırılmıştır (17). Hastalar geçmiş 12 ay içerisinde kalp yetersizliğine bağlı hastaneye yatış öyküsü olanlardan seçilmiştir. Hastalar standart tedaviye ek olarak ivabradin veya plasebo kollarına randomize edilmişler ve 23 ay boyunca izlenmişlerdir. Bu çalışmada hastaların %26'sının tam doz beta bloker aldığı belirtilmiştir. Ivabradin tedavisi ile çalışmanın kardiyovasküler nedenlere bağlı ölüm veya kalp yetersizliğine bağlı hospitalizasyonu içeren primer sonlanım noktaları için %18'lik relatif risk azalması sağlandığı bildirilmiştir. Birleşik mortalite ve morbidite sonlanım noktası için ivabradin tedavisi ile elde edilen net risk azalma oranı %4.2 olarak bulunmuştur. Ivabradin tedavisi ile sol ventrikül fonksiyonlarında ve yaşam kalitesinde artış saptandığı da bildirilmiştir. Ivabradin tedavisi alan hastalarda semptomatik bradikardi oranı %5 iken plasebo grubunda bu oran %1 olarak bulunmuştur. Görsel yan etkiler ivabradin alan hastaların %3'ünde saptanırken, aynı yan etki oranının plasebo grubunda %1 olduğu görülmüştür (17).

Ivabradinin kalp yetersizliğinde kullanımı ile ilgili düzenlenen daha önceki 'Morbidity-mortality Evaluation of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease and Left Ventricular Dysfunction (BEAUTIFUL)' çalışmasında kalp hızı 60 / dk'nın üzerinde ve ejeksiyon fraksiyonu %40'ın altında olan 10917 hasta ivabradin veya plasebo kollarına randomize edilmiş ve 19 ay izlenmişlerdir (18). Ivabradin tedavisi ile bu çalışmada kardiyovasküler ölüm, miyokart enfarktüsü veya kalp yetersizliği nedeniyle hastaneye yatış oranlarında plaseboya göre farklılık saptanmamıştır. Buna karşın ivabradin tedavisinin iyi tolere edildiği bildirilmiştir (18).

Bu çalışmalar ışığında son AKC kılavuzunda ivabradinin hastaneye yatış oranının azaltılması için, optimal beta bloker tedavisi altında kalp hızı 70/dk'nın üzerinde seyreden sistolik kalp yetersizliği (EF <%35) hastalarında standart tedaviye eklenmesi önerilmiştir (sınıf 2a endikasyon). Beta bloker ilaçları tolere edemeyen sistolik kalp yetersizliği (EF <%35) hastalarında da, kalp hızı 70/dk'nın üzerinde ise ivabradin kullanımı düşünülebilir (sınıf 2b endikasyon) (4).

Kalp yetersizliğinde cihaz tedavisinde yenilikler

Biventriküler pacing

Önceki kılavuzlarda şu kriterlere sahip hastalara kardiyak resenkrizasyon tedavisi (KRT) uygulanması önerilmiştir (3);

1. Optimal medikal tedaviye rağmen NYHA sınıf 3 ve 4 semptom gösteren hastalar
2. Ejeksiyon fraksiyonu %35 altında olan hastalar
3. QRS süresinin 120 ms üzerinde olması
4. Ritmin sinüs olması

Yakın zamanlarda yapılan 2 randomize kontrollü çalışmada fonksiyonel kapasitesi daha iyi durumda olan geniş QRS'li kalp yetersizliği hastaları üzerinde KRT'nin etkinliği araştırılmış ve olumlu sonuçlar bildirilmiştir (19, 20). Bu çalışmalardan 'Resynchronization/Defibrillation for Ambulatory Heart Failure Trial (RAFT)' çalışmasında fonksiyonel kapasitesi NYHA sınıf 2 (%80) ve sınıf 3 (%20) olup QRS süresi 120 ms üzerinde olan kalp yetersizliği hastaları (EF $\leq$ %30) optimal tedaviye ek olarak ICD veya KRT-Defibrilatör (KRT-D) kollarına randomize edilmişler ve 40 ay süresince izlenmişlerdir (19). Sonuçta KRT-D tedavisi ile ölüm ve kalp yetersizliğine bağlı hastaneye yatış oranlarında %25 relatif risk azalması sağlandığı bildirilmiş, tüm nedenlere bağlı mortalitede ise %25 azalma tespit edilmiştir. QRS süresi 150 ms ve daha üzeri olan hastalarda relatif yararlanım daha fazla olmuştur.

Fonksiyonel kapasitesi nispeten daha iyi olan hastaların çalışıldığı 'Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT)' çalışmasında EF değeri %30'un altında ve QRS süresi 130 ms ve üzerinde olan tümü sinüs ritminde 1820 hasta (%80 NYHA sınıf 2 ve %20 NYHA sınıf 1) optimal tedaviye ek olarak ICD veya CRT-Defibrilatör (CRT-D) kollarına randomize edilmişlerdir (20). Ortalama 2.4 yıllık takip döneminden sonra gruplar arasında mortalite oranları açısından anlamlı fark saptanmaz iken kalp yetersizliği ile ilgili olay

görülme sıklığında CRT-D ile %41 azalma sağlandığı saptanmıştır. Bu azalmanın primer olarak QRS süresi 150 ms ve daha üzerinde olan hastalardan kaynaklandığı bildirilmiştir.

Bu çalışmalar ışığında son AKC kılavuzunda nispeten hafif semptomları olan kalp yetersizliği hastalarına QRS süresi ≥ 150 ms ise veya sol dal bloğu ile birlikte ≥ 130 ms ise CRT takılması önerilmiştir (4).

Sol ventrikül sistolik fonksiyonları korunmuş kalp yetersizliği tedavisinde yenilikler

Bu gruptaki hastalarda halen mortalite ve morbiditeyi tutarlı şekilde düşüren tedavi mevcut değildir. Bu grup hastalar için önerilen tedavi eşlik eden hipertansiyon, diyabet veya miyokardiyal iskemi gibi risk faktörlerinin agresif şekilde kontrol altına alınması ve sıvı retansiyonuna bağlı semptomlar için diüretik ilaçların kullanılmasıdır (3, 4). Küçük çaplı iki çalışmada verapamilin bu hastalarda semptomları ve efor kapasitesini olumlu etkilediği tespit edilmiştir (4).

Yakın zamanlarda konu ile ilgili çeşitli ajanlarla mortalite ve morbidite çalışmaları yapılmıştır. Kandesartan ile yapılan 'Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM-preserved)', perindopril ile yapılan 'Perindopril for Elderly People with Chronic Heart Failure (PEP-CHF)' ve irbesartan ile yapılan 'Irbesartan in Heart Failure with Preserved Systolic Function Trial (I-Preserve)' çalışmalarında kardiyovasküler ölüm ve kalp yetersizliğine bağlı hastaneye yatış oranlarında azalma izlenmemiştir (4).

Bu grup hastalar üzerinde beta blokerler ile yapılmakta olan 'Beta-blocker in heart failure with normal left ventricular ejection fraction (beta-PRESERVE)' ve spiranolakton ile yapılmakta olan 'Treatment of preserved cardiac function heart failure with an aldosteron antagonist (TOPCAT)' çalışmaları halen devam etmektedir (21, 22).

Kalp yetersizliğinde komorbid durumların tedavisinde yenilikler

Pulmoner hipertansiyon

Sol kalp hastalıkları pulmoner hipertansiyonun en sık nedenidir (23, 24). Sistolik veya diyastolik sol ventrikül disfonksiyonu veya kapak hastalıklarına bağlı artan sol atriyal basınç pulmoner vasküler yatakta pasif olarak basınç artışına neden olmaktadır. Bazı hastalarda pasif basınç artışının tetiklediği pulmoner arteriyel vazokonstriksiyon ve vasküler yeniden şekillenme ile karakterize aktif süreç pulmoner arteriyel basıncı daha da artırabilmektedir. Bu hastalarda ortalama pulmoner arter basıncı ile pulmoner kapiller kama basıncı arasındaki fark olarak tanımlanan transpulmoner basınç gradiyentinin hesaplanması önemlidir. Transpulmoner basınç gradiyentinin 12 mmHg üzerinde olduğu durumlarda orantısız pulmoner hipertansiyon varlığından söz edilir. Bu hastalarda pasif basınç artışının pulmoner arteriyel yatakta aktif yeniden şekillenmeyi başlattığı düşünülür (23, 24).

Sol kalp yetersizliği ile ilgili yapılan çoğu çalışmada pulmoner hipertansiyon varlığının diğer prognostik faktörlerden bağımsız olarak prognozu öngördüğü saptanmıştır (25). Kardiyak transplantasyon alanında sağlanan tüm gelişmelere karşın pulmoner hipertansiyon varlığı halen mortalite için önemli bir risk faktörüdür. Kılavuzlar farmakolojik olarak düşmeyen şiddetli pulmoner hipertansiyon varlığının (sistolik pulmoner arter basıncı >50 mmHg, pulmoner vasküler direnç >5 Wood, transpulmoner gradient >16 mmHg) transplantasyon için kontrendikasyon oluşturduğunu kabul etmektedir (26). Geçmiş yıllardaki çalışmalarda, pulmoner hipertansiyon nedeniyle transplantasyonun kontrendike olduğu son dönem kalp yetersizliği hastalarında sol ventrikül destekleyici cihazlarının ventrikülü dekomprese ederek pulmoner hipertansiyonu azalttığı ve transplantasyona imkân sağladığı gösterilmiştir (25).

Sol ventrikül sistolik disfonksiyonu olan daha hafif hastalarda ADE inhibitörü, beta bloker ve gerektiğinde resenkrizasyon tedavisi ile çoğunlukla pulmoner hipertansiyon gerilemektedir (25). Buna karşın medikal ve cihaz tedavisine dirençli orantısız pulmoner hipertansiyon vakalarında pulmoner arteriyel yeniden şekillenmeye yönelik spesifik tedavi uygulanması düşünülmüş ve konu ile ilgili çeşitli çalışmalar yapılmıştır. Teorik olarak pulmoner vazodilatasyon ile kompliansı yeterli olmayan bir sol ventrikül varlığında kardiyak dolum basınçlarında ani yükselme riski mevcuttur. Örnek olarak inhale nitrik oksitin uygulamadan kısa süre sonra pulmoner kapiller kama basıncında artışa neden olduğu gösterilmiştir (25, 27). Bu nedenle pulmoner arteriyel hipertansiyonun spesifik tedavisinde kullanılan ajanlar sol kalp yetmezliğine bağlı pulmoner hipertansiyon tedavisinde zararlı olabilirler. Literatürdeki küçük çaplı çalışmalarda prostaglandin analogları ve endotelin antagonistleri ile sol kalp yetersizliğine bağlı pulmoner hipertansiyon tedavisinde olumlu etki sağlanmadığı bildirilmiştir (25).

Pulmoner arteriyel hipertansiyon spesifik tedavisinde kullanılan diğer bir ilaç grubu ise fosfodiesteraz-5 inhibitörleridir. Günümüzde bu grup ajanlar içerisinde yalnızca sildenafil kalp yetersizliğine bağlı pulmoner hipertansiyon tedavisinde denenmiştir. Pulmoner vasküler yatak üzerine olan olumlu etkilerinin yanında sildenafilin kardiyomiyosit apoptozunu ve hipertrofini engellediği öne sürülmüştür (28). Lewis ve ark. (29) kalp yetersizliğine bağlı pulmoner hipertansiyon hastaları üzerinde yaptıkları randomize, plasebo kontrollü çalışmada 12 haftalık sildenafil tedavisi ile 6 dakikalık yürüme testi mesafesinde ve yaşam kalitesi skorlarında artış, hastaneye yatış oranlarında ise azalma olduğunu bildirmişlerdir. Buna ek olarak pulmoner vasküler direnç ve kardiyak debiyi içeren hemodinamik verilerde de anlamlı iyileşme saptanmıştır. Stabil sol kalp yetmezliği olan hastalarda sildenafil ile yapılan diğer çalışmalarda pulmoner arter basıncında ve pulmoner vasküler dirençte azalma, endotel fonksiyonlarında korunma, egzersiz kapasitesinde ve kardiyopulmoner egzersiz testindeki 'peak VO_2 ' değerlerinde artış tespit edilmiştir (25). Yakın zamanda yayımlanan bir çalışmada Guazzi ve ark. (30) sildenafilin sistolik kalp yetersizliği olan hastalarda kli-

nik durumu ve fonksiyonel kapasiteyi arttırmasının yanında sol ventrikül diyastolik fonksiyonunu ve kardiyak geometriyi de olumlu yönde etkilediğini göstermişlerdir.

Yakın zamanda üzerinde çalışılmaya başlanan bir diğer konu ise sol ventrikül sistolik fonksiyonu korunmuş kalp yetersizliği hastalarında görülen pulmoner hipertansiyonun tedavisidir. Böylelikle henüz net tedavisi olmayan bu durum için erken evreden itibaren etkin olabilecek tedavi gelişimi mümkün olabilecektir. Konu ile ilgili yapılan bir çalışmada sildenafil ile pulmoner basınç ve direnç değerlerinde azalma, sağ ventrikül fonksiyon ve boyutlarında düzelme ve sol ventrikül diyastolik fonksiyonlarında kısmi iyileşme gözlemlendiği bildirilmiştir (31). Sildenafil'in sol kalp yetersizliği ile ilgili pulmoner hipertansiyonda kullanımı ile ilgili umut verici gözlemlerden sonra fosfodiesteraz inhibitörlerinin morbidite ve mortaliteye olan etkilerinin daha net değerlendirilebileceği geniş çaplı klinik çalışmalar düzenlenmeye başlanmıştır. Konu ile ilgili ilk çok merkezli klinik çalışma olan 'Phosphodiesterase-5 inhibition to improve quality of life and exercise capacity in diastolic heart failure (RELAX)' çalışmasında diyastolik kalp yetmezliği hastalarında kronik sildenafil kullanımının etkileri test edilecektir. Halen devam etmekte olan bu çalışmanın hasta popülasyonu yüksek oranda yaşlı, hipertansiyon ve sol ventrikül hipertrofisi olan ve çoğunlukla kadın hastalardan oluşmaktadır. Hastaların %40'ına yakın kısmında pulmoner hipertansiyon bulunduğu bildirilmiştir. Çalışmanın ana sonlanım noktaları metabolik egzersiz kapasitesi, sol ventrikül kitlesi ve sol ventrikül fonksiyonundaki değişiklikler olacaktır (25).

İleri evre kalp yetersizliği hastalarında sildenafil tedavisinin etkilerini araştıran retrospektif ve tek merkezli bir çalışmada kronik sildenafil tedavisinin iyi tolere edildiği, hastaların çoğunun fonksiyonel kapasitesinin arttığı ve 16 hastanın 2'sinde klinik düzelmeye bağlı olarak transplantasyondan vazgeçildiği bildirilmiştir (32).

Mevcut veriler ışığında kalp yetersizliği hastalarında sildenafil iyi tolere edildiği ve kardiyovasküler ve pulmoner fonksiyonlarda olumlu etkileri olduğu gözlenmektedir. Fosfodiesteraz inhibitörleri, standart tedavi ile halen semptomatik olan veya tedaviye rağmen pulmoner hipertansiyonu gerilemeyen kalp yetersizliği hastalarında bir tedavi seçeneği olabilir. Konu ile ilgili daha net öneriler için takip süresi uzun olan geniş çaplı çalışmaların sonuçlarına ihtiyaç vardır.

Anemi ve demir eksikliği

Erkeklerde hemoglobin (Hb) konsantrasyonunun 13 g/dL, kadınlarda ise 12 g/dL'nin altında olması olarak tanımlanan anemi kalp yetersizliği hastalarında sık görülür. Kalp yetersizliği hastalarında anemi etyolojisi multifaktöryel olup; böbrek yetersizliği, pro-inflamatuvar sitokin aktivasyonu, hemodilüsyon ve kronik hastalığa bağlı eritropoezde izlenen değişiklikler anemi gelişimine neden olabilir (2). Bu hastalara endojen eritropoetin hormonuna karşı kemik iliği cevabında azalma olduğu öne sürülmüştür (2). Anemi kalp yetersizliği hastalarında daha düşük fonksiyonel kapasite ile ilişkili olup bu hastalarda mortalite ve hastaneye yatış için bağımsız risk faktörüdür (33). Kalp yetersiz-

liğinde anemi şiddeti ile klinik sonuç arasındaki ilişkinin araştırıldığı bir çalışmada Hb değerinde 1 g/dL azalma ile yıllık toplam mortalite oranının %2 arttığı gösterilmiştir (34). Anemi tanısı konulduğunda düzeltilebilir nedenler araştırılmalı ve tedavi edilmelidir. Kalp yetersizliği hastalarında özellikle demir eksikliği araştırılmalıdır. Bu hastalarda malnutrisyon, malabsorbsiyon ve kardiyak kaşeksiye bağlı demir eksikliği gelişebilir. Bunun yanında bu hastalarda sıklıkla kullanılan aspirin ve oral antikoagülanlar gastrointestinal sistemden mikroskopik kan kaybına neden olarak demir eksikliğini arttırabilirler (2).

Kalp yetersizliği hastalarında demir eksikliğinin intravenöz (İ.V.) demir ile tedavi edilmesinin araştırıldığı 'Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF' çalışmasında, demir eksikliği olan kalp yetersizliği hastaları İ.V. demir sükröz verilen veya tedavi verilmeyen olmak üzere 2 gruba randomize edilmişlerdir (35). Intravenöz demir sükröz verilen grupta efor kapasitesi ve semptomlarda anlamlı düzelme olduğu görülmüş, yararlanımın anemik hastalarda daha fazla olduğu saptanmıştır.

Kalp yetersizliği hastalarında daha stabil bir demir preparatı olan demir karboksimaltozun etkinliğinin araştırıldığı 'Ferric carboxymaltose in patients with heart failure and iron deficiency (FAIR-HF)' çalışmasında fonksiyonel kapasitesi NYHA sınıf 2 ve 3 olan ve hemoglobin değerleri 9.5 ile 13.5 g/dL arasında olan 459 hasta 2:1 oranında İ.V. demir karboksimaltoz veya İ.V. salin gruplarına randomize edilmişlerdir (36). Altı aylık tedavi sonrasında demir tedavisi alan grupta hastaların fonksiyonel kapasiteleri ve yaşam kalitelerinin arttığı görülmüştür. Bu çalışmada İ.V. demir karboksimaltoz verilen anemik olan veya olmayan tüm hastalarda benzer yararlanım olduğu saptanmıştır.

Anemisi olan kalp yetersizliği hastalarında eritropoetin-stimüle eden ajanların (ESA) etkisi küçük çaplı kontrolsüz çalışmalarda araştırılmış; kardiyak fonksiyonlar ve fonksiyonel kapasitede artış ile birlikte hastaneye yatış oranlarında azalma saptanmıştır (37). Buna karşın bu çalışmaların çoğunda demir ve ESA birlikte kullanılmıştır (37, 38). Nedeni belli olmayan anemisi olan kalp yetersizliği olan hastaları üzerinde ESA'ların etkisini araştıran geniş çaplı, randomize bir çalışma halen devam etmektedir (39).

Kalp yetersizliği tedavisinde gelecek

Kalp yetersizliği tedavisinde gelecekte sağlanması öngörülen ilerlemeler başlıca 3 başlık altında sınıflandırılabilir;

1. Etkinliği kanıtlanmış tedavilerin optimizasyonu
2. Geniş çaplı klinik çalışmalarda yeteri kadar temsil edilmemiş hasta grupları için tedavi geliştirilmesi
3. Yeni terapötik hedefler için yeni tedavilerin geliştirilmesi

Etkinliği kanıtlanmış tedavilerin optimizasyonu

Renin-angiyotensin-aldosteron sistemi ile sempatik sinir sisteminin etkilerini bloke eden ilaçlar günümüzde sistolik kalp yetersizliği tedavisinde standart tedavidir. Bu tedavilerin etkilerinin optimi-

ze edilmesi için klinik çalışmalarda etkinliğin gösterildiği dozlara çıkılması önemlidir. Buna karşın, ADE inhibitörleri ve β -blokerlerin etkileri için hastalar arasında geniş biyolojik varyasyon olduğu gösterilmiştir (2). Gelecekte bu ilaçların dozlarının kişiye göre ayarlanması söz konusu olabilecektir. Bu amaçla farmakogenomik yaklaşımın kullanıldığı çalışmalar devam etmektedir.

ADE geninin DD genotipinin ADE inhibitörü tedavisinde altı dahi ADE aktivitesinde artış ile ilişkili olduğu gösterilmiştir (2). Hem β 1, hem de β 2 adrenerek reseptörlerde çeşitli tek- nükleotid polimorfizmleri tanımlanmıştır (2). Bu polimorfizmlerin kalp yetersizliği hastalarında β -reseptör blokerlerine ve β -reseptör parsiyel agonistlerine yanıtı önemli derecede etkilediği saptanmıştır. 'A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure (BEST)' çalışmasında genel olarak bucindolol tedavisinin sistolik kalp yetersizliği hastalarında yararlı olmadığı gösterilmiştir (40). Buna karşın β 1 reseptörü 389. kodonunda arginin değişikliği (sıklık AMP fonksiyon artışına neden olan) olan hastalarda bucindolol diğer hastalara göre daha faydalı olmuştur. Tüm bu çalışmaların retrospektif çalışma olmaları nedeniyle farmakogenomik yaklaşımların rutin kullanımları için prospektif çalışmaların sonuçlarının beklenmesi gerektiği bildirilmiştir (2).

Geniş çaplı klinik çalışmalarda yeteri kadar temsil edilmemiş hasta grupları için tedavi geliştirilmesi

Akut kalp yetersizliği Akut kalp yetersizliği tedavisinde öncelikli amaç hemodinamik stabilizasyon ile ventilasyon ve oksijenizasyon desteğinin sağlanmasıdır. Hemodinamik stabilizasyon için dobutamin ve milrinon gibi inotropik ajanlar, nitroglicerinin gibi vazodilatörler ve nesiritid gibi natriüretik peptidler kullanılmaktadır. Pek çok çalışmada inotropik ajanların miyokardiyal oksijen tüketimini ve aritmi gelişimini uyarak mortaliteyi arttırdığı gösterilmiştir (41). Genel olarak günümüzde akut kalp yetersizliğinde kullanılan ajanlardan hiçbirisiyle plasebo kontrolü randomize çalışmalarda mortalite yararlanması sağlanamamıştır. Bu grup hastalarda yeni ilaçların geliştirilmesine şiddetle ihtiyaç duyulmaktadır.

Sol ventrikül sistolik fonksiyonları korunmuş kalp yetersizliği: Yazımızda daha önce de belirtildiği gibi bu grup hastalar için halen etkinliği kanıtlanmış tedavi bulunmamaktadır. Bu grup hastaların tedavisi için pek çok ilaç geliştirilme ve test edilme aşamasındadır.

Yeni terapötik hedefler için yeni tedavilerin geliştirilmesi

Bilinen sistemler için yeni hedefler: Renin-anjiyotensin-aldosteron sisteminin (RAAS) inhibisyonu için direk renin inhibitörleri test edilmektedir. Teorik olarak bu ajanların kullanımı ile RAAS'ın daha proksimalden blokajı mümkün olacaktır. Böylelikle anjiyotensin 1 ve anjiyotensin 2'nin refleks aktivasyonunun engellenmesi ve yan etki insidansının azaltılması beklenmektedir. Bu grubun peptid olmayan ve oral kullanılabilen bir üyesi olan aliskiren, ADE inhibitörü ve β -bloker kullanan kalp yetersizliği hastaları üzerinde test edilmiştir (42). Bu çalışmada aliskiren genel olarak iyi

tolere edilmiş ve plaseboya kıyasla hastaların plazma NT-proBNP ve idrar aldosteron düzeylerinde anlamlı azalma sağladığı gösterilmiştir. Bu olumlu gözlemlerden sonra sistolik kalp yetersizliği hastalarında aliskirenin test edildiği geniş çaplı prospektif bir çalışma olan 'Aliskiren trial of minimizing outcomes for patients with heart failure (ATMOSPHERE)' çalışması başlatılmıştır (43). Çalışma halen devam etmektedir. Aliskirenin akut kalp yetersizliği hastaları üzerindeki etkilerinin araştırıldığı çok merkezli, geniş ölçekli ve plasebo kontrollü 'Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)' çalışması da halen devam etmektedir (44).

Kardiyorenal sendrom için geliştirilmekte olan tedaviler:

Kardiyorenal sendromun patofizyolojisinde intrarenal hemodinamiklerde bozulma, transrenal perfüzyon basıncında azalma ve sistemik nörohormonal aktivasyon rol oynar (2).

Adenozin antagonistleri kardiyorenal sendromda kullanılabilecek, adenozin reseptörlerini bloke edip diürezis arttıran yeni bir ilaç grubudur. Glomerüler filtrasyon azaldığında adenozin salgılamakta ve A1 reseptörleri aracılığı ile afferent arteriollerde konstriksiyon sağlanmaktadır. Renal kan akımında azalma proksimal tübüllerden sodyum emilimini arttırmaktadır. Adenozin antagonistleri ile teorik olarak renal kan akımının ve sodyum atılımının artırılması mümkündür (2). Furosemid alan kalp yetersizliği hastalarına bir A1 reseptör antagonisti olan BG9719'un uygulandığı bir çalışmada adenozin antagonistin diürezis önemli olarak arttırdığı ve furosemide bağlı gelişmesi beklenen renal fonksiyonlardaki bozulmayı engellediği gösterilmiştir (2). İntravenöz yolla uygulanan bir A1 reseptör antagonisti olan rolofilin böbrek yetersizliği olan akut kalp yetersizliği hastalarında denenmiştir. Erken faz çalışmalarda umut verici sonuçlar gözlenirse de, 2000 hastalık geniş çaplı bir çalışmada bu ajan ile anlamlı yararlanım elde edilememiştir (2).

Relaksin kalp yetersizliğinde izlenen hemodinamik ve renovasküler adaptasyonda önemli rol oynayan bir peptiddir. Relaksinin etkileri arasında nitrik oksit üretiminin artışı, endotelin ve anjiyotensin 2'nin inhibisyonu ile vasküler endotelial büyüme faktörü ve matriks metalloproteinazların üretiminin uyarılması sayılabilir (2). Relaksin bu mekanizmalar ile sistemik ve renal vazodilatasyonu sağlayıp arteriyel kompliansı artırır. Kronik kalp yetmezliği hastalarında relaksin ile hemodinamik parametrelerde olumlu değişiklikler olduğu tespit edilmiştir (2). 'Relaxin for the treatment of patients with acute heart failure (RELAX-AHF)' çalışmasında akut kalp yetersizliği hastalarında relaksinin etkileri araştırılmış ve relaksin ile dispnenin erkenden düzeldiği ve 60 günlük takip süresinde kardiyovasküler ölüm ve hastaneye tekrar yatış ve renal disfonksiyon oranlarında anlamlı azalma olduğu saptanmıştır (45).

Sıklık guanilat siklaz yolu ile etki eden ajanlar kalp yetersizliği tedavisinde denenmeye başlanmışlardır. Nesiritide ve ürodilatın partikül halindeki guanilat siklaz yoluyla etki göstererek vazodilatör, natriüretik ve diüretik etki gösterirler (2). Akut kalp yetersizliği hastaları üzerinde ürodilatının etkilerinin araştırıldığı çalışmalarda nörohormonal aktivasyon ve hipotansiyon gelişmeden diürezis sağlandığı ve pulmoner arter basıncının düştüğü

gösterilmiştir (2). Cinaciguat ise çözünebilir sıklık guanilat sıklaz üzerinden etki eden yeni bir ajandır. Etki mekanizmasının farklılığı nedeniyle etkilerinin nesiritide veya ürodilatin ile sağlanan etkileri arttıracaklığı düşünülmüştür. Buna karşın erken faz çalışmalarda bu tedavi ile akut kalp yetersizliği hastalarında semptomatik iyileşme sağlanamamış ve düşük dozlarda bile hipotansiyon geliştirdiği izlenmiştir (46).

Adrenomedullin normal fizyolojik şartlarda dolaşımın düzenlenmesinde önemli düzenleyici rol oynadığı düşünülen bir peptiddir (2). Vazodilatör, natriüretik, antifibrotik ve nörohormonal düzenleyici etkileri olmasından dolayı adrenomedullinin akut kalp yetersizliği ve kardiyorenal sendrom tedavisinde kullanılabileceği düşünülmektedir. Küçük çaplı pilot çalışmalarda olumlu hemodinamik etkiler gözlenmiştir (2).

Doğrudan miyokardın hedef alındığı geliştirilmekte olan tedaviler: Kalp yetersizliğinde süreci başlatan asıl olay miyokardiyal kontraktilitenin azalması olup hücresele ve moleküler seviyede bu olayın gelişim mekanizmaları iyi anlaşılmıştır. Yakın zamanda bir kardiyak miyozin aktivatörü olan 'omecamtiv mecarbil' ve bir Na/K ATPaz inhibitörü olan 'istaroksim' kalp yetmezliğinde çalışmaya başlanmıştır. İstaroksim aynı zamanda sarkoplazmik retikulum kalsiyum ATPaz izoform 2a'yı da inhibe etmektedir. Böylece istaroksim ile sistol sırasında sitozolik kalsiyum miktarında artış sağlanırken diyastolde ise kalsiyum sekestrasyonu sağlanmakta ve hem sistolik hem de diyastolik fonksiyonlarda yararlı etkiler oluşturulmaktadır (2). İstaroksimin akut kalp yetersizliğinde etkilerinin araştırıldığı bir klinik çalışma olan HORIZON-HF çalışmasında tedavi ile hastaların pulmoner kama basınçlarının düştüğü, sistolik kan basınçlarının yükseldiği ve diyastolik sertliğin ('stiffness') azaldığı tespit edilmiştir (47). 'Omecamtiv mecarbil' selektif bir kardiyak miyozin aktivatörü olup miyokardiyal oksijen ihtiyacını arttırmadan ve sistol süresini uzatarak inotropik etki gösterir. Bu ajanla akut kalp yetersizliği hastaları üzerinde yapılan faz 2 çalışmalarda umut verici sonuçlar elde edilmiştir (48).

Kalp yetersizliği hastalarında yeniden şekillenmeyi ('remodelling') azalttığı gösterilen RAAS blokerleri ve β -blokerleri mortalite ve morbidite üzerine olan kuvvetli etkilerinin anlaşılmasından sonra yeniden şekillenme üzerine etkili olabilecek yeni ajanlar üzerinde çalışmaya başlanmıştır. Bu amaçla 'pifrenidon' gibi doğrudan antifibrotik büyüme faktörü inhibitörleri, 'tranilast' gibi enflammatuvar sitokin inhibitörleri, metalloproteinaz inhibitörleri ve ryanodin reseptör stabilize edici ajanlar gibi pek çok ajan araştırma çalışmalarında kalp yetersizliği modelleri üzerinde denenmektedir (2, 49).

Sonuç

Kalp yetersizliği halen mortalite ve morbiditesi yüksek olan bir durumdur. Klinik sonuçların düzeltilmesi için halen kullanılmakta olan tedavilerin optimizasyonu yanında yeni tedavi stratejilerine ihtiyaç duyulmakta ve bu amaçla pek çok araştırma yapılmaktadır.

Gelecekte kalp yetersizliğinin gelişmeden önlenmesi üzerine odaklanılacağı ve bu amaçla yeni ilaçların geliştirileceği düşünülmektedir. Tanı ve risk değerlendirmesindeki gelişmeler ile spesifik hasta gruplarına daha erken dönemde daha etkin tedaviler uygulanabilecektir. Ayrıca tedavinin, farmakogenomi kullanılarak kişilere göre optimizasyonu sağlanacak ve her hasta için yüksek etkinlik elde edilecektir. Yakın zamanda üzerinde daha fazla durulmaya başlanan bir başka konu da ko-morbid durumların tedavisidir. Bu durumların etkin tedavisi ile kalp yetersizliği sürecinin ilerlemesinin yavaşlatılacağı düşünülmektedir.

Çıkar çatışması: Bildirilmemiştir.

Peer-review: İç ``peer-review`` değerlendirmesi.

Yazarlık Katkıları: Fikir - B.M.; Tasarım&Dizayn - B.M.; Denetleme - B.M.; Kaynaklar - B.M.; Literatür taraması - A.K.; Yazı yazar - A.K.; Eleştirel inceleme - B.M.

Kaynaklar

- Değertekin M, Erol C, Ergene O, Tokgözoğlu L, Aksoy M, Erol MK, ve ark. Türkiye'deki erişkin popülasyonda kalp yetersizliği prevalans ve prediktörleri: Heart failure prevalence and predictors in Turkey (HAPPY) çalışması. Turk Kardiyol Dern Ars 2012; 40: 298-308. [CrossRef]
- Sata Y, Krum H. The future of pharmacological therapy for heart failure. Circ J 2010; 74: 809-17. [CrossRef]
- Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29: 2388-442. [CrossRef]
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33: 1787-847. [CrossRef]
- Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ. 2011 update to National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006. Med J Aust 2011; 194: 405-9.
- Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA 2009; 301: 1451-9. [CrossRef]
- Konstam MA, Neaton JD, Dickstein K, Drexler H, Komajda M, Martinez FA, et al. Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial. Lancet 2009; 374: 1840-8. [CrossRef]
- Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999; 341: 709-17. [CrossRef]

9. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309-21. [\[CrossRef\]](#)
10. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11-21. [\[CrossRef\]](#)
11. Dyer AR, Stamler J, Shekelle RB, Schoenberger JA, Stamler R, Shekelle S, et al. Pulse pressure-III. Prognostic significance in four Chicago epidemiologic studies. *J Chronic Dis* 1982; 35: 283-94. [\[CrossRef\]](#)
12. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. *Am Heart J* 1987; 113: 1489-94. [\[CrossRef\]](#)
13. Jouven X, Empana JP, Schwartz PJ, Desnos M, Courbon D, Ducimetiere P. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005; 352: 1951-8. [\[CrossRef\]](#)
14. Cooney MT, Vartiainen E, Laatikainen T, Juolevi A, Dudina A, Graham IM. Elevated resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. *Am Heart J* 2010; 159: 612-9.e3.
15. Kolloch R, Legler UF, Champion A, Cooper-Dehoff RM, Handberg E, Zhou Q, et al. Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST). *Eur Heart J* 2008; 29: 1327-34. [\[CrossRef\]](#)
16. McAlister FA, Wiebe N, Ezekowitz JA, Leung AA, Armstrong PW. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med* 2009; 150: 784-94.
17. Böhm M, Swedberg K, Komajda M, Borer JS, Ford I, Dubost-Brama A, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet* 2010; 376: 886-94. [\[CrossRef\]](#)
18. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 807-16. [\[CrossRef\]](#)
19. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; 363: 2385-95. [\[CrossRef\]](#)
20. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; 361: 1329-38. [\[CrossRef\]](#)
21. Zhou J, Shi H, Zhang J, Lu Y, Fu M, Ge J. Rationale and design of the beta-blocker in heart failure with normal left ventricular ejection fraction (beta-PRESERVE) study. *Eur J Heart Fail* 2010; 12: 181-5. [\[CrossRef\]](#)
22. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, et al. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am Heart J* 2011; 162: 966-72. [\[CrossRef\]](#)
23. Hooper MM, Barbera JA, Channick RN, Hassoun PM, Lang IM, Manes A, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: 85-96. [\[CrossRef\]](#)
24. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: 43-54. [\[CrossRef\]](#)
25. Haddad F, Kudenko K, Mercier O, Vrtovec B, Zamanian RT, de Jesus Perez V. Pulmonary hypertension associated with left heart disease: characteristics, emerging concepts, and treatment strategies. *Prog Cardiovasc Dis* 2011; 54: 154-67. [\[CrossRef\]](#)
26. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates-2006. *J Heart Lung Transplant* 2006; 25: 1024-42. [\[CrossRef\]](#)
27. Chen JM, Levin HR, Michler RE, Prusmack CJ, Rose EA, Aaronson KD, et al. Reevaluating the significance of pulmonary hypertension before cardiac transplantation: determination of optimal thresholds and quantification of the effect of reversibility on perioperative mortality. *J Thorac Cardiovasc Surg* 1997; 114: 627-34. [\[CrossRef\]](#)
28. Guazzi M. Sildenafil and phosphodiesterase-5 inhibitors for heart failure. *Curr Heart Fail Rep* 2008; 5: 110-4. [\[CrossRef\]](#)
29. Lewis GD, Shah R, Shahzad K, Camuso JM, Pappagianopoulos PP, Hung J, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation* 2007; 116: 1555-62. [\[CrossRef\]](#)
30. Guazzi M, Vicenzi M, Arena R, Guazzi MD. PDE5 inhibition with sildenafil improves left ventricular diastolic function, cardiac geometry, and clinical status in patients with stable systolic heart failure: results of a 1-year, prospective, randomized, placebo-controlled study. *Circ Heart Fail* 2011; 4: 8-17. [\[CrossRef\]](#)
31. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation* 2011; 124: 164-74. [\[CrossRef\]](#)
32. Potter BJ, White M, Carrier M, Pellerin M, L'Allier PL, Pelletier GB, et al. Hemodynamic and clinical benefits associated with chronic sildenafil therapy in advanced heart failure: experience of the Montréal Heart Institute. *Can J Cardiol* 2012; 28: 69-73. [\[CrossRef\]](#)
33. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* 2010; 16: 1-194. [\[CrossRef\]](#)
34. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, et al. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008; 52: 818-27. [\[CrossRef\]](#)
35. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008; 51: 103-12. [\[CrossRef\]](#)
36. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361: 2436-48. [\[CrossRef\]](#)
37. Lawler PR, Filion KB, Eisenberg MJ. Correcting anemia in heart failure: the efficacy and safety of erythropoiesis-stimulating agents. *J Card Fail* 2010; 16: 649-58. [\[CrossRef\]](#)
38. Silverberg DS, Wexler D, Blum M, Iaina A, Sheps D, Keren G, et al. Effects of treatment with epoetin-beta on outcomes in patients with anaemia and chronic heart failure. *Kidney Blood Press Res* 2005; 28: 41-7. [\[CrossRef\]](#)
39. McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, et al. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): A Phase III, anemia correction, morbidity-mortality trial. *Eur J Heart Fail* 2009; 11: 795-801. [\[CrossRef\]](#)

40. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med* 2001; 344: 1659-67. [\[CrossRef\]](#)
41. Abraham WT, Adams KF, Fonarow GC, Costanzo MR, Berkowitz RL, LeJemtal TH, et al. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol* 2005; 46: 57-64. [\[CrossRef\]](#)
42. McMurray JJ, Pitt B, Latini R, Maggioni AP, Solomon SD, Keefe DL, et al. Aliskiren Observation of Heart Failure Treatment (ALOFT) Investigators. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail* 2008; 1: 17-24. [\[CrossRef\]](#)
43. Krum H, Massie B, Abraham WT, Dickstein K, Kober L, McMurray JJ. Direct renin inhibition in addition to or as an alternative to angiotensin converting enzyme inhibition in patients with chronic systolic heart failure: rationale and design of the Aliskiren Trial to Minimize OutcomeS in Patients with HEart FailuRE (ATMOSPHERE) study. *Eur J Heart Fail* 2011; 13: 107-14. [\[CrossRef\]](#)
44. Gheorghiade M, Albaghdadi M, Zannad F, Fonarow GC, Böhm M, Gimpelewicz C, et al. Rationale and design of the multicentre, randomized, double-blind, placebo-controlled Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT). *Eur J Heart Fail* 2011; 13: 100-6. [\[CrossRef\]](#)
45. Teerlink JR, Metra M, Felker GM, Ponikowski P, Voors AA, Weatherley BD, et al. Relaxin for the treatment of patients with acute heart failure (Pre-RELAX-AHF): A multicentre, randomised, placebo-controlled, parallel-group, dose-finding phase IIb study. *Lancet* 2009; 373: 1429-39. [\[CrossRef\]](#)
46. Gheorghiade M, Greene SJ, Filippatos G, Erdmann E, Ferrari R, Levy PD, et al. Cinaciguat, a soluble guanylate cyclase activator: results from the randomized, controlled, phase IIb COMPOSE programme in acute heart failure syndromes. *Eur J Heart Fail* 2012; 14: 1056-66. [\[CrossRef\]](#)
47. Shah SJ, Blair JE, Filippatos GS, Macarie C, Ruzyllo W, Korewicki J, et al. Effects of istaroxime on diastolic stiffness in acute heart failure syndromes: results from the Hemodynamic, Echocardiographic, and Neurohormonal Effects of Istaroxime, a Novel Intravenous Inotropic and Lusitropic Agent: a Randomized Controlled Trial in Patients Hospitalized with Heart Failure (HORIZON-HF) trial. *Am Heart J* 2009; 157: 1035-41. [\[CrossRef\]](#)
48. Cleland JG, Teerlink JR, Senior R, Nifontov EM, McMurray JJ, Lang CC, et al. The effects of the cardiac myosin activator, omecamtiv mecarbil, on cardiac function in systolic heart failure: a double-blind, placebo-controlled, crossover, dose-ranging phase 2 trial. *Lancet* 2011; 378: 676-83. [\[CrossRef\]](#)
49. Landmesser U, Wollert KC, Drexler H. Potential novel pharmacological therapies for myocardial remodelling. *Cardiovasc Res* 2009; 81: 519-27. [\[CrossRef\]](#)

The effect of distance-based learning on the fifth stage medical students' perception in peripheral vascular diseases course: a questionnaire survey

Periferik damar hastalıkları stajında uzaktan eğitim sisteminin beşinci sınıf tıp öğrencilerinin algılaması üzerine etkisi: Anket çalışması

Mustafa Saçar, Gökhan Önem¹, Akile Sarıoğlu Büke², Ahmet Baltalarlı¹

Department of Cardiovascular Surgery, Faculty of Medicine, Onsekiz Mart University, Çanakkale-Turkey

Department of ¹Cardiovascular Surgery, ²Main Coordinator of the Undergraduate Education, Faculty of Medicine, Pamukkale University, Denizli-Turkey

Task-based learning (TBL), a part of the active learning process, is an educational model integrating problem-based learning system with the multidisciplinary training viewpoint. "Task" is used in a meaning of clinical "duty" or "work" (1-3).

E-learning, distance education and computer-supported education systems have gained popularity in undergraduate education. Many medical schools have adopted course management systems to facilitate e-learning activities. Modular object-oriented dynamic learning environment (Moodle) is the most commonly used (4).

The aim of the study was to assess the effects of distance-based learning in combination with the traditional teaching system on the undergraduate medical students' perception by means of a satisfaction questionnaire.

The educational program for the students in their fifth years in our Medical Faculty has been constituted on the basis of TBL for ten years. The principal aim of the program of the peripheral vascular diseases course carried out by the Cardiovascular Surgery Clinic is to provide the students with: (i) an access to the fundamental learning objectives, (ii) an implementation of their theoretical knowledge in a clinical practice, and (iii) an improvement of their clinical skills.

The feedbacks of the fifth stage students on the Peripheral Vascular Disease course collected over 3 years were evaluated. Afterwards, web-based electronic portal named "Moodle" (4) was

installed with the aim of contributing to the solution of the problems confronted with during the courses. Our clinic was the first one in our medical school to introduce Moodle platform for the students.

There were two groups in stage V in the spring term with 27 students. All of them were included in the study. The students were equipped with individual passwords for access to the system (Fig. 1).

The lecture notes of the voluntary teaching staff were made available for download immediately after their presentations. Summaries, presentations, case report samples, videos with applied examples, practical examination cards, educational scenario examples and quizzes were uploaded. The system was enriched with an interactive discussion platform. Except for the addition of the computer-supported system, no change was made in the running of the course-scheduled program.

The students were asked to complete pre-course and post-course questionnaires to evaluate their feedbacks on the peripheral vascular diseases course carried out in combination with a computer-supported education system. The questionnaire enabled participants to evaluate the diverse parts of the running of the course including its content, ability to facilitate students' access to the course material, contribution to the practical implementations and the elimination of the anxiety about the exams. Participants' responses were rated on a 2-point Likert scale (1=agree, 2=disagree).

Address for Correspondence/Yazışma Adresi: Dr. Mustafa Saçar, Çanakkale Onsekiz Mart Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi Anabilim Dalı, Çanakkale-Türkiye Phone: +90 258 211 85 85 E-mail: mustafasacar@hotmail.com

Accepted Date/Kabul Tarihi: 12.09.2012 **Available Online Date/Çevrimiçi Yayın Tarihi:** 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.079



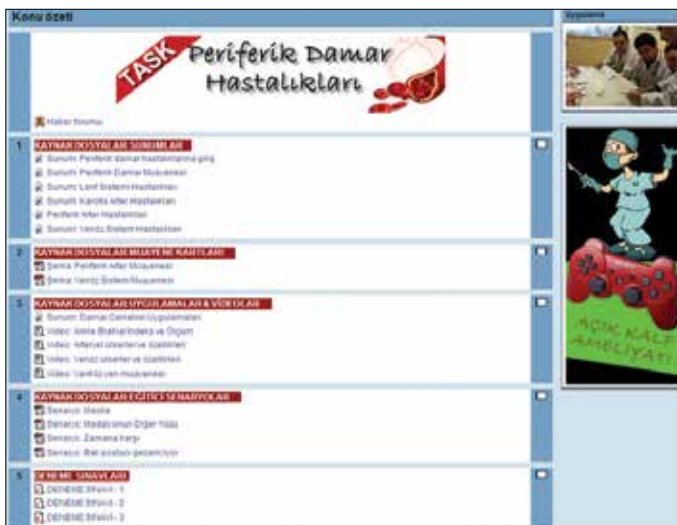


Figure 1. Computer supported education system prepared for peripheral vascular disease course

Table 1. Results of the pre-course and post-course questionnaire and feedbacks of the students on Peripheral Vascular Disease course

Concept	Pre-course (n=27)	Post-course (n=27)	*p
Concern about attainment of the presentation documents, n (%)	10 (37.0)	2 (7.4)	<0.05
Inadequate supply of supplementary source materials, n (%)	7 (25.9)	2 (7.4)	<0.05
Insufficiency in visual material, n (%)	13 (48.1)	5 (18.5)	<0.05
Concern about Block exam, n (%)	15 (55.5)	4 (14.8)	<0.05
Concern about TUS, n (%)	17 (62)	11 (40.7)	<0.05
Insufficiency in the content of the scenarios, n (%)	6 (22.2)	4 (14.8)	NS
Insufficiency in surgical practices, n (%)	5 (18.5)	3 (11.1)	NS
Data are presented as number (percentage)			
*Mc-Nemar Chi-square test			
NS - not significant, TUS - Examination for speciality in medicine			

The statistical analysis of the data obtained from the inquiry was made with SPSS 17.0 for Windows (SPSS, Inc., Chicago, USA) using *Mc-Nemar* Chi-square test. Differences of $p < 0.05$ were considered significant.

At the beginning of the course, one third of the students had anxiety about the access to the presentation documents. This percentage was found to be significantly decreased with the introduction of the new system ($p < 0.05$). The problems originating from the inadequate supply of supplementary source materials were shown to be decreased due to the computer supported education system ($p < 0.05$). The respondents' view that the visual material was insufficient changed significantly at the end of the course ($p < 0.05$). The implementation of the new system was found to reduce the anxiety about the exams ($p < 0.05$) (Table 1).

No difference was observed in the content of the scenarios prepared for the course ($p > 0.05$). Additionally, no difference was found between the views of the students regarding the inadequacy of the surgical implementations ($p > 0.05$).

It is not always possible to represent every disease in the curriculum during the clinical education. In these situations, various videos properly prepared with regard to the learning contents can support the education system (5). Most of the students indicated that although they had seen the arterial and venous system diseases on the patients, they understood them more clearly with the videos on the digital system.

On-line formative evaluations have the potential to provide the students with a chance for self-evaluation whenever and wherever they desire (6). In our study, the outcomes of these evaluations were visible on the system by the students and the teaching staff. Therefore, the missing points in the given lecture come on the scene and the complementation of them is provided by giving an immediate feedback to the students and making the required changes in the system.

A cornerstone of medical education is the practicum. Nevertheless, acquiring common skills before practicing on real patients is essential for the physician (7). For that purpose, we benefit from structured scenarios. Students are encouraged to deliver learning objectives from these scenarios. Then, they make researches according to these objectives. This learning method directs the students towards deep learning (8, 9).

At the end of the course, the question bank and the documents in the digital environment were left open to maintain access of the students after their graduation. In that way, the participants will have an access to the system wherever they want after the graduation, can update their knowledge and can exchange considerations with their colleagues.

Our results indicate that the combination of the traditional teaching system with a computer-supported education system results in an increased students' satisfaction, decreased concern about the exams, and increment in the attainment of the source materials. E-learning may have a particular role in explaining complicated disease mechanisms in cardiovascular surgery.

Conflict of interest: None declared.

Peer-review: Internally peer-reviewed.

Authorship contributions: Concept - M.S., A.B.; Design - A.S.B.; Supervision - G.Ö., M.S.; Resource - M.S., A.B.; Analysis &/or interpretation - A.S.B.; Literature search - M.S.; Writing - M.S., G.Ö.; Critical review - A.S.B.

References

1. Harden RM, Laidlaw JM, Ker JS, Mitchell HE. AMEE Medical Education Guide No 7: Task-based learning: an educational strategy for undergraduate, postgraduate and continuing medical education, Parts 1 & 2. *Med Teacher* 1996; 18: 7-13. [CrossRef]
2. Williams SM, Beattie HJ. Problem based learning in the clinical setting-a systematic review. *Nurse Educ Today* 2008; 28: 146-54. [CrossRef]

3. Harden R, Crosby J, Davis MH, Howie PW, Struthers AD. Task-based learning: the answer to integration and problem-based learning in the clinical years. *Med Educ* 2000; 34: 391-7. [\[CrossRef\]](#)
4. Dougiamas M, Taylor PC. Moodle: using learning communities to create an open source course management system. In: Lassner D, McNaught C. editors. *World Conference on Educational Multimedia, Hypermedia and Telecommunications*. Honolulu, HI: Assoc. for the Advancement of Computing in Education; 2003.p.171-8.
5. Azer SA. Twelve tips for creating trigger images for problem-based learning cases. *Med Teach* 2007; 29: 93-7. [\[CrossRef\]](#)
6. Seluakumaran K, Jusof FF, Ismail R, Husain R. Integrating an open-source course management system (Moodle) into the teaching of a first-year medical physiology course: a case study. *Adv Physiol Educ* 2011; 35: 369-77. [\[CrossRef\]](#)
7. Norman GR. Introduction. In: Schmidt HG, de Volder ML, editors. *Tutorials in Problem-Based Learning: A New Direction in Teaching the Health Professions*. Assen, Maastricht: van Gorcum; 1984.p.125-7.
8. Davis MH, Harden RM. Problem-based learning: A practical guide. *Med Teach* 1999; 20: 317-22. [\[CrossRef\]](#)
9. Wood DF. ABC of learning and teaching in medicine: Problem based learning. *BMJ* 2003; 326: 328-30. [\[CrossRef\]](#)

Acute coronary syndrome with intraventricular thrombus after using erythropoietin



Eritropoetin kullanımı sonrası intraventriküler trombus ile birlikte akut koroner sendrom

Introduction

Erythropoietin (EPO) is a hemopoietic hormone, which controls erythropoiesis, produced by the renal interstitium in response to hypoxia (1). Furthermore, erythropoietin receptors were found on endothelial cells, fibroblasts and cardiomyocytes (1). Erythropoietin was associated with significant reduction in infarct size and apoptosis, improvement in ischemia-induced neovascularization and increase in left ventricular function (2-5).

We describe a professional wrestler, who had taken intravenous EPO with the intention of doping 1 day before the contest, with acute coronary syndrome (ACS) with intraventricular thrombus.

Case report

A-29-year-old professional wrestler man was referred with a history of substernal chest pain and cold sweating during a traditional oil wrestling contest. He confessed intravenous erythropoietin 4000 i.u. usage with the intention of doping 1 day before the contest. He had not the medical history of diabetes, hypertension, smoking nor family history. Physical examination and laboratory findings were normal (total cholesterol: 176 mg/dL, high-density lipoprotein cholesterol: 46 mg/dL, low-density lipoprotein cholesterol: 99 mg/dL and triglyceride: 155 mg/dL). ECG showed ST-T changes in leads V1 to V6 (Fig. 1a). Two-dimensional transthoracic echocardiography (TTE) showed akinesia of the anterior, septal and apical segments with apical thrombus (1.1cm x 1.1 cm) (Fig. 1b). Left ventricular ejection fraction was 45%. Coronary angiogram was performed, which revealed widespread thrombus in the mid and distal left anterior descending coronary artery (Fig. 2a, Video 1-3. See corresponding video/movie images at www.anakarder.com). A decision of medical therapy and periodic follow up was made. Intravenous tirofiban was administered for 2 days. But also simultaneously acetylsalicylic acid 300 mg/d, clopidogrel 75 mg/d, metoprolol 25 mg bid, simvastatin 20 mg/d were given orally. One week later a control coronary angiogram and TTE were performed which showed nearly total resolution of intracoronary thrombus (Fig. 2b) and intraventricular thrombus. The patient was made an uneventful recovery and was discharged on the seventh day. The patient was called via telephone five years later. He is very good in condition and he is continuing oil wrestling with having some championships.

Discussion

Erythropoietin has long been identified as a primary regulator of erythropoiesis. In particular, the tight interactions of EPO with the nitric oxide pathway, apoptosis, ischemia, cell proliferation and platelet activation appear of great interest (2-5). Erythropoietin was associated with significant reductions in infarct size and apoptosis, improvements in ischemia-induced neovascularization, increases in left ventricular function and preventions of ventricular remodeling (2-5). Erythropoietin might reduce the infarct size by inhibiting apoptotic cell death. Nevertheless, this reduction in myocardial damage was accompanied by prevention of left ventricular dilation and improved left ventricular ejection fraction. Although enhanced EPO synthesis is viewed as an appropriate compensatory mechanism in the cardio-renal syndrome, which features conges-

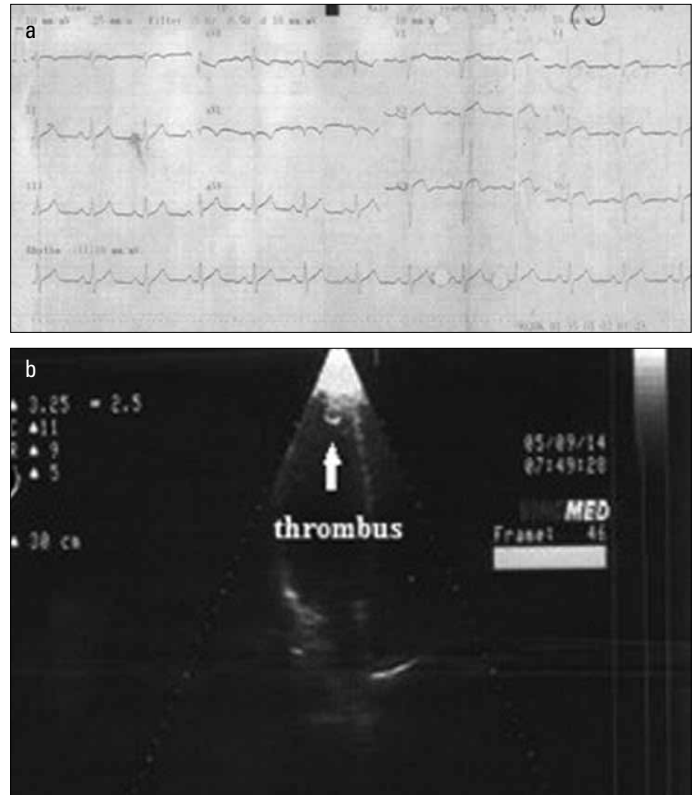


Figure 1. a) Electrocardiogram showing ST changes in V3-V6 leads b) Echocardiography showing an apical thrombus in left ventricle

tive heart failure and chronic renal failure, maladaptive excessive EPO synthesis in the advanced stages of these diseases appears to be predictive of higher mortality. Increased EPO values may lead to hypertension, seizures, vascular thrombosis, thromboembolism and death, possibly related to abruptly increased hematocrit values (6).

A case of late thrombosis of a sirolimus-eluting stent, 16 months after implantation, is described (7). Two weeks prior to presentation with stent thrombosis the patient had a 50% dose increase of long term erythropoietin. In patients with STEMI who had successful reperfusion with primary or rescue PCI, a single intravenous bolus of epoetin alpha within 4 hours of PCI did not reduce infarct size and was associated with higher rates of adverse cardiovascular events (8).

The prothrombotic effect of erythropoietin may have precipitated the thrombotic event. The precise mechanism by which EPO induces a thrombotic event, remains unclear. Prothrombotic effect of EPO might associated with abruptly increased hematocrit values, enhanced platelet production or reactivity, stimulation of endothelial cells or reduced coagulation inhibitors (9, 10).

We reported a case of ACS thought to be associated with using intravenous EPO. The presence of both intracoronary and intraventricular thrombus is very interesting. Intracoronary thrombus may be related to embolism of intraventricular thrombus.

Even to date, there is no consensus as to the best management when treating ACS caused by coronary thrombus. In this case, tirofiban infusion achieved successful treatment intracoronary and intraventricular thrombus.

Conclusion

When intracoronary thrombus is detected with coronary angiography, we must investigate an intraventricular thrombus and using an unusual drugs or using drug abuse in young patients.

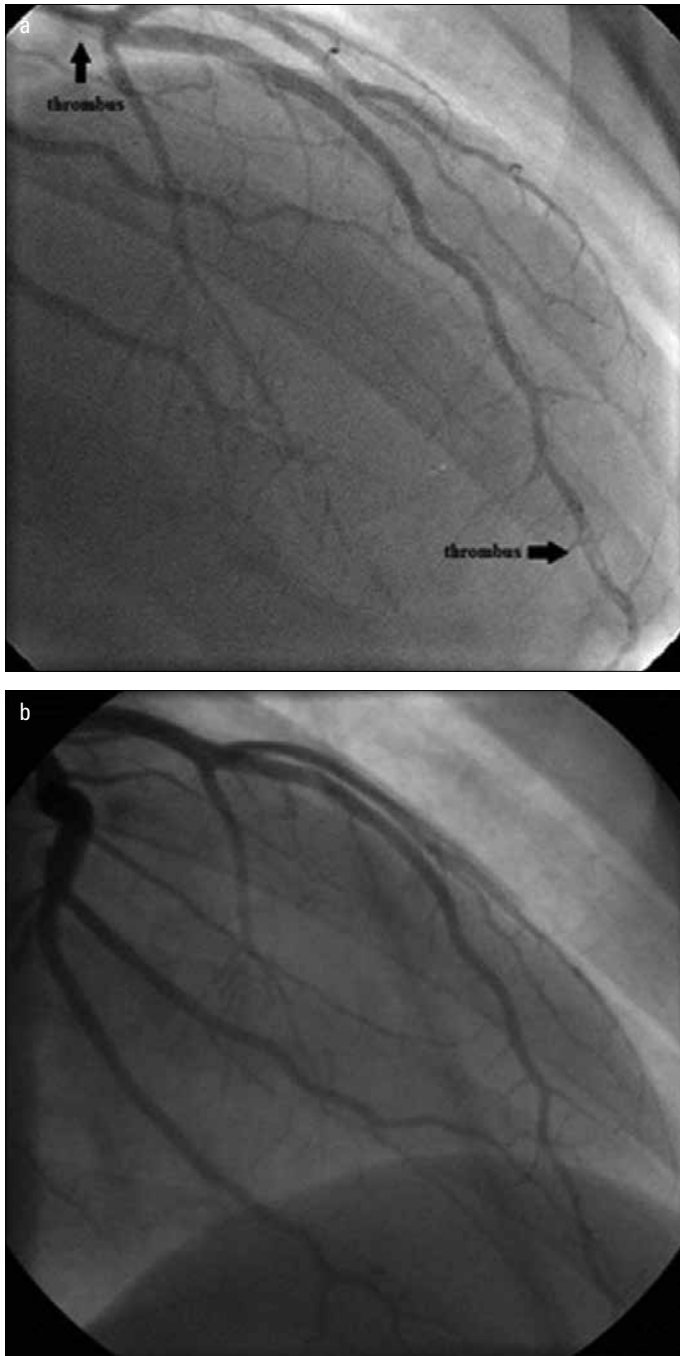


Figure 2. a) Thrombi are seen in the mid (extending to first septal artery) and distal left anterior descending artery, b) Thrombi are seen disappeared on control angiography

Alparslan Kurtul, Mustafa Duran¹, Onur Kadir Uysal¹, Ender Örnek
Clinic of Cardiology, Etlik İhtisas Education and Research Hospital,
Ankara-Turkey

¹Clinic of Cardiology, Kayseri Education and Research Hospital,
Kayseri-Turkey

Video 1. Coronary angiography showing a thrombus in the distal left anterior descending artery (antero-posterior caudal view)

Video 2. Coronary angiography showing thrombi in the mid (extending to first septal artery) and distal left anterior descending artery (right anterior oblique cranial view)

Video 3. Thrombi are seen in the mid (extending to first septal artery) and distal left anterior descending artery (lateral view)

References

1. Jelkmann W. Erythropoietin: structure, control of production, and function. *Physiol Rev* 1992; 72: 449-89.
2. Parsa CJ, Matsumoto A, Kim J, Riel RU, Pascal LS, Walton GB, et al. A novel protective effect of erythropoietin in the infarcted heart. *J Clin Invest* 2003; 112: 999-1007. [CrossRef]
3. Lipsic E, van der Meer P, Henning RH, Suurmeijer AJ, Boddeus KM, van Veldhuisen, DJ, et al. Timing of erythropoietin treatment for cardioprotection in ischemia/reperfusion. *J Cardiovasc Pharmacol* 2004; 44: 473-9. [CrossRef]
4. Moon C, Krawczyk M, Ahn D, Ahmet I, Paik D, Lakatta EG, et al. Erythropoietin reduces myocardial infarction and left ventricular functional decline after coronary artery ligation in rats. *Proc Natl Acad Sci USA* 2003;100: 11612-7. [CrossRef]
5. Parsa CJ, Kim J, Riel RU, Pascal LS, Thompson RB, Petrofski JA, et al. Cardioprotective effects of erythropoietin in the reperfused ischemic heart: a potential role for cardiac fibroblasts. *J Biol Chem* 2004; 279: 20655-62. [CrossRef]
6. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; 339: 584-90. [CrossRef]
7. Gladding PA, Webster MW, Kay P. Late drug-eluting stent thrombosis and erythropoietin: cause and effect? *Heart Lung Circ* 2007; 16: 305-7. [CrossRef]
8. Najjar SS, Rao SV, Melloni C, Raman SV, Povsic TJ, Melton L, et al. REVEAL Investigators. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA* 2011; 305: 1863-72. [CrossRef]
9. Fuste B, Serradell M, Escolar G, Cases A, Mazzara R, Castillo R, et al. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. *Thromb Haemost* 2002; 88: 678-85.
10. Stohlawetz PJ, Dzirlo L, Hergovich N, Lackner E, Mensik C, Eichler HG, et al. Effects of erythropoietin on platelet reactivity and thrombopoiesis in humans. *Blood* 2000; 95: 2983-9.

Address for Correspondence/Yazışma Adresi: Dr. Mustafa Duran,
Kayseri Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, Kayseri-Türkiye
Phone: +90 505 391 16 20
E-mail: mduran2@gmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013



©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.080

Variant high origin of both right and left coronary arteries from the ascending aortic wall

Çıkan aort duvarından yüksek kökenli hem sağ ve sol koroner arter

Introduction

We report here the interesting case of anomalous origin of both coronary arteries. The prevalence of high takeoff (more than 1 cm above the sinotubular junction) is reported as 6% (1, 2). Presence of coronary artery anomalies may create challenges during coronary

angiography and other procedures during which attention to be paid on the position of the coronary orifice. In adults, the clinical interest in coronary anomalies relates to their occasional association with sudden death, myocardial ischemia, congestive heart failure, or endocarditis.

Case Report

During routine student's dissection, this anomaly was observed in a donated male cadaver aged, 60 years. He had never been medically treated and no traumatic findings.

On dissection, both lungs and pericardium appeared to be normal. The right coronary ostia was circular shaped (Fig. 1, 2) with a diameter of 4 mm located 18 mm above the rim of the sinotubular junction originating at the right anterolateral aspect of the ascending aorta with an angle of 45 degree. Its further course was normal.

The left coronary ostia was pocket shaped (Fig. 1, 2) with a diameter of 6 mm located 17 mm above the rim of the sinotubular junction originating at the left anterolateral aspect of the ascending aorta with an angle of 80 degree. After origin, it was divided into anterior interventricular and left circumflex branch at a distance of 20 mm and continued in its normal course.



Figure 1. Radiography taken to show coronary course in the specimen



Figure 2. Pathology view of coronary arteries and its ostia

Discussion

Ectopic high origin (high takeoff of the coronary ostia) of coronary arteries has been defined as having ostia originating more than 5 mm above the supra valvular ridge or 10 mm above the sino tubular junction, which is seen in our case. In a study by Eckart et al. (3), coronary artery abnormalities were the most common cardiac abnormality (61%). Some authors have mentioned that in acute high ectopic origins of the coronary artery, increase in blood flow during exercise made the artery pull the upper border of the aortic wall, and push the lower border upward, resulting in transient flow impairment of the anomalous ectopic coronary artery (4, 5). High take-off of the coronary arteries may cause difficulty in cannulating the vessels during coronary arteriography. Sudden death also has been reported which is mainly due to impairment in the diastolic coronary artery flow. Knight et al. (6) has found the mean ostial positions in relation to the aortic annulus were 17 mm and 15.3 mm for the right and left coronary ostia respectively (whereas in our study, it is 18 mm- right and 17 mm- left).

Conclusion

This person survived till 60 years and had a natural death even though having high take off origin of both side of coronary arteries. This concludes that he was leading a non-stressful life. High origin of the coronary artery is a potential source of sudden death that should be considered when no other significant autopsy findings are present. We believe that this case will be useful for cardiologist in detecting this infrequent anomaly and also its implication in forensic practice.

Raghavendra Rao, Bondel Shwetha¹

Ramaiah International Medical School, Anatomy, Bangalore, Karnataka-India

¹Sapthagiri Institute of Medical Sciences and Research Centre, Anatomy, Bangalore-India

References

1. Montaudon M, Latrabe V, Iriart X, Caix P, Laurent F Congenital coronary arteries anomalies: review of the literature and multidetector computed tomography (MDCT)-appearance. *Surg Radiol Anat* 2007; 29: 343-55. [CrossRef]
2. Angelini P. Coronary artery anomalies- current clinical issues: definitions, classification, incidence, clinical relevance, and treatment guidelines. *Tex Heart Inst J* 2002; 29: 271-8.
3. Eckart RE, Scoville SL, Campbell CL, Shry EA, Staiduhar KC, Potter RN, et al. Sudden death in young adults: a 25- year review of autopsies in military recruits. *Ann Intern Med* 2004; 141: 829-34.
4. Lipsett J, Cohle SD, Berry PJ, Russell G, Byard RW. Anomalous coronary arteries: a multi-center paediatric autopsy study. *Pediatr Pathol* 1994; 14: 287-300. [CrossRef]
5. Taylor AJ, Rogan KM, Virmani R. Sudden cardiac death associated with isolated congenital artery anomalies. *J Am Coll Cardiol* 1992; 20: 640-7. [CrossRef]
6. Knight J, Kurtcuoglu V, Muffly K, Marshall W Jr, Stolzmann P, Desbiolles L, et al. Ex Vivo and in vivo coronary ostial locations in humans. *Surg Radiol Anat* 2009; 31: 597-604. [CrossRef].

Address for Correspondence/Yazışma Adresi: Dr. Bondel Shwetha, Sapthagiri Institute of Medical Sciences and Research Centre, Anatomy, Bangalore-India

Phone: 09740123366 E-mail: swetha12doc@yahoo.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.081



Miyokart enfarktüsü sonrası implante edilen ICD tarafından sağ ventrikül uyarılmasına bağlı kötüleşen kalp yetersizliğinin resenkronizasyon ile tedavisi

Worsening of heart failure due to right ventricular apical pacing by ICD implanted after myocardial infarction and treatment with resynchronization

Giriş

Kronik sağ ventrikül apikal (VA) uyarısı ventriküler dissenkroni, artmış serum BNP ve kalp yetersizliği ile ilişkilidir (1). Bu olgu sunumunda miyokart enfarktüsü (ME) sonrası ventriküler taşikardi (VT) nedeniyle implante edilebilir kardiyoverter-defibrilatör (ICD) implante edilen bir hastada, izlemde atriyoventriküler tam blok gelişmesi sonucunda ICD tarafından sağ ventrikül apikal uyarılmasına bağlı kötüleşen kalp yetersizliği anlatılmıştır.

Olgu Sunumu

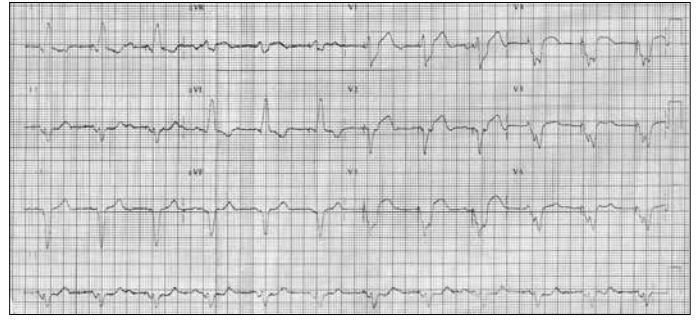
Üç yıl önce akut ME geçiren, izlemde VT nedeniyle ICD implante edilen 66 yaşındaki erkek hasta optimal medikal tedavi almasına rağmen NYHA III nefes darlığı ile koroner yoğun bakım ünitesine yatırıldı. Öyküsünden ME sonrası altıncı ayda ejeksiyon fraksiyonunun (EF) %32 ve Holterde süresiz VT saptanması üzerine tek odacıklı ICD implante edildiği, bir yıl önce devamlı yavaş hızlı VT nedeniyle başka bir merkezde başarılı radyofrekans ablasyonu yapıldığı öğrenildi. Üç yıl önce çekilen EKG'sinde sinüs ritmi, eski anteroseptal ME örneği görüldü ve QRS süresi 160 ms olarak ölçüldü. Yeni EKG'sinde pil ritmi saptandı ve QRS süresi 240 ms idi (Şekil 1, 2). EF'si %26 idi. Mitral akım E dalga hızının lateral mitral anülüs E' miyokardiyal hızına oranı (E/E') 17 olarak bulundu. Hastanın ICD'sinin pil fonksiyonu görmesi, sağ ventrikül apikal uyarılması sonrası kalp yetersizliği semptomlarının giderek kötüleşmesi nedeniyle hastaya ICD işlevli biventriküler kalp pili implantasyonu kararı verildi. İşlem sonrası QRS süresi 160 ms olarak ölçüldü (Şekil 3). Bir ay sonra kontrole çağırılan hastada NYHA I-II dispne vardı. EF %28 ve E/E' oranı 9 olarak ölçüldü.

Tartışma

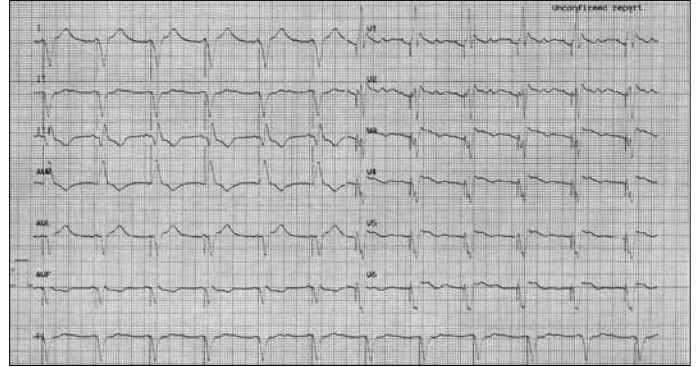
Kronik sağ ventriküler apikal pacing ventrikül fonksiyonlarını kötüleştirmekte ve hastanın fonksiyonel kapasitesini ventrikül fonksiyonu normal olsa dahi bozmaktadır (2). EF'si azalmış hastalarda sağ ventriküler uyarı-



Şekil 1. Anteriyor miyokart enfarktüsü sonrasında QRS süresinde uzama ve QRS'te fragmantasyon izlenmektedir



Şekil 2. İzlemde atriyoventriküler tam blok gelişen hastada ICD tarafından sağ ventrikül apikal uyarılmasına bağlı olarak QRS süresinin belirgin olarak uzadığı görülmektedir



Şekil 3. Resenkronizasyon tedavisi sonrasında QRS'te daralma dikkati çekmektedir. CRT - D sonrasında hastanın semptomlarında ve eko-kardiyografik bulgularında belirgin iyileşme gözlenmiştir

dan biventriküler kalp pili uygulamasına geçişin klinik yararı gösterilmiştir (3). Bu nedenle ICD endikasyonu olan ve ileride pacemaker gereksinimi gelişebilecek kalp yetersizliği hastalarında defibrilatör işlevli kardiyak resenkronizasyon tedavisi (CRT-D) öncelikli olarak düşünülmelidir. Sol ventrikül sistolik disfonksiyonu ve hafif düzeylerde kalp yetersizliği olan hastalarda, özellikle QRS süresinin 150 ms'nin üzerinde olması durumunda CRT'nin kalp yetersizliğinin kötüleşmesini önlediği, kalp yetersizliği nedeniyle hastaneye yatışları ve mortaliteyi azalttığı gösterilmiştir (4).

Miyokart enfarktüsü (ME) sonrası hastane döneminde sebat eden intraventriküler ileti defekti gelecekte atriyoventriküler (AV) blok riskinin yüksek olduğunu gösterir ve kötü prognostik bir bulgudur. Yüksek dereceli AV blok için risk faktörleri 1. derece AV blok, bifasiküler blok veya alterne sağ dal-sol dal bloğu ve yeni gelişen dal bloğu olarak belirlenmiştir. Birinci derece AV blokla birlikte bilateral dal bloğu veya yeni gelişen dal bloğu en yüksek riski taşımaktadır.

Akut ME sonrasında AV blok risk derecelendirmesi için elektrofizyolojik çalışma rutin olarak kullanılmamaktadır. Ancak, ileti sistemindeki bozukluğun yerini belirlemek için His demeti elektrogramı kullanılabilir. Distal ileti sisteminde blok saptanması yüksek dereceli AV blok riskini artırmaktadır. Anteriyor ME sonrası sıklıkla distal ileti sistemi etkilenmektedir. EKG'de PR mesafesi normal olup, dal bloğu bulunan hastaların yaklaşık yarısında His-ventrikül (HV) intervali normalden uzundur.

Akut ME sonrası kalıcı kalp pili endikasyonu olan tüm hastalar aynı zamanda ICD ve CRT açısından da değerlendirilmelidir. Geçici 2. veya 3. derece AV blok ile beraber kalıcı dal bloğu bulunan hastalara kalp pili implante edilmelidir. Bu hastalarda blok yerini belirlemek için elektrofizyolojik çalışma yapılabilir. Akut ME geçiren ve AV blokla birlikte dal bloğu gelişen birçok hastaya sol ventrikül disfonksiyonu nedeniyle birincil korunma amaçlı ICD implantasyonu da gerekmektedir.

Bizim hastamızda anteriyor ME sonrası ejeksiyon fraksiyonu %30'un altına düşmüştür ve QRS süresinin 160 ms olması intraventriküler ileti sis-

teminde hasar bulunduğunu düşündürmektedir. Ayrıca yavaş ventriküler taşikardi nedeniyle yapılmış olan radyofrekans ablasyon da ileti sistemindeki hasarı artırmış olabilir. Sağ ventrikül uyarılmasına ek olarak atriyoventriküler dissenkroninin de kalp yetersizliğini kötüleştirdiği düşünülmüştür. Hastanın cihazının CRT-D olarak değiştirilmesiyle sol ventrikül doluş basıncında düşüş ve kalp yetersizliği semptomlarında düzelme sağlanmıştır.

Sonuç

Miyokart enfarktüsü sonrası VT nedeniyle ICD implante edilmeden önce elektrofizyolojik çalışma ile ileti sistemindeki hasar bölgesinin belirlenmesi ve yüksek dereceli AV blok riskinin öngörülebilmesi mümkündür. Böyle bir hastada AV blok nedeniyle ICD'nin sağ ventrikül apikal uyarı yapması ve atriyoventriküler dissenkroni hastanın kalp yetersizliğini kötüleştirebilir. Sol ventrikül işlevlerinin kötüleşmesinin önüne geçilebilmesi amacıyla elektrofizyolojik çalışmada distal ileti sistemi kusuru gösterilen hastalarda CRT-D düşünülebilir.

Ali Deniz, Mehmet Kanadaşı, Mesut Demir, Ayhan Usal
Çukurova Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı,
Adana-Türkiye

Kaynaklar

1. Abreu CD, Nunes Mdo C, Barbosa MM, Rocha MO, Ribeiro AL. Ventricular dyssynchrony and increased BNP levels in right ventricular apical pacing. *Arq Bras Cardiol* 2011; 97: 156-62. [CrossRef]
2. Zhang XH, Chen H, Siu CW, Yiu KH, Chan WS, Lee KL, et al. New-onset heart failure after permanent right ventricular apical pacing in patients with acquired high-grade atrio-ventricular block and normal left ventricular function. *J Cardiovasc Electrophysiol* 2008; 19: 136-41. [CrossRef]
3. van Geldorp IE, Vernooij K, Delhaas T, Prins MH, Crijns HJ, Prinzen FW, et al. Beneficial effects of biventricular pacing in chronically right ventricular paced patients with mild cardiomyopathy. *Europace* 2010; 12: 223-9. [CrossRef]
4. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, et al. The Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med* 2010; 363: 2385-95. [CrossRef]

Yazışma Adresi/Address for Correspondence: Dr. Ali Deniz,
Çukurova Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı,
Adana-Türkiye
Tel: +90 322 338 60 60 E-posta: alideniz78@gmail.com
Çevrimiçi Yayın Tarihi/Available Online Date: 21.02.2013



©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.082

Renal coloboma syndrome associated with double- chambered right ventricle

Renal kolobom sendromu ile çift odacıklı sağ ventrikül birlikteliği

Introduction

Renal coloboma syndrome (RCS) (papillorenal syndrome) is an autosomal dominant entity characterized by hypodysplastic kidneys and optic nerve abnormalities ranging from optic pit to total optic disc coloboma (1, 2). The double-chambered right ventricle (DCRV) is a rare

congenital heart abnormality caused by anomalous location of hypertrophic muscle bands creating an obstacle for the right ventricular ejection (3). In this paper we discuss clinical properties of a patient with papillorenal syndrome associated with congenital heart disease (CHD) including DCRV. To the best of our knowledge, this association has not been reported.

Case Report

A 21-year-old man without any ocular history presented to our clinic with loss of vision in his right eye for two months. His initial ophthalmologic examination revealed optic disc pit in both eyes and serous macular detachment in the right eye (Fig. 1). Slit lamp examination was unremarkable. His best-corrected visual acuity (BCVA) was 20/100 in the right and 20/20 in the left eye.

The patient had a history of surgery for atrial septal defect (ASD), pulmonary valve stenosis (PVS) and deformity of conus arteriosus when he was 3-year-old. Cardiac magnetic resonance imaging and echocardiography demonstrated DCRV, aneurysmal formation of the membranous septum, pulmonary and tricuspid regurgitation (Fig. 2). No treatment was given due to compensated cardiac disease.

He had also been suffering from vomiting, fatigue and spasms for two months. Blood work-up showed elevated serum creatinine (8.72

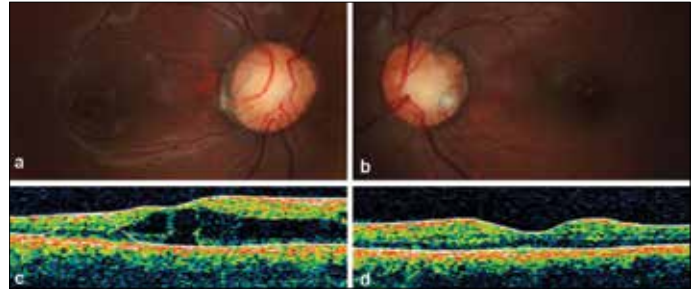


Figure 1. Dilated fundus exam revealing optic pit in both eyes (a, b). There is an optic pit-related serous macular detachment in the right eye (c)

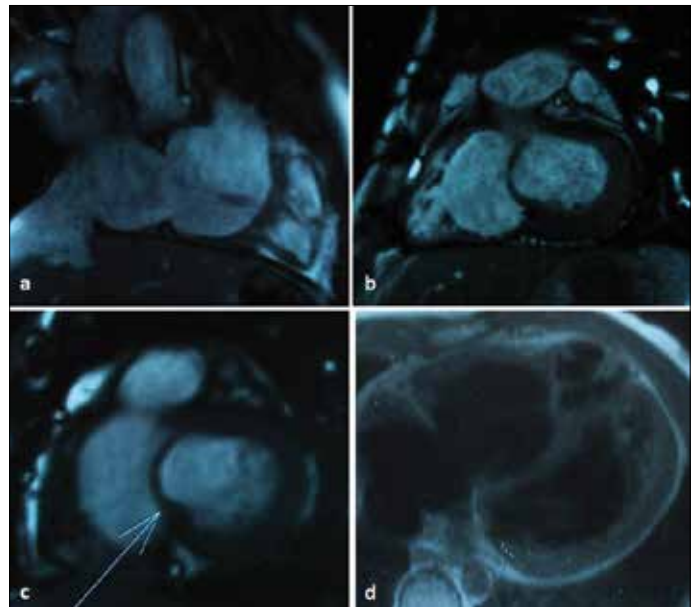


Figure 2. Cardiac MRI demonstrating anomalous muscle bundle dividing right ventricle into proximal and distal chambers (a, d), and membranous interventricular septal aneurysm (b, c)

MRI - magnetic resonance imaging

mg/dL), urea (200 mg/dL), phosphorus (5.84 mg/dL), parathyroid hormone (1196 pg/mL) and decreased levels of Fe⁺ (26 µg/dL), red blood cell (3.83x10⁶/pL) and hemoglobin (11.6 g/dL). Urinalysis revealed proteinuria. Abdominal ultrasonography and computed tomography showed bilateral renal hypoplasia (Fig. 3) and a diagnosis of end-stage renal failure was made. Renal transplantation was performed, followed by six-month hemodialysis treatment. Two months after the successful renal transplantation, serous submacular fluid reduced and macular anatomy recovered but BCVA remained at the same level. The patient received no ophthalmologic treatment for the optic pit.

Discussion

Renal coloboma syndrome is inherited autosomal dominantly and PAX2 is the only gene known to be associated with RCS (4). PAX2 has critical roles in eye and renal embryogenesis.

Primitive eye is separated into two parts (later forms a fissure) by sonic hedgehog (SHH). During 3th week of gestation SHH upregulates PAX2 which is leading to fissure closure (5). Optic pit or coloboma can occur if this fissure fails to close between 3th and 7th weeks. Coloboma is frequently associated with other congenital abnormalities one of which is kidney. As with most organs, differentiation of the kidney involves epithelial mesenchymal interactions. During the 5th week PAX2 and WNT proteins promotes these interactions leading to formation of renal tubules (5).

In contrast to renal development, WNT proteins act as an inhibitor role in cardiac development. During the 4th to 7th weeks, the heart undergoes into a typical four-chambered structure with endocardial cushions, which have critical role in many cardiac deformities (5). DCRV is relatively rare as an isolated anomaly (approximately 0.5-2% of CHD) with no inheritance pattern (6). Patients with DCRV frequently have other congenital cardiac anomalies. The most common associated cardiac lesions include ventricular septal defect, PVS and subaortic stenosis (7). The embryological basis of DCRV has not been clearly described and DCRV coexisting ASD and PVS may be the result of conus arteriosus deformity. Development of aneurysmal formation of the membranous septum in our patient was probably caused by septal infarct secondary to abnormal septal hypertrophy rather than an embryological defect.

In our case there might be a defect concerning those molecular mediators that mentioned above in any stage of development (at most probably between 3-7 weeks) and PAX2 does not appear to be the only

factor in this association. Therefore identifying PAX2 mutation is not necessary for definite diagnosis which is particularly based on clinical evaluation. Mutations in PAX2 have been identified in 50% of persons with RCS (1, 8) and it is estimated that about half of individuals with RCS do not have a known genetic basis (9). In our patient PAX2 gene were amplified from extracted DNA by using polymerase chain reaction primers. Mutation screening was performed by single strand conformation polymorphism. No pathologic allelic variant was observed. We consider that other gene mutations different from PAX2 may also cause this clinical entity.

Conclusion

Renal coloboma syndrome is a multisystem disorder and a collaborative approach including specialists in ophthalmology, cardiology nephrology and medical genetics is necessary for a definite diagnosis. To the best of our knowledge, this is the first case report of RCS coexisting with DCRV.

Patient consent: We confirm that the patient has given written informed consent to the publication of this original article.

Disclosures: None of the authors has any conflicts of interest to disclose.

Gökçen Gökçe, Yalçın Gökoğlu¹, Volkan Hürmeriç², Fazıl Cüneyt Erdurman², Osman Melih Ceylan², Ali Hakan Durukan², Güngör Sobacı²

**Clinic of Ophthalmology, Sarıkamış Military Hospital, Kars-Turkey
From Departments of ¹Cardiology and ²Ophthalmology, Gülhane Military Medical Academy, Ankara-Turkey**

References

1. Bower MA, Schimmenti LA, Eccles MR. Renal Coloboma Syndrome. In: Pagon RA, Bird TD, Dolan CR, editors. GeneReviews™. 2007; [updated 2012 Jul 12]. [Internet]. Seattle (WA): University of Washington, Seattle; 1993.
2. Hürmeriç V, Durukan AH, Mumcuoğlu T, Erdurman FC, Bayraktar MZ. Macular Detachment Developed in a Patient with Optic Disc and Choroid Coloboma. *MN Ophthalmology* 2007; 14: 147-9.
3. McElhinney DB, Chatterjee KM, Reddy VM. Double-chambered right ventricle presenting in adulthood. *Ann Thorac Surg* 2000; 70: 124-7. [CrossRef]
4. Schimmenti LA, Manligas GS, Sieving PA. Optic nerve dysplasia and renal insufficiency in a family with a novel PAX2 mutation, Arg115X: further ophthalmologic delineation of the renal-coloboma syndrome. *Ophthalmic Genet* 2003; 24: 191-202. [CrossRef]
5. TW Sadler. *Langman's Medical Embryology*. 11th Ed. Lippincott Williams & Wilkins. 2009.
6. Hoffman P, Wójcik AW, Rózaski J, Siudalska H, Jakubowska E, Wodarska EK, et al. The role of echocardiography in diagnosing double chambered right ventricle in adults. *Heart* 2004; 90: 789-93.
7. Park JG, Ryu HJ, Jung YS, Kim KJ, Lee BR, Jung BC, et al. Isolated double-chambered right ventricle in a young adult. *Korean Circ J* 2011; 41: 272-5. [CrossRef]
8. Schimmenti LA. Renal coloboma syndrome. *Eur J Hum Genet* 2011; 19: 1207-12. [CrossRef]
9. Dureau P, Attie-Bitach T, Salomon R, Bettembourg O, Amiel J, Uteza Y, et al. Renal coloboma syndrome. *Ophthalmology* 2001; 108: 1912-6. [CrossRef]

The case report was presented partly at the Joint Congress of SOE AAO June 4-7, 2011 in Geneva Switzerland.

Address for Correspondence/Yazışma Adresi: Dr. Gökçen Gökçe, Sarıkamış Asker Hastanesi, Göz Hastalıkları Servisi, Sarıkamış, Kars- Türkiye
Phone: +90 505 492 76 20 E-mail: drgokcengokce@gmail.com
Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013



©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.083

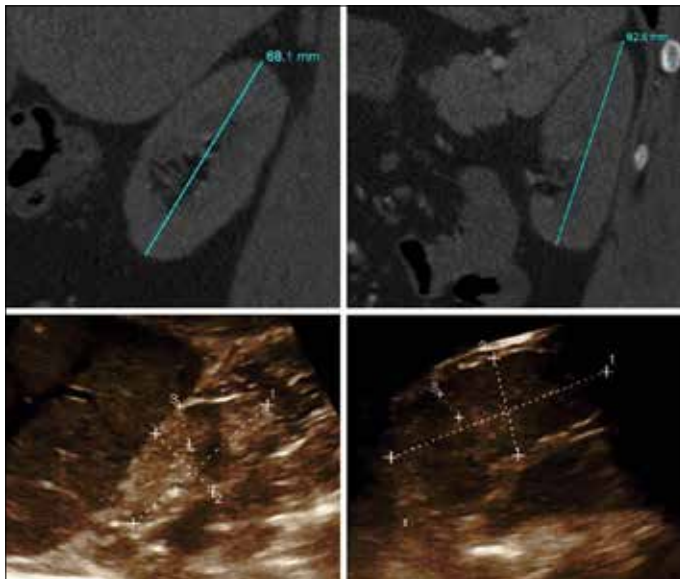


Figure 3. Abdominal ultrasonography and computed tomography views of bilateral renal hypoplasia

Thoraco-Omphalopagus conjoined

Torako-Omfalopaguslu yapışık ikizler

Introduction

Conjoined twins are rarely seen in medical practice, and the incidence is reported as 1 in 50.000 to 1 in 100.000 live births; 60% of these die in utero or are stillborn (1). The thoracopagus is the most common type, accounting for 40% of all conjoined twins cases (2). Thoracopagus conjoined twins have the highest incidence of cardiovascular abnormalities; they may have cardiac abnormalities in any type of fusion, and 90% of these twins share a common pericardial sac. The type of cardiac fusion is a critical factor for mortality (3).

Case Report

A 33-year-old mother presented a conjoined twin pregnancy at 35 weeks of gestation. Ultrasonographic examination had not been made until the week of the birth. Her pregnancy was spontaneous. There was no remarkable risk factor for congenital anomalies in her history. Female thoracoomphalopagus twins weighing 3000 g in total were delivered by cesarean section. The Apgar scores were 4 at 1 minute (min) and 6 at 5 min. The twins shared the thorax and abdomen (Fig. 1). Postnatal echocardiographic examination revealed that the babies shared a four-chamber heart with two ventricles and two atria (Fig. 2). The left ventricle (LV) connected to two aorta (Ao-1, Ao-2) and one pulmonary artery (PA-1) (Fig. 3, 4), while the right ventricle (RV) connected to only one pulmonary artery (PA-2) (Fig. 5). The pulmonary and systemic venous return could not be displayed. Multidetector computed tomography was planned to display the anatomical and vascular structure of the heart. However, the twins died shortly after birth due to cardiovascular collapse and progressive metabolic acidosis despite maximal inotropic and ventilatory support. The parents were informed that the infants had inseparable hearts and could not be saved. They refused the post-mortem examination.



Figure 1. Photo (A) and X-ray (B) images of the twins showing the shared thorax and abdomen

(Permissions to use the pictures of twins in publication are obtained from parents)

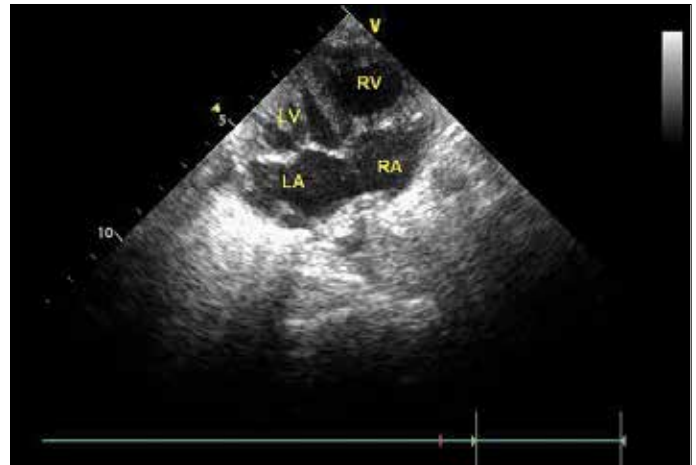


Figure 2. Echocardiogram showing a four-chambered heart with two ventricles and two atria

LA - left atrium, LV - left ventricle, RA - right atrium, RV - right ventricle

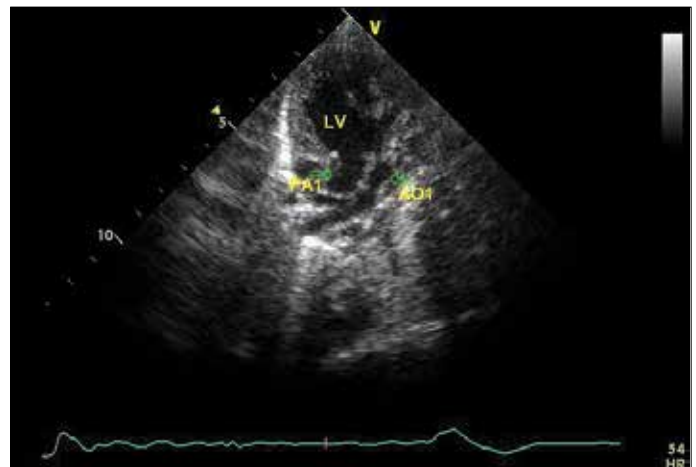


Figure 3. Echocardiogram showed aorta-1 and pulmonary artery-1 connecting the left ventricle

Ao - aorta-1, LV - left ventricle, PA - pulmonary artery-1

Discussion

Thoracopagus conjoined twins with a fused heart always have complex abnormal cardiac anatomy (4-7). The degree of cardiac fusion is most often the pivotal factor in the prognosis (6). Leachman et al. (4) classified twinning on the basis of cardiac fusion as follows: separate normal hearts (type A), fused atria with separate ventricles (type B), and fused atria and ventricles (type C). Andrews et al. (5) reported echocardiography results in the evaluation of 23 sets of conjoined twins with thoracic level fusion, and classified them into four groups as: group A: separate hearts, separate pericardium; group B: separate hearts, common pericardium; group C: fused atria, separate ventricles; and group D: atrial and ventricular fusion. Thoracopagus and thoraco-omphalopagus twins have complex cardiac abnormal anatomy in both classifications. The present twins were thoraco-omphalopagus with a four-chambered heart. Three great arteries connected the left ventricle, while only one pulmonary artery connected the right ventricle. McMahon et al. (8) reported cardiac malformations in a review of 1262 cases of all types of conjoined twins. Of all the cases studied, 314 twins were thoracopagus and typically shared a single multi-chambered

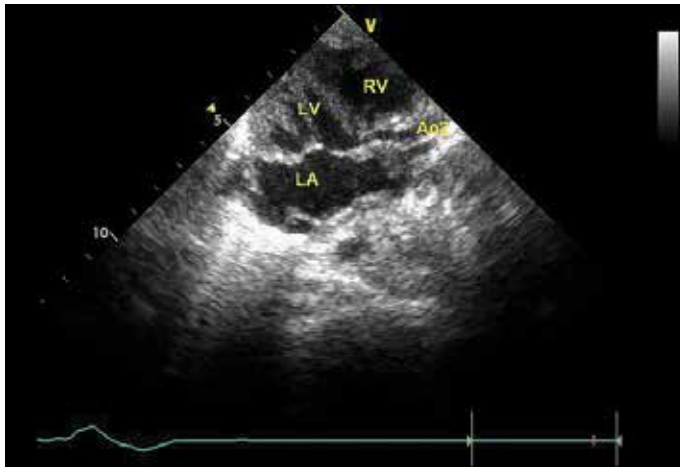


Figure 4. Echocardiogram showing aorta-2 connecting the left ventricle
Ao2 - aorta-2, LA - left atrium, LV - left ventricle, RV - right ventricle

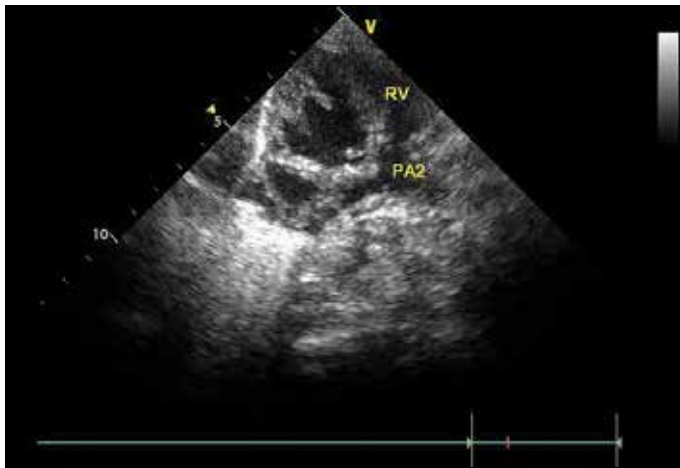


Figure 5. Echocardiogram showing pulmonary artery-2 connecting the right ventricle
PA2 - pulmonary artery-2, RV - right ventricle

heart; there were from one to four atria and from one to four ventricles, with several variations of the great vessels, and triple-outlet connection was observed in only three cases of all 1262 twins. The present case had a triple-outlet connection from the left ventricle; two aorta and one pulmonary artery were visualized as connecting the left ventricle. Spitz et al. (2) classified management of 17 conjoined twins in three distinct categories. The nonoperative management group includes twins with inseparable hearts as with our case. The present twins also had only a single four-chambered heart and triple-outlet left ventricle. This also distinguishes our

case from the other cases of cardiac fusion in conjoined twins reported in the literature; however, the prognosis was not different (1-8). Our twins died on the first day due to heart failure and progressive metabolic acidosis. For inseparable twins, early diagnosis may be offered to the parents if they wish to consider pregnancy termination (9).

Conclusion

Although conjoined twins, especially thoracopagus type, are known to present several cardiac anomalies, a shared single four-chambered heart with triple-outlet left ventricle is a rare condition. The abnormalities can be determined in the fetal period with regular monitoring of the pregnancy and fetal echocardiographic examination.

Kadir Şerafettin Tekgündüz, Haşim Olgun*, İbrahim Caner, Naci Ceviz*

Divisions of Neonatology and *Pediatric Cardiology, Department of Pediatric, Faculty of Medicine, Atatürk University, Erzurum-Turkey

References

1. Spitz L, Kiely EM. Conjoined twins. JAMA 2003; 289: 1307-10. [CrossRef]
2. Spitz L, Kiely EM. Experience in the management of conjoined twins. Br J Surg 2002; 89: 1188-92. [CrossRef]
3. Gilbert-Barness E, Debich-Spicer D, Opitz JM. Conjoined twins: morphogenesis of the heart and a review. Am J Med Genet 2003; 120A: 568-82. [CrossRef]
4. Leachman RD, Latson JR, Kohler CM, McNamara DG. Cardiovascular evaluation of conjoined twins. Birth Defects 1967; 3: 52-65.
5. Andrews RE, McMahon CJ, Yates RW, Cullen S, de Leval MR, Kiely EM, et al. Echocardiographic assessment of conjoined twins. Heart 2006; 92: 382-7. [CrossRef]
6. McMahon CJ, Mullins CE, Vick GW 3rd, Caville CC, Bezold LI, Nihill MR. Cardiac catheterization in diagnosis and management of congenital heart disease in thoracopagus conjoined twins. Catheter Cardiovasc Interv 2000; 51: 159-67. [CrossRef]
7. Liu HC, Lo CW, Weng ZC, Hwang B, Lee PC. Various modalities for evaluation of a fused heart in conjoined twins. Pediatr Cardiol 2012; 33: 192-200. [CrossRef]
8. McMahon CJ, Spencer R. Congenital heart defects in conjoined twins: outcome after surgical separation of thoracopagus. Pediatr Cardiol 2006; 27: 1-12. [CrossRef]
9. Baldwin VJ. Pathology of multiple pregnancy. New York: Springer-Verlag; 1994. [CrossRef]

Address for Correspondence/Yazışma Adresi: Dr. Kadir Şerafettin Tekgündüz, Atatürk Üniversitesi Tıp Fakültesi, Yakutiye Araştırma Hastanesi, Yenidoğan Kliniği, Erzurum-Türkiye
Phone: +90 442 231 69 97 E-mail: kadirtek79@yahoo.com
Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.084



Letters to Editor-in-Chief

Baş Editöre mektuplar

Sayın Editör

Dergimizin 2013 Şubat sayısında yayınlanan ‘Artan yazı sayısı ve okuyucu mektupları’ (“Güzün abla!!!”) – Editörden’ başlıklı yazınızı büyük bir ilgiyle okuduk. Ne yazık ki ülkemizde *bilim ve bilimsel olma* algısı bizce olması gerekenden çok farklı bir noktada. Ve yine ne yazık ki kişinin bilimselliği *Pubmed’deki yazı sayısı* ya da *akademik “title”*ı olarak görülmekte. Oysa bilimsel üretim süreci yalnızca data toplamakla, yazı yazmakla, yazılan yazıyı kabul ettirmekle kalmamalı. Bir başkası tarafından bilim dünyasına sunulan bir yazıyı da bilgisi, ilgisi, deneyimi doğrultusunda yorumlayabilmek, katkıda bulunmak, eleştirmek kısacası yayın aşamasında hakem olarak görev almak da olmalıdır. Kendi makalesinin değerlendirilmesi ya da kabul aşamasında aceleci davranan pek çok araştırmacı herhangi bir derginin herhangi bir konuda hakemliğine başvurması durumundaysa yine aynı aceleciliği bu kez *hakemlik davetini reddetme* konusunda gösteriyor ya da cevap bile vermeyerek yazının değerlendirme sürecinin daha da uzamasına neden oluyor. Bugüne kadar dergimize birçok yazı yolladık ve doğal olarak bunların bir kısmı kabul edildi, bir kısmıysa reddedildi. Önümüzdeki günlerde –eğer uygun görürseniz- dergimizin yayın sürecinde yazılarımızla olduğu kadar, ilgili olduğumuz konularda hakemlik sürecinde de daha aktif görev almaktan onur duyarız.

Sonsuz Hürmet ve Saygılarımızla

Dr. X ve Dr. X

Yazarın Cevabı

Sayın Dr. X ve Dr. X,

Şubat sayımızda yayınlanan “Artan yazı sayısı ve okuyucu mektupları” (“Güzün abla!!!”) başlıklı *editörden* yazıma ilgi gösterip, bu konuda fikirlerinizi bildirdiğiniz için çok teşekkür ederim. E-postanızda, bilimsellik ile ilgili belirttiğiniz tüm görüşlerinize (*hakemlik vs.*) katılıyorum ve size çok hak veriyorum. Aynı düşüncelere sahip olduğumuzdan dolayı çok mutlu oldum. Sizin bu güzel yorumlarınızı ve düşüncelerinizi izniniz olursa, isimli veya isimsiz “Editöre Mektup” olarak yayınlamak isterim.

Bu konuda en kısa sürede cevabınızı bekler, sonsuz selam, sevgi ve saygılarımla gözlerinizden öperim.

Saygılarımla

Prof. Dr. Bilgin Timuralp, EFESC
AKD Baş Editörü

Sayın Editör

Zaman ayırıp yazdığınız cevapla bizleri onurlandırdığınız ve gönderdiğimiz elektronik postayı yayınlamayı düşündüğünüz için teşekkür

ederiz. Size gönderdiğimiz mektubu yazmamızdaki tek amaç; sizin bu konuda kardiyoloji camiasına ince bir kırgınlığınız ya da siteminiz (*hakemlik konusunda*) olduğu düşüncesini taşıyarak naçizane yanınızda olduğunuzu hissettirmektir. Hocam, Size yolladığımız yazı – biz kaleme alsak ta- aslında bizler ve Siz gibi düşünen insanlar adına yazılmış ortak bir düşüncenin, duygunun ifadesidir. Yazı hedef kitlesi olan okuyucu tarafından okunduğunda, okuyucunun algısında iki kişinin yazdığı bir düşünceden ziyade bu düşüncüyü ifade eden bir topluluk olduğu fikrinin hakim olacağını düşünüyoruz. Yazının ne şekilde yayınlanacağı konusunda tabii ki Siz daha uygununu ve doğrusunu bilirsiniz, ancak biz bu düşüncedeki isimsiz kişiler olarak kalmak isteriz.

Sonsuz hürmet ve saygılarımızla

Dr. X ve Dr. X

Ischemic stroke in the course of thrombolytic treatment of prosthetic valve thrombosis: thrombolysis is suggested

Protez kapak trombozunun trombolitik tedavisi sırasında iskemik inme: Tromboliz önerilir

Dear Editor,

We have read with great interest the excellent report Özkan et al. (1). This woman of 25 years old with diagnosis of prosthetic valve thrombosis (PVT) received thrombolytic therapy-low-dose and prolonged infusion of tissue-type plasminogen activator (tPA). After the two hours the infusion was finished and was diagnosed and checked for cerebral computed tomography (CT) scan a cerebral embolism as a complication. Thrombolytic treatment was continued. The final result was successful for both (PVT and ischemic stroke).

We should make some considerations

The PVT is a serious complication of cardiac valve replacement because it is dangerous in the sick person's life. The initial therapeutic decision must be immediate. Currently, the initial therapeutic decision is difficult and controversial. Clinical practice guidelines express no uniform opinions. The European Society of Cardiology proposed surgery as the initial treatment, regardless of clinical status and the size of the thrombus. The Society of Heart Valve Disease recommends that the first choice be thrombolysis in all cases of PVT, unless such treatment is contraindicated. The American Heart Association and American College of Cardiology reserve thrombolysis only for patients with non-obstructive PVT and hemodynamic stability. The American College of Chest Physicians recommends that the main criterion in the therapeutic decision be the size of thrombus, indicating thrombolysis as the treatment choice if the thrombus has an area of $+0.8 \text{ cm}^2$ and surgery in older thrombi. On the basis of the evidence displayed in many studies and our experience over more 20 years, our working group suggests

that continuing the search for the best therapy for PVT is no longer necessary. Two therapeutic alternatives exist for managing these severe patients (thrombolytic therapy and surgery), but they are complementary. We propose thrombolysis as the initial treatment if no contraindications are present (e.g., thrombi + 10 mm). Surgery is reserved for patients with contraindications to thrombolysis, those in whom this therapy is unsuccessful, and per se, who present with stroke and left atrial thrombus (2).

The main related limitation with the thrombolytic treatment is when the cerebral embolism occurs. An interesting option to treat this complication during the thrombolytic treatment in the PVT is the thrombolysis continuity as it has reported in this case for Özkan et al. (1).

In the year 2004, Lengyel et al. (3) indicated that twenty cases of non-hemorrhagic stroke or transient ischemic attack have been treated with thrombolysis, with only one hemorrhagic transformation.

In the year 2005 were published the guidelines of the Society of Heart Valves Disease for the management of PVT and recommend as an indication Class III the thrombolysis in presence of ischemic stroke documented for cerebral CT scan before the 4 hours that initiate the symptoms (4).

We suggest that the thrombolytic therapy in the ischemic stroke can be effective in the first 3 hours of the beginning of symptoms if the cerebral scan do not show signs of hemorrhages. It is generally recommended to interrupt thrombolysis for PHVT if there is clinical evidence of a cerebrovascular accident during treatment, and to perform an urgent cranial CT scan to differentiate between a hemorrhagic and ischemic origin. If there is no evidence of brain hemorrhage on CT scan, thrombolytic therapy can be restarted (5).

Fidel Manuel Caceres-Loriga
Department of Cardiology, Institute of Cardiology and
Cardiovascular Surgery, Havana-Cuba

References

1. Özkan M, Gürsoy OM, Atasoy B, Uslu Z. Management of acute ischemic stroke occurred during thrombolytic treatment of a patient with prosthetic mitral valve thrombosis: continuing thrombolysis on top of thrombolysis. Anadolu Kardiyol Derg 2012; 12: 689-90.
2. Cáceres-Loriga FM, Santos-Gracias J, Pérez-López H. Thrombolysis versus reoperation in the management of prosthetic valve thrombosis. Am J Cardiol 2011; 108: 753. [CrossRef]
3. Lengyel M. Management of prosthetic valve thrombosis. J Heart Valve Dis 2004; 13: 329-34.
4. Lengyel M, Horstkotte D, Völler H, Mistiaen WP; Working Group Infection, Thrombosis, Embolism and Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. J Heart Valve Dis 2005; 14: 567-75.
5. Cáceres-Loriga FM, Pérez-López H, Santos-Gracia J, Morlans-Hernandez K. Prosthetic heart valve thrombosis: pathogenesis, diagnosis and management. Int J Cardiol 2006; 110: 1-6. [CrossRef]

Address for Correspondence/Yazışma Adresi: Fidel Manuel Caceres-Loriga, MD,
Department of Cardiology, Institute of Cardiology and
Cardiovascular Surgery, Havana-Cuba
Phone: 5378360824
E-mail: caceresm@infomed.sld.cu

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.085



Author Reply

Dear Author,

Thank you very much for your comprehensive and encouraging comments on our article published in "letter to editor" section of Anatolian Journal of Cardiology that I was entirely agree and feel nothing to add on top of it.

Mehmet Özkan
Clinic of Cardiology, Kartal Koşuyolu Yüksek İhtisas Education and
Research Hospital, İstanbul-Turkey

Address for Correspondence/Yazışma Adresi: Dr. Mehmet Özkan,
Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Kardiyoloji
Kliniği, İstanbul-Türkiye
Phone: +90 532 255 15 13 Fax: +90 216 459 63 21
E-mail: memoozkan1@gmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

Influence of gender, C- reactive protein and triglycerides in risk prediction of coronary heart disease

Koroner arter hastalığı riskini öngörmeye cinsiyet, C-reaktif protein ve trigliseridin etkisi

Dear Editor,

Having read the article entitled "Clinical biomarkers of high-density lipoprotein dysfunction among middle-aged Turks" by Onat et al. (1), where the mentioned author studied some clinical biomarkers of high-density lipoprotein dysfunction in a stratified adult Turkish population. We would like to join the discussion about the influence of gender, and C-reactive protein (CRP) and triglycerides (TG) levels in risk prediction of coronary heart disease (CHD). For this purpose, we show the results of our small-sample study of schizophrenic patients on long-term clozapine, a drug that consistently raises CRP levels, where we evidenced that women had lower CRP increases than men (about a half) in response to a constant stimulus as clozapine long-term treatment. Also, we found that elevated CRP levels were associated with high levels of cholesterol, low-density lipoprotein and body mass index (2).

Cholesterol and TG, rise CRP levels through the activation of toll-like receptor 4 (TLR4) and subsequently liberation of proinflammatory cytokines such as tumor necrosis factor and interleukin -6, among others. This CRP-release, in turn, can activate TLR4 and lead, under certain circumstances and/or stimuli to a self-perpetuating cholesterol/TG-CRP loop (3, 4).

Moreover, TLR4 constitutes a link between nutrition, lipids and proinflammatory cytokines, being TG and cholesterol from any source, including diet, the most common metabolic-triggers for TLR4 (5). This TLR4 activation is also gender-dependent, with an LPS-stimulated accumulation of proinflammatory cytokines, significantly decreased in women (6), where its production would be facilitated by the presence of elevated levels of TG.

Putting it all together, we can conclude that women, whose innate immune response TLR4-mediated as mentioned also by Imahara (6) is

more decreased than men, requires higher levels of TG than men to stimulate production of CRP, TLR4 mediated, and that TG constitutes a clinical biomarker of impaired antiinflammatory or atheroprotective function in women, while in men it would be CRP, whose release would not depend on TG; in agreement with the findings of Onat et al. (1), about the usefulness of CRP and TG, among others, as clinical biomarkers of impaired or atheroprotective high-density lipoprotein antiinflammatory function for men and women, respectively.

Roberto Lozano, Reyes Marin*, M-Jesus Santacruz*
Clinics of Pharmacy and *Psychiatry, Hospital Real Ntra Sra de Gracia, Zaragoza-Spain

References

1. Onat A, Can G, Murat S, Çiçek G, Örnek E, Yüksel H. Clinical biomarkers of high-density lipoprotein dysfunction among middle-aged Turks. *Anadolu Kardiyol Derg* 2012; 12: 628-36.
2. Lozano R. Reducing serum cholesterol levels in women. *Neuropsychiatr Dis Treat* 2012; 8: 405-6. [CrossRef]
3. Calabro P, Chang DW, Willerson JT, Yeh ET. Release of C-reactive protein in response to inflammatory cytokines by human adipocytes: linking obesity to vascular inflammation. *J Am Coll Cardiol* 2005; 46: 1112-3. [CrossRef]
4. Liu N, Liu J, Ji Y, Lu P. Toll-like receptor 4 signaling mediates inflammatory activation induced by C-reactive protein in vascular smooth muscle cells. *Cell Physiol Biochem* 2010; 25: 467-76. [CrossRef]
5. Budick-Harmelin N, Dudas J, Demuth J, Madar Z, Ramadori G, Tirosh O. Triglycerides potentiate the inflammatory response in rat Kupffer cells. *Antioxid Redox Signal* 2008; 10: 2009-22. [CrossRef]
6. Imahara SD, Jelacic S, Junker CE, O'Keefe GE. The influence of gender on human innate immunity. *Surgery* 2005; 138: 275-82. [CrossRef]

Address for Correspondence/Yazışma Adresi: Dr. Roberto Lozano,
Ramon y Cajal 60, 50004 Zaragoza-Spain
Phone: +34976444300
E-mail: rlozano@salud.aragon.es

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013



©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.086

Author Reply

Sex divergence in rise of serum CRP to pro-inflammatory mediators
Proinflatuvar mediyatörlerin serum CRP artışında cinsiyet farkı

Dear Author,

Regarding prediction of coronary heart disease, for which we tried to identify clinical biomarkers in the population at large in our recently published study (1), Lozano et al. (2) commented on the influence of gender on circulating C-reactive protein (CRP), representing the inflammatory response of the organism. Concurring with our conclusion that, added to fasting triglyceride concentrations, elevated CRP was proposed to mark high-density lipoprotein (HDL) dysfunction in cardiometabolic diseases among men but not in women (in whom elevated complement C3 was identified as independent marker), the author pointed out that, in the long-term treatment of schizophrenic patients with clozapine, a drug that consistently raises CRP levels, women respond with about half as great a rise in CRP as men.

We have reached the opinion since our study was concluded, that this sex difference on CRP is related to the association of circulating

lipoprotein [Lp] (a) with triglycerides and the possible concomitant existence of autoimmune activation, a slow process which comprises aggregation between certain damaged proteins and protective serum proteins, and predominates in females (3). HDL dysfunction in males is usually, though not exclusively, due to simple pro-inflammatory state whereas it is associated in women commonly with inflammation-induced autoimmune process as well which often involves Lp(a) and apolipoprotein A-I. The immune complex formation is associated with complement C3 elevation (4) and with less independence from other clinical markers of systemic inflammation (including fasting triglycerides) and a lesser degree of rise in CRP levels. Hence, the divergence between sexes in rise of CRP levels to certain pro-inflammatory mediators. One may speculate whether clozapine, beyond stimulating CRP release, affects in women the induction of autoimmune processes.

Altan Onat
Emeritus Professor, Cerrahpaşa Medical Faculty, İstanbul University, İstanbul-Turkey

References

1. Onat A, Can G, Murat S, Çiçek G, Örnek E, Yüksel H. Clinical biomarkers of high-density lipoprotein dysfunction. *Anadolu Kardiyol Derg* 2012; 12: 628-36. [CrossRef]
2. Lozano R, Marin R, Santacruz MJ. Influence of gender, C-reactive protein and triglycerides in risk prediction of coronary heart disease. *Anadolu Kardiyol Derg* 2013; 13: 00-00.
3. Onat A, Can G, Yüksel H. Dysfunction of high-density lipoprotein and its apolipoproteins: New mechanisms underlying cardiometabolic risk in the population at large. *Türk Kardiyol Dern Ars* 2012; 40: 365-83.
4. Onat A, Can G, Rezvani R, Cianflone K. Complement C3 and cleavage products in cardiometabolic risk. *Clin Chim Acta* 2011; 412: 1171-9. [CrossRef]

Address for Correspondence/Yazışma Adresi: Prof. Dr. Altan Onat,
Nispetiye Cad. 59/24 Etiler PK: 34335, İstanbul-Türkiye
Phone: +90 212 351 62 17
E-mail: alt_onat@yahoo.com.tr

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

Can isolated ST elevation in aVR lead be a sign of acute pulmonary embolism?

aVR'de izole ST yükselmesi akut pulmoner emboli belirtisi olabilir mi?

Dear Editor,

Pulmonary embolism (PE) remains the major challenge of acute chest disease. The clinical and electrocardiographic manifestations may deviate to a diagnosis of acute coronary syndrome and even myocardial infarction. The current report documents the case of a 42-year-old woman who presented to the emergency department with chest pain and dyspnea. She had no known history of ischemic heart disease, cardiomyopathy, arrhythmia, or central nervous system disease. She had a 6-year history of minimal tobacco use. On examination, the patient's blood pressure was 100/60 mm Hg in the supine position; oxygen saturation, 96%; and heart rate, 123 beats per minute and regular. Her electrocardiogram showed interestingly isolated ST elevation in aVR lead and

diffuse ST depression in all other leads (Fig. 1). Troponin I was top normal. Chest X-ray findings were unremarkable. As a result, therapy for acute coronary syndrome was initiated and arrangements were made for emergency cardiac catheterization for suspected acute coronary occlusion. Results from an angiogram, however, failed to reveal coronary artery disease and was normal. After cardiac catheterization, transthoracic echocardiography revealed moderate right ventricular enlargement with mildly reduced function and displacement of the interventricular septum into the left ventricle; however, left ventricular systolic function was normal. In addition, pulmonary artery pressure was elevated moderately but the patient did not demonstrate "McConnell's sign". CT angiography revealed massive bilateral pulmonary embolism.

As stated previously, ST-segment elevation associated with PE is rare, and the direct relationship remains unclear. Anteroseptal or anterior ST-segment elevation was noted in few cases (1-3). Recently it is noted that the presence of STE in lead aVR in patients with APE is associated with poor prognosis. The presence of STE in lead aVR could be an easily obtainable and noninvasive ECG parameter, helpful in risk stratification of patients with APE (3, 4). Most ECG abnormalities associated with PE are thought to be a consequence of a sudden pressure overload on a non-compensatory right ventricle. This additional strain may induce global or focal myocardial ischemia. Therefore, another potential theory suggests that ST elevation in PE results from epicardial or micro-vascular coronary vasospasm induced by such strain. A third theory suggests that severe hypoxemia induces a catecholamine surge, which increases myocardial workload and results in ischemia (1, 3-5). Also the serum potassium level in our patient at the time of the ECG was 5.5 mEq/L, lower than that seen in some cases of ST-segment elevation (1, 5). In addition the severity of metabolic acidosis in our patient (bicarbonate, 20.3 mEq/L) is less than that seen in cases associated with ST elevation attributed to metabolic abnormalities. Indeed the most interesting finding in our case is ST elevation only in aVR lead that may be seen in few cases of acute coronary syndrome.

In conclusion; specific abnormal findings on ECGs may provide clues to the diagnosis and according to previous studies (3, 4) for risk stratification of PE in patients presenting with chest pain, dyspnea, or both; however, the present case illustrates the rare and interesting association of PE with ST-segment elevation in the aVR lead. Therefore, we recommend that physicians consider the presence of PE in patients with chest pain or dyspnea, even when ST-segment elevation is present in aVR lead.

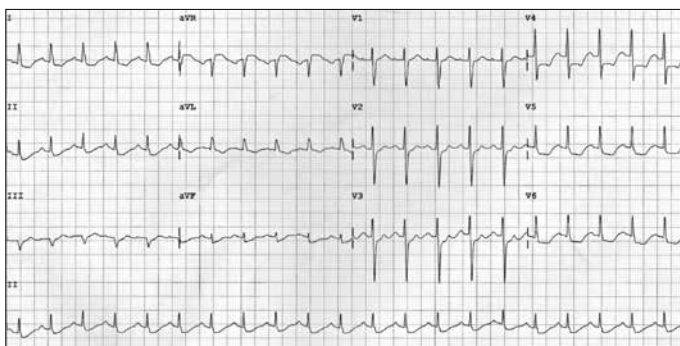


Figure 1. A 12-lead electrocardiogram in patient with acute pulmonary thromboembolism, note the ST segment elevation in aVR lead

Anita Sadeghpour, Azin Alizadeasl¹

Echocardiography research center, Tehran University Medical Science, Tehran-Iran

¹Department of Cardiology, Tabriz University, Tabriz-Iran

References

1. Perugini E, Di Diodoro L, Pallotti MG, Gallelli I, Villani C, Scaramuzzino G, et al. Electrocardiographic diagnosis of acute myocardial infarction in the era of primary percutaneous coronary intervention and hub and spoke networks. *G Ital Cardiol (Rome)* 2010; 11: 630-44.
2. Raghav KP, Makkuni P, Figueredo VM. A review of electrocardiography in pulmonary embolism: recognizing pulmonary embolus masquerading as ST-elevation myocardial infarction. *Rev Cardiovasc Med* 2011; 12: 157-63.
3. Janata K, Höchtel T, Wenzel C, Jarai R, Fellner B, Geppert A, et al. The role of ST-segment elevation in lead aVR in the risk assessment of patients with acute pulmonary embolism. *Clin Res Cardiol* 2012; 101: 329-37. [CrossRef]
4. Kukla P, Dlugopolski R, Krupa E, Furtak R, Szelemej R, Mirek-Bryniarska E, et al. Electrocardiography and prognosis of patients with acute pulmonary embolism. *Cardiol J* 2011; 18: 648-53. [CrossRef]
5. Özer N, Yorgun H, Canpolat U, Ateş AH, Aksöyek S. Pulmonary embolism presenting with evolving electrocardiographic abnormalities mimicking anteroseptal myocardial infarction: a case report. *Med Princ Pract* 2011; 20: 577-80. [CrossRef]

Address for Correspondence/Yazışma Adresi: Dr. Azin Alizadehasl,
Department of Cardiology, Tabriz University, Tabriz-Iran
Phone: +98 21 239 221 45 Fax: +98 21 220 420 26
E-mail: alizadeasl@yahoo.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.087



A deadly chain of events in a case; Deep venous thrombosis, pulmoner embolism, patent foramen ovale and cerebral embolism

*Bir vakada ölümcül olaylar zinciri; derin ven
trombüsü, pulmoner emboli, patent foramen ovale
ve serebral emboli*

A 67-year-old overweight female with history of hypertension was admitted to our emergency room due to mental confusion, weakness of the right side of the body and shortness of breath starting 12 hours ago. She had stable hemodynamic status with a blood pressure of 140/70 mmHg and heart rate of 106 bpm. Her physical examination was unremarkable with sinus rhythm.

She was diagnosed acute stroke and underwent a cranial magnetic resonance imaging (MRI). Her cranial MRI showed a large infarct in the left middle cerebral artery region (Fig. 1). For the determination of the source of embolus, her echocardiographic examination demonstrated moderate pulmonary hypertension of 65 mmHg accompanying mild right ventricle dilatation with spared apical motion (McConnell sign). The cardiac chambers including main pulmonary artery were clear, and ejection fraction was normal (65%). Transesophageal echocardiography was performed for further evaluation of the interatrial septum. The contrast study demonstrated a large amount of bubble passing through a tunnel like patent foramen ovale (PFO) (<10 mm) (Fig. 2-4. Video 1-3. See corresponding video movie images at www.anakarder.com). All tests were normal except for a slight elevation of D-dimer (500 mg/L). With suspected pulmonary embolism (PE), we performed a tomographic pulmonary angiography, and it revealed a large thrombus partially obstructing the proximal parts of

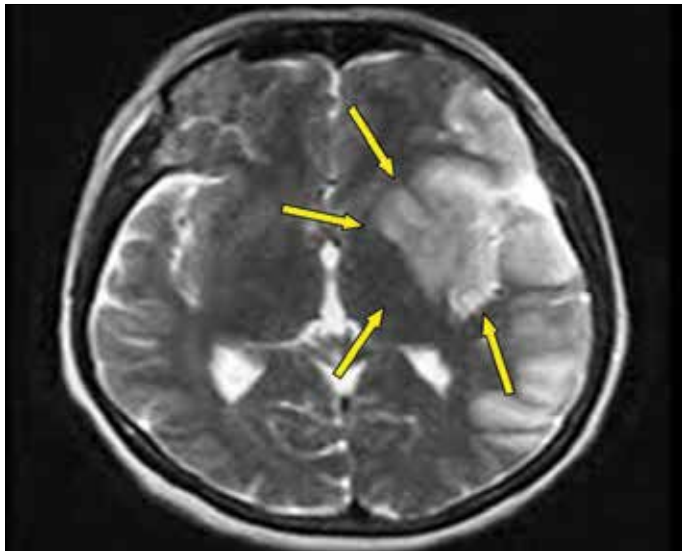


Figure 1. Brain MRI images of acute cerebral infarctions in the left middle cerebral artery territory (arrows)

MRI - magnetic resonance imaging, MCA - middle cerebral artery



Figure 2. TEE image from 120 degree midesophageal level shows a PFO. (Arrow) After administration of agitated saline both spontaneously and Valsalva maneuver, plenty of bubble passed through right to left atrium (Arrow)

PFO - patent foramen ovale, TEE - transesophageal echocardiography

both pulmonary arteries (Fig. 5). Low-molecular-weight heparin with anti-platelet therapy was started. An extensive thrombus was also detected in the right femoral vein using lower extremity veins with duplex ultrasound. As a result, paradoxical cerebral embolism as well as PE caused by deep venous thrombosis (DVT) and its association with PFO was diagnosed evidently. During her follow-up period, her hemodynamic condition remained stable, and all imaging tests were repeated after 8 days. Her echocardiographic examination showed a decrease in the pulmonary artery pressure to 40 mmHg without any remarkable changes of the right heart size. In addition, a slight reduction of thrombus in the pulmonary arteries was detected by tomographic pulmonary angiography. After a short period of time, her clinical condition deteriorated and on her cranial tomography, severe hemorrhage was observed in previous cerebral infarct region. Unfortunately, the patient was eventually died.

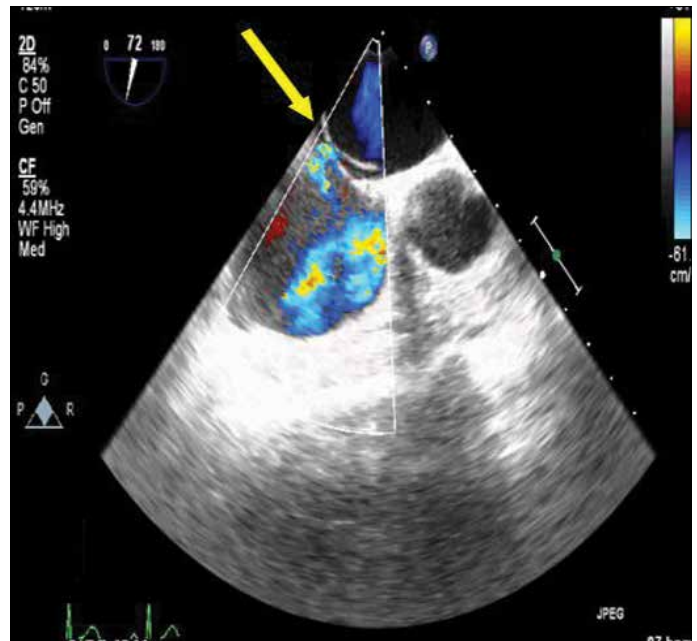


Figure 3. TEE image from 120 degree midesophageal level shows a PFO. (Arrow) After administration of agitated saline both spontaneously and Valsalva maneuver, plenty of bubble passed through right to left atrium (Arrow)

PFO - patent foramen ovale, TEE - transesophageal echocardiography

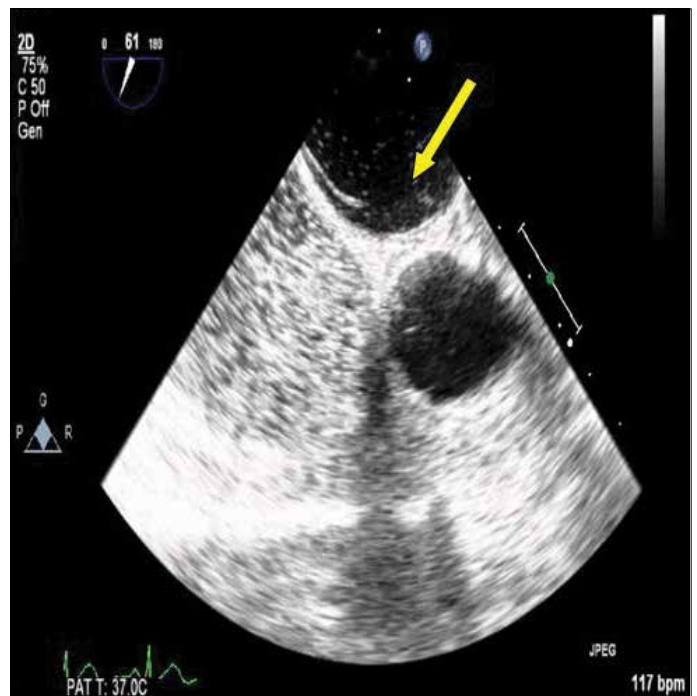


Figure 4. 3D Real time TEE image form 120 degree midesophageal level shows an PFO (Arrow)

PFO - patent foramen ovale, TEE - transesophageal echocardiography

PE is an important clinical entity characterized by still a high mortality rate if not diagnosed early. The most common cause of PE is DVT. The risk level of all patient with PE should be determined to plan an appropriate therapy on the basis of three crucial factors; hemodynamic status, right ventricular dilatation and myocardial injury (1). In case of PE, the right heart pressures will increase, and in the presence of PFO, the passage

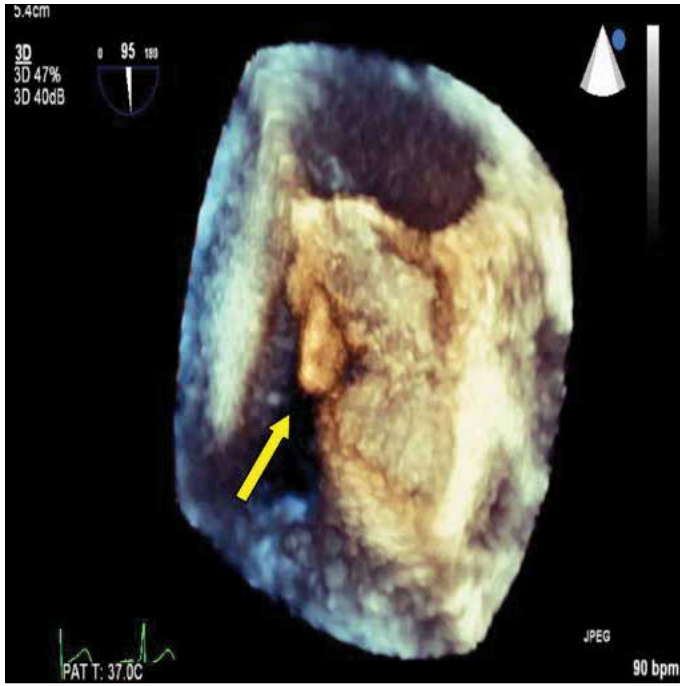


Figure 5. Computed tomographic scan of the chest with contrast agent. (A) Bilateral pulmonary embolism. Arrow point to the pulmonary emboli (Arrow)

become much easier (2, 3). It is always possible that DVT may lead to systemic embolism through the PFO, called as paradoxical embolism (4). If a cerebral embolism exists, the clinical condition may be predominantly neurologic, and PE may be overlooked. In the event of cryptogenic stroke, the existence of PFO and DVT is generally searched, respectively. In these patients, PE should be kept in mind and investigated. The presence of DVT, PE, PFO and systemic embolism in a case together seems to be the most frightening and deadly association, as seen in our case.

Murat Eroğlu, Murat Yalçın*, Zafer Işılak*, Murat Veliöğlu**
Department of Emergency Medicine, *Cardiology and **Radiology,
Gülhane Military Medical Academy, Haydarpaşa Hospital,
İstanbul-Turkey

Video 1. TEE color image from 120 degree midesophageal level shows an PFO

PFO - patent foramen ovale, TEE - transesophageal echocardiography

Video 2. TEE color image from 120 degree midesophageal level shows after administration of agitated saline both spontaneously and Valsalva maneuver, plenty of bubble passed through right to left atrium

PFO - patent foramen ovale, TEE - transesophageal echocardiography

Video 3. 3D Real time TEE 120 degree midesophageal level shows an PFO

PFO - patent foramen ovale, TEE - transesophageal echocardiography

References

1. Olin JW. Pulmonary embolism. Rev Cardiovasc Med 2002; 2: 68-75.
2. Loscalzo J. Paradoxical embolism: clinical presentation, diagnostic strategies, and therapeutic options. Am Heart J 1986; 112: 141-5. [CrossRef]
3. Fauveau E, Cohen A, Bonnet N, Gacem K, Lardoux H. Surgical or medical treatment for thrombus straddling the patent foramen ovale: Impending paradoxical embolism? Report of four clinical cases and literature review. Arch Cardiovasc Dis 2008; 101: 637-44. [CrossRef]

4. Wu LA, Malouf JF, Dearani JA, Hagler DJ, Reeder GS, Petty GW, et al. Patent foramen ovale in cryptogenic stroke: current understanding and management options. Arch Intern Med 2004; 164: 950-6. [CrossRef]

Address for Correspondence/Yazışma Adresi: Dr. Murat Eroğlu,
Gülhane Askeri Tıp Akademisi Haydarpaşa Hastanesi,
Acil Tıp Bölümü, İstanbul-Türkiye
Phone: +90 216 542 21 19 Fax: +90 216 344 78 80
E-mail: meroglu@gata.edu.tr

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.088

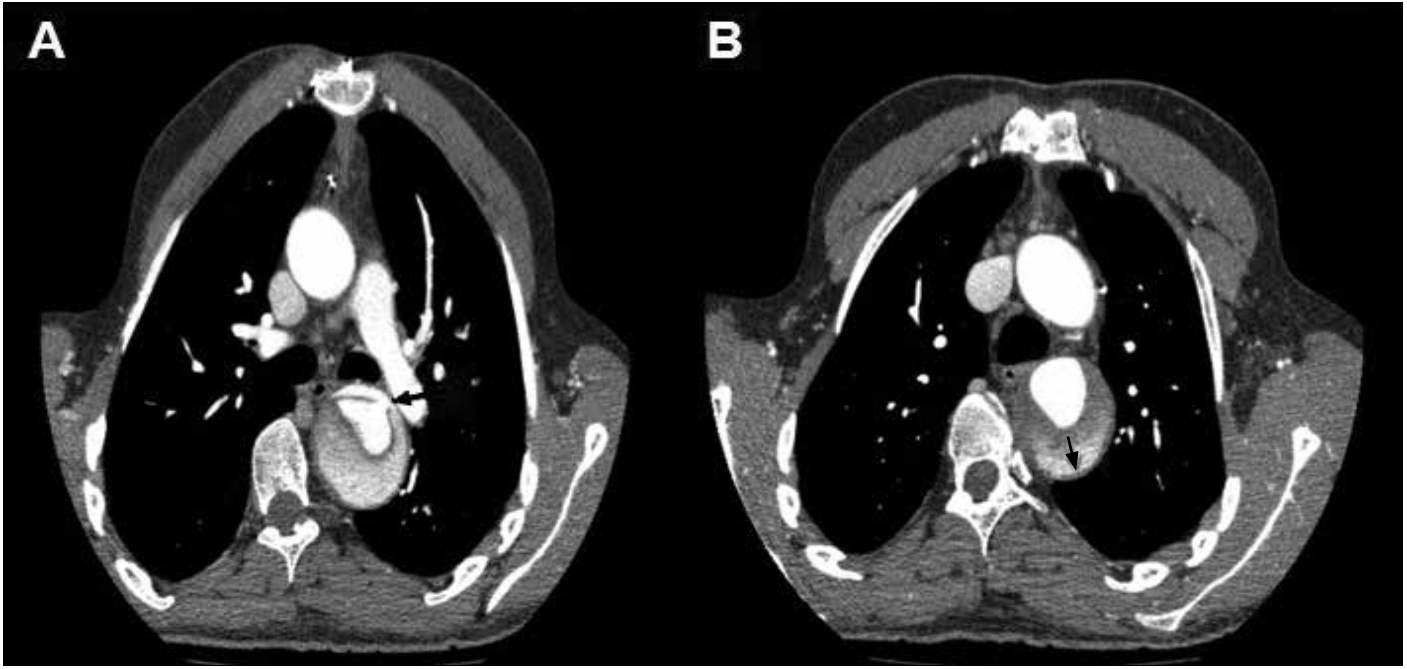


Komplike akut Tip B diseksiyonla başvuran Marfan sendromlu hastada başarılı endovasküler greft-stent tedavisi

Successful endovascular stent-graft treatment in a patient with Marfan syndrome presenting with complicated acute Type B dissection

Yirmi bir yaşında erkek hasta, acil servise ani başlayan sırt ağrısı, her iki bacakta uyuşma ve karın ağrısı yakınması ile başvurdu. Hastanın özgeçmişinde, iki yıl önce Ghent kriterlerine göre Marfan sendromu tanısı alıp, mitral valve prolapsusuna bağlı ileri derecede mitral yetersizlik, asendan aort anevizması ve orta dereceli aort yetersizlik nedeniyle de Benthal ve mitral protez kapak operasyonu hikayesi bulunmaktaydı. Yırtılır tarzda sırt ağrısı olan hastanın her iki femoral nabızının zayıf olduğu saptandı. Bunun üzerine yapılan bilgisayarlı tomografide sol subklavyan arter distalinde desendan aortada intimal yırtık ve diseksiyon flebi görüldü (Şekil 1A, B). Hasta; medikal tedaviye dirençli şiddetli karın ve sırt ağrılarının devam etmesi ve hemodinamik stabilitenin bozulması üzerine endovasküler greft stent uygulaması için kateter laboratuvarına alındı. Sağ koldan yapılan aortografide diseksiyon flebinin (yalancı lümenin) her sistolde kanla dolarak abdominal aortada lümenal daralmaya yol açtığı görüldü (Video 1. Video/hareketli görüntüler www.anakarder.com' da izlenebilir). İntimal yırtık alanı aortografide belirlendikten sonra (Video 2. Video/hareketli görüntüler www.anakarder.com'da izlenebilir) sağ femoral arter yolundan intimal yırtığın proksimalindeki sağlam dokuyu da içine alacak şekilde greft stent implante edildi (Video 3. Video/hareketli görüntüler www.anakarder.com'da izlenebilir). İşlem sonrasında kontrol aortografi ile endoleak olmadığı saptanan hasta, işlemin üçüncü gününde olaysız taburcu edildi (Video 4. Video/hareketli görüntüler www.anakarder.com' da izlenebilir).

Stanford Tip B diseksiyon komplike değilse bugün için kabul gören tedavi seçeneği medikal tedavidir. Ancak, komplike akut tip B diseksiyon (KATBD) hayatı tehdit eden bir klinik tablodur ve acil girişimsel tedavi gerektirir. Bu amaçla, açık cerrahi onarım uzun yıllardır başarı ile uygulanan konvansiyonel metoddur. Son dekatda ise, endovasküler greft stent (EGS) uygulaması da pratikte kullanılmaya başlanmıştır. KATBD'de açık cerrahi ve EGS'nin karşılaştırıldığı bir çalışmada EGS'nin hastane içi erken dönem sonuçlarının daha iyi olduğu ortaya konulmuştur (1). EGS'nin orta dönem sonuçlarının açıklandığı başka bir çalışmada ise; 1. ve 5. yıl sağ kalım oranları sırasıyla %79, %61 saptanmıştır (2). Beş çalışmanın değerlendirmeye alındığı meta-analizde ise; Yazarlar



Şekil 1. A) Bilgisayarlı tomografide sol subklavyen arter distalinde intimal yırtık (ok) ve B) diseksiyon flebi (iki başlı ok) izlenmektedir

EGS'nin erken dönem mortaliteyi azaltmış olmasına rağmen, yeniden girişim oranlarının ve bazı hasta guruplarındaki başarısının düşük olması nedeniyle, uzun dönem sonuçları ve randomize kontrollü çalışmaların sonuçları açıklanmadan cerrahinin yerini almasına şüpheyle baktıklarını belirtmişler (3). EGS'nin başarısının tartışıldığı önemli bir grup ise Marfan sendromlu KATBD hastalarıdır. Marfan sendromunda muhtemel kollojen dokunun farklılığından dolayı EGS tedavisinden sonra erken ve geç endoleak komplikasyonu diğer KATBD hastalarına kıyasla daha fazla görülmektedir (4). Günümüzde, Marfan sendromlu KATBD hastalarında EGS, bizim hastamızda da olduğu gibi daha önceden açık kardiyak cerrahi geçirmiş hastalarda daha güçlü önerilmektedir (5).

Marfan sendromlu KATBD'lerde kanıta dayalı tedavi seçeneğini belirlemek için randomize klinik çalışmalara ihtiyaç vardır. Girişimsel tedavi seçeneğini düşünen hekimler, erken ve geç endoleak komplikasyonu yönünden hastayı iyi değerlendirmelidirler.

Can Yücel Karabay, Cihan Dünder, Kürşat Tigen, Cevat Kırmacı
Kartal Koşuyolu Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği,
İstanbul- Türkiye

Video 1. İşlem öncesinde sağ koldan yapılan aortografi

Video 2. İntimal yırtıktan yalancı lümen opak akışı

Video 3. Endovasküler stent greftin yerleştirilmesi

Video 4. İşlem sonrası aortografi

Kaynaklar

1. Fattori R, Tsai TT, Myrmel T, Evangelista A, Cooper JV, Trimarchi S, et al. Complicated acute type B dissection: is surgery still the best option?: a report from the International Registry of Acute Aortic Dissection. JACC Cardiovasc Interv 2008; 1: 395-402. [CrossRef]
2. Ehrlich MP, Rousseau H, Heijmen R, Piquet P, Beregi JP, Nienaber CA, et al. Midterm results after endovascular treatment of acute, complicated type B aortic dissection: The Talent Thoracic Registry. J Thorac Cardiovasc Surg 2013; 145: 159-65. [CrossRef]
3. Zhang H, Wang ZW, Zhou Z, Hu XP, Wu HB, Guo Y. Endovascular stent-graft placement or open surgery for the treatment of acute type B aortic dissection: a meta-analysis. Ann Vasc Surg 2012; 26: 454-61. [CrossRef]

4. Marcheix B, Rousseau H, Bongard V, Heijmen RH, Nienaber CA, Ehrlich M, et al. Stent-grafting of dissected descending aorta in patients with Marfan's syndrome: mid-term results. JACC Cardiovasc Interv 2008; 1: 673-80. [CrossRef]
5. Botta L, Russo V, La Palombara C, Rosati M, Di Bartolomeo R, Fattori R. Stent-graft repair of descending aortic dissection in patients with Marfan syndrome: an effective alternative to open reoperation? J Thorac Cardiovasc Surg 2009; 138: 1108-14. [CrossRef]

Yazışma Adresi/Address for Correspondence: Dr. Can Yücel Karabay,
Denizer Cad. Koşuyolu Kalp Eğitim ve Araştırma Hastanesi
Cevizli, Kartal- Türkiye
Tel: +90 505 957 78 72 Faks: +90 216 459 63 21
E-posta: karabaymd@yahoo.com

Çevrimiçi Yayın Tarihi/Available Online Date: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.089



Warfarin kullanan hastalara ilaca ilişkin verilen grup eğitiminin bilgi düzeylerine etkisi

The effect of group education about drug usage in the patient's on warfarin therapy

Tromboembolik olaylarda tedavi amacıyla yaygın olarak antikoagülan bir ilaç olan warfarin kullanılmaktadır. Warfarine alternatif ilaç gelişiminde hızlı bir ivme olsa da bu ilaçların günde iki kez kullanımı, ilaç unutulduğunda nasıl uygulama yapılacağı, doz aşımındaki önlemler ve yan etkiler ile ilgili hala net olmayan sonuçlar vardır. Bu durum Warfarinin bir süre daha klinik pratikte yoğun olarak kullanılacağı anla-

Tablo 1. Hastaların warfarin kullanımına ilişkin bazı klinik özellikleri ve eğitim öncesi-sonrası bilgi puan ortalamaları

Özellikler	Sayı n	Yüzde %
Warfarin kullanım süresi		
Bir yıldan az	6	15
1-5 yıl	19	47.5
6 ve üzeri yıl	15	37.5
İlave kronik hastalık		
Hipertansiyon	10	43.5
Diyabetes mellitus	7	30.4
Koroner arter hastalığı	3	13.0
Diğer (Akdeniz anemisi, kanser)	3	13.0
Hedeflenen INR* değerini bilme	24	60
Düzenli ilaç kullanma	38	95
Düzenli kan testini yaptırma	37	92.5
Warfarin kullanımına ilişkin yaşanan sorunlar		
Burun, diş eti kanamaları, sebpsiz ciltte morluklar	12	71.6
Mide kanaması	5	29.4
Warfarin kullanımına ilişkin Bilgi Düzeyi		
	Eğitim öncesi	Eğitim sonrası
Bilgi düzeyi puan ortalaması $\bar{X} \pm SD$	4.7 $\pm$ 2.8**	8.1 $\pm$ 1.2**
*International Normalized Ratio		
**p<0.001		

mına gelmektedir. Warfarin dozunun ayarlanması için düzenli olarak INR (International Normalized Ratio) kontrolü yapılmalıdır. Çünkü fazla anti-koagülasyon kanama riskini; yetersiz antikoagülasyon ise tromboembolik riski artırmaktadır (1). Klinik pratikte de bu ilacı herhangi bir endikasyonla kullanan hastalarda, sık kanama ve özellikle protez kapak trombüsleri gözlenmektedir ve ne yazık ki tedavi yönetimi son derece güçtür. Oral antikoagülan kullanan hastaların ilaç yönetimine yönelik bireysel yönetim bilgi ve becerisinin geliştirilmesi ile ölüm riski, majör komplikasyon riski önemli derecede azalmakta, teröpatik INR aralığını sürdürme süresi artmaktadır (2). Bu nedenle warfarin kullanan hastaların ilacın kullanım nedeni, önemi, etkisinin kontrolü, ilaç-ilaç ve ilaç-besin etkileşimlerine ilişkin eğitim stratejilerinin geliştirilmesi oldukça önemlidir. Eğitim yaklaşımlarında bireysel eğitime ilaveten görsel, yazılı materyallerin kullanılması ve grup eğitimi eğitimin etkinliğini daha da artıracaktır (3). Özellikle hasta ve yakınlarının bir arada olduğu grup eğitiminde eğitime katılan bireylerin deneyimlerini paylaşması, karşılıklı hekim-hemşire- hasta etkileşimleri hastaların hem bilgi düzeylerini arttıracak hem de sosyal destek sisteminin gelişmesine katkı sağlayacaktır.

Bu çalışmada warfarin kullanan hastalara ilacın etkisi, yan etkisi, ilaç izlemi ve ilaç kullanımına ilişkin öz-bakım aktivitelerine yönelik sağlık ekibi (hekim, hemşire) tarafından inter aktif yöntemle verilen eğitimin hastaların bilgi düzeylerine etkisine bakıldı.

Ön test-son test tipte yapılan çalışmada, bir üniversite hastanesi kardiyoloji polikliniğine başvuran hasta ve yakınlarına eğitim için randevu verildi. Eğitim öncesi hastaların ilaç kullanımı, izlem ve öz-bakım aktivitelerine ilişkin bilgi düzeylerini belirlemek için "Veri Toplama Formu" ile veriler toplandı. Daha sonra bir hekim ve iki hemşire tarafından başlangıçta onbeş dakikalık sunum tarzında daha sonra ise soru cevap şeklinde interaktif eğitim toplantısı yapıldı. Eğitimin süresi 40- 60

ortalama 50 dakika sürdü. Eğitimin etkinliğini değerlendirmek için eğitim sonrası "Veri Toplama Formu" tekrar uygulandı. İlaça ilişkin bilgi düzeyinin değerlendirilmesinde sıfır (0)'dan 10'a kadar numaralandırılan sayısal skala kullanıldı. İstatistiksel analizde; eşleştirilmiş t testi ve tek-rarlayan ölçümler ANOVA testi kullanıldı. p≤ 0.05 anlamlı kabul edildi

Çalışmaya katılan 40 hastanın %60'ı kadın, çoğunluğu (%77.5) evli ve yaş ortalaması 55.2±12.7 idi. Hastaların %57.5'inde ilave kronik hastalığın olduğu, bunların %43.5'inde hipertansiyon, %30.4'ünde diyabetes mellitus olduğu belirlendi. Hastaların çoğunluğunun (%72.5) mitral kapak hastalığı, %17.5'inin ise operasyon sonrası emboli nedeniyle warfarin kullandığı, tamamına yakınının ilacı düzenli kullandığı ve istenen sıklıkta INR testini yaptırdığı belirlendi. Hastaların %42.5'inde warfarin kullanımına bağlı sorunlar yaşandığı, bu sorunların çoğunluğunun (%71) sebpsiz yere ciltte morluklar, burun ve diş etinde kanamalar gibi minör, %29.4'ünün ise mide kanaması gibi major komplikasyonun yaşandığı saptandı.

Hastaların warfarin ilacını kullanımına ilişkin bilgi puan ortalamasının eğitim öncesi (4.7±2.8) orta, eğitim sonrası ise (8.1±1.2) yüksek düzeyde olduğu, eğitim öncesi ve sonrası bilgi puan ortalamaları arasında istatistiksel olarak ileri düzeyde anlamlı fark olduğu belirlendi (p<0.001) (Tablo 1). Çalışmamızda hastaların düzenli ilaç kullanma ve INR kontrolünü yaptırma önerilerine uyumun yüksek olduğu ortaya çıkmıştır. Çalışmamızda, hastaların warfarine ilişkin bilgi düzeylerinin orta ve hekim, hemşire tarafından interaktif yöntemle verilen grup eğitiminin bilgi düzeylerini artırmada oldukça etkili olduğu sonuçları diğer çalışma sonuçları ile uyumludur (2-5).

Sonuç olarak warfarin kullanan hastalara, sağlık ekibi tarafından ilaca yönelik eğitim programların geliştirilmesi ve sürdürülmesi ile hastaların ilaca ilişkin bilgi, uyumlarında ve hasta güvenliğinin artmasında, warfarin kullanımına ilişkin komplikasyonların dolayısıyla maliyetin azalmasında etkili olacaktır.

Türkay Özcan, Meral Altıok*, Fatma Babalıklı
Mersin Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı ve
***Sağlık Yüksekokulu, Mersin-Türkiye**

Kaynaklar

1. Demirbağ R. Warfarin kullanan hastalara genotip tayini istenmeli mi? Turk Kardiyol Dern Arş 2010; 38: 383-4.
2. Metlay JP, Hennessy S, Localio AR, Han X, Yang W, Cohen A, et al. Patient reported receipt of medication instructions for warfarin is associated with reduced risk of serious bleeding events. J Gen Intern Med 2008; 23: 1589-94. [CrossRef]
3. Mazor KM, Baril J, Dugan E, Spencer F, Burgwinkle P, Gurwitz JH. Patient education about anticoagulant medication: is narrative evidence or statistical evidence more effective? Patient Educ Couns 2007; 69: 145-57. [CrossRef]
4. Smith MB, Christensen N, Wang S, Strohecker J, Day JD, Weiss JP, et al. Warfarin knowledge in patients with atrial fibrillation: implications for safety, efficacy, and education strategies. Cardiology 2010; 116: 61-9. [CrossRef]
5. Mercan S, Enç N. Educational needs of patients with warfarin. J Card Nur 2011; 1: 12-7.

Yazışma Adresi/Address for Correspondence: Dr. Türkay Özcan,
Mersin Üniversitesi Tıp Fakültesi Hastanesi, Eski Otogar Yanı,
Mersin-Türkiye
Tel: +90 532 602 98 88 Faks: +90 324 337 43 05
E-posta: iozcan@mersin.edu.tr

Çevrimiçi Yayın Tarihi/Available Online Date: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.090

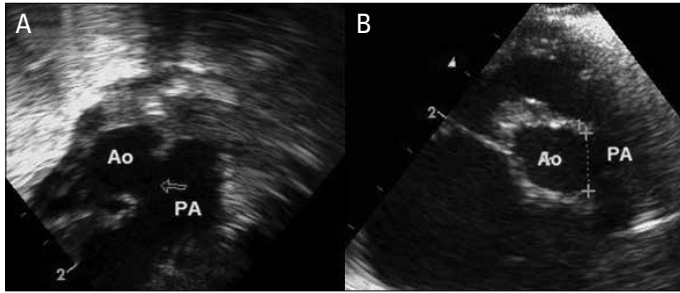


Çok düşük doğum ağırlıklı prematüre bir bebekte başarılı aortopulmoner pencere cerrahisi

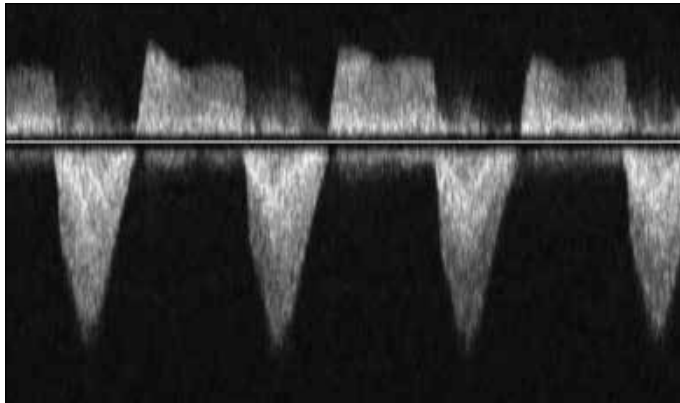
Successful surgical closure of aortopulmonary window in a very low birth weight premature infant

Yirmi sekiz haftalık 1200 gr doğmuş 8 günlük erkek olgu, solunum sıkıntısı nedeniyle hastanemize sevk edildi. Fizik muayenede patolojik olarak taşikardi ve takipne, interkostal ve subkostal çekilme, S2 sertliği, tüm odaklarda duyulan devamlı üfürüm ve hepatomegali saptandı. Kan basıncı 64/18 mmHg ölçüldü. Telekardiyografide kardiyomegali ve konjesyon bulguları mevcut idi. Ekokardiyografide apikal anterior açılama (Şekil 1A) ve parasternal kısa eksen (Şekil 1B) görüntülemelerde; aort ve pulmoner kapakların hemen üstünde, çıkan aort ve ana pulmoner arter arasında 6 mm genişliğinde soldan sağa şantlı defekt (Video 1, 2. Video/hareketli görüntüler www.anakarder.com' da izlenebilir), suprasternal görüntülemelerde inen aortada retrograd diastolik akım paterni (Şekil 2) olduğu izlendi. Ayrıca 3 mm boyutlarında patent foramen ovale (PFO), orta derecede mitral ve triküspit kapak yetersizliği saptandı. Aortopulmoner pencereye bağlı konjestif kalp yetersizliği tanısı ile medikal tedavi başlandı ve cerrahi kapatma için kalp damar cerrahisine danışıldı.

Aortopulmoner pencere normal olarak gelişen iki semilüner kapağın hemen üzerinde, çıkan aort ile ana pulmoner arter arasındaki anormal ilişkidir ve aortikopulmoner septasyonda embriyolojik hayatta oluşan defektler nedeniyle oluşur. Tüm doğuştan kalp hastalıkları arasındaki insidansı %1'den azdır (1). Semilüner kapakların varlığı aortopulmoner pencere (APP) defektini trunkus arteriosusdan ayırır (1, 2). Yüksek sol-sağ şant sebebiyle yenidoğan döneminde konjestif kalp yetersizliği, gelişme geriliği ve pulmoner hipertansiyon gelişebilir. Bu nedenle yenidoğan



Şekil 1. Ekokardiyografide apikal anterior açılama (A) ve parasternal kısa eksen (B) görüntülemelerde çıkan aorta ile ana pulmoner arter arasındaki defekt



Şekil 2. Ekokardiyografide inen aortada CW Doppler ile alınan retrograd diastolik akım paterni

döneminde erken cerrahi girişim planlanmalı ve geriye dönüşümsüz pulmoner vasküler hastalık gelişmeden defekt kapatılmalıdır (2, 3).

Richardson sınıflamasına göre APP anatomik olarak üç tipe ayrılmaktadır. Tip 1'de defekt dairesel kenarlıdır, çıkan aort ile ana pulmoner arter arasında yerleşir ve küçük-orta genişliktedir, tip 2'de nispeten spiral şeklindedir ve sağ pulmoner arter çıkışına kadar yayılma gösterir, tip 3'de ise sağ pulmoner arter çıkan aorttan ayrılır (4). Aortopulmoner pencereye eşlik eden başka bir kardiyak defekt yoksa veya minör defektler (atriyal septal defekt, ince PDA, PFO gibi) varsa basit APP'den bahsedilir. Eşlik eden kardiyak defekt, büyük arterlerin transpozisyonu, Fallot tetralojisi ve aortik ark anomalileri gibi daha önemli patolojiler ise, kompleks APP olarak değerlendirilir (3, 5). Olgumuzdaki defekt tip 1 basit APP'ye uymaktaydı.

Tanıda ekokardiyografi yeterli bir yöntemdir (3). Kalp kateterizasyonu ve anjiyografi daha çok akciğer vasküler hastalığının araştırılması için daha sonraki yaşlarda yapılmaktadır (3). Tip 1 APP cerrahi tedavisinde ekstrakorporeal dolaşım altında otolog veya PTFE (politetrafloroetilen) yama ile kapatma, her iki arterin ayrılıp ayrı ayrı yama konulması gibi teknikler tanımlanmıştır (2-5). İnotrop destek tedavisi sonrası defekt transaortik yolla perikard yama ile tek seansta başarılı bir şekilde kapatıldı. Ektrakorporeal dolaşım sonrası yoğunbakım ünitesinde açık sternum durumunda iki gün izlendikten sonra sternum kapatılarak hasta ekstübe edildi. Operasyon sonrası izlemde komplikasyon gelişmedi. Kontrol ekokardiyografilerinde defektin tamamen kapandığı, inen aortadaki retrograd diastolik akım paterninin kaybolduğu izlendi. Mitral ve triküspit kapak yetersizliklerinin postop ikinci haftada düzeldiği saptandı ve hasta şifa ile taburcu edildi.

Bu olgu, bilgilerimize göre literatürdeki en küçük yaş ve en düşük ağırlıkla opere edilip şifa ile taburcu edilen APP olgusudur. Erken dönemde konjestif kalp yetersizliği, gelişme geriliği ve pulmoner hipertansiyon gelişmesi nedeniyle APP'nin vakit kaybedilmeden medikal destek tedavi ile birlikte çok düşük doğum ağırlıklı prematüre bebeklerde bile başarılı bir şekilde opere edilebileceğini ve operasyonun geciktirilmemesi gerektiğini vurgulamak istiyoruz.

Önder Doksöz, Savaş Demirpençe, Timur Meşe, Osman Nejat Sarıosmanoğlu*

İzmir Dr. Behçet Uz Çocuk Hastanesi, Çocuk Kardiyolojisi ve *Kalp-Damar Cerrahisi Klinikleri, İzmir-Türkiye

Video 1. Ekokardiyografide apikal anterior açılama ile elde edilen görüntüde çıkan aorta ile ana pulmoner arter arasındaki defekt

Video 2. Ekokardiyografide renkli Doppler görüntülemelerde çıkan aorta ile ana pulmoner arter arasındaki sol-sağ şantlı defekt görüntüsü

Kaynaklar

1. Ödemiş E, Güzeltaş A, Bilici M, Öztürk E. Closure of nonrestrictive aortopulmonary window in an infant by the transcatheter approach. *Anadolu Kardiyol Derg* 2012; 12: 364.
2. Şaşmaz A, Alkan T, Ersoy C, Paker T, Akçevin A, Bayer V, et al. Our surgical experiences with aortopulmonary window. *Anadolu Kardiyol Derg* 2006; 6: 77-8.
3. Erez E, Dagan O, Georgiou GP, Gelber O, Vidne BA, Birk E. Surgical management of aortopulmonary window and associated lesions. *Ann Thorac Surg* 2004; 77: 484-7. [CrossRef]
4. Richardson JV, Doty DB, Rossi NP, Ehrenhaft JL. The spectrum of anomalies of aortopulmonary septation. *J Thorac Cardiovasc Surg* 1979; 78: 21-7.
5. Backer CL, Mavroudis C. Surgical management of aortopulmonary window: a 40-year experience. *Eur J Cardiothorac Surg* 2002; 21: 773-9. [CrossRef]

Yazışma Adresi/Address for Correspondence: Dr. Önder Doksöz, İzmir Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi, Çocuk Kardiyolojisi Kliniği, İzmir-Türkiye
Tel: +90 232 489 56 56 Faks: +90 232 489 53 15
E-posta: doksozender@yahoo.com

Çevrimiçi Yayın Tarihi/Available Online Date: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.091



Almanac 2012: congenital heart disease. The journals present selected research that has driven recent advances in clinical cardiology

Michael Burch¹, Nathalie Dedieu²

¹Great Ormond Street Hospital, London-UK

²Department of Paediatric Cardiology, Royal Brompton Hospital, London-UK

ABSTRACT

This Almanac highlights recent papers on congenital heart disease in the major cardiac journals. Over 100 articles are cited. Subheadings are used to group relevant papers and allow readers to focus on their areas of interest, but are not meant to be comprehensive for all aspects of congenital cardiac disease. (*Anadolu Kardiyol Derg 2013; 13(0): 000-000*)

Epidemiology

The prevalence of congenital heart disease in Europe was recently reported in two major papers. Data from a central database for 29 population-based registries in 16 countries showed a total prevalence of 8 per 1000 (1). The overall detection rate of non-chromosomal congenital heart disease prenatally was only 20%, although 40% of severe cases were diagnosed before birth. It was estimated that each year in the European Union 36 000 children are live born with congenital heart disease and another 3000 are diagnosed with congenital heart disease but die as a termination of pregnancy for fetal abnormality. In a systematic review (2) of 114 papers and 24091 867 live births the prevalence of congenital heart disease increased over time from 0.6/1000 in 1930 to 9.1/1000 after 1995. The rate stabilised in the past 15 years but equates to 1.35 million children born each year with congenital heart disease. The prevalence was higher in Europe than in North America.

An increased risk of congenital heart disease was seen with assisted reproductive techniques using data from the Paris Registry of Congenital Malformations (3). The higher risk varied with the method of assisted reproductive technique and the type of cardiac abnormality. The authors speculate that this may be due to the reproductive technology or to the underlying reason for infertility of the couple.

Genetics

Three-quarters of patients with 22q11.2 deletion syndrome (22q11.2DS) have congenital heart disease and although it is common practice to test all children with typical cardiac lesions for 22q11.2DS, many adult patients have not been investigated. An adult population of 479 patients with typical lesions (tetralogy of Fallot and pulmonary atresia and ventricular septal defect) was reviewed (4). Twenty patients were already known to have 22q11.2DS but a microdeletion was detected in a further 24

Address for Correspondence: Michael Burch MD, Great Ormond Street Hospital, London WC1N 3JH-UK

E-mail: burchm@gosh.nhs.uk

Acknowledgement of permission for re-publication: The article was first published in Heart (Burch M, Dedieu N. Almanac 2012: congenital heart disease. The national society journals present selected research that has driven recent advances in clinical cardiology. Heart Published Online First: 2 September 2012 doi:10.1136/heartjnl-2011-301538.) and is republished with permission.

Received Date: 21 May 2012 **Accepted Date:** 29 May 2012 **Available Online Date:** 2 September 2012 **Available Reproduction Online Date:** 30.01.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com

doi:10.5152/akd.2013.064



patients. The authors consider that as the syndrome has important clinical and reproductive implications, genetic testing should be considered in all adult patients with tetralogy of Fallot and pulmonary atresia with ventricular septal defect.

Tetralogy of Fallot is common in individuals with hemizygous deletions of chromosome 22q11.2 that remove the cardiac transcription factor TBX1. TBX1 exons were sequenced in 93 patients with non-syndromic tetralogy (5). Single nucleotide polymorphism analysis was performed in 356 patients with tetralogy, their parents and healthy controls. Three new variants not present in 1000 chromosomes from healthy ethnically matched controls were identified. This study demonstrated that rare TBX1 variants with functional consequences are present in a small proportion of patients with non-syndromic tetralogy. The thorny issue of the use and interpretation of genetic tests was reviewed by Caleshu et al. (6)

Familial transposition of the great arteries was shown to be caused by multiple mutations in the laterality genes (7) in a study of seven families. This provides evidence that some cases of familial transposition are caused by mutations in laterality genes and therefore are part of the same disease spectrum of heterotaxy syndrome, and argues for an oligogenic or complex mode of inheritance in these pedigrees. The editorial by Keavney (8) considered this a useful step forward in understanding transposition. Homocysteine is known to be an independent risk factor for congenital heart disease and genetic abnormalities which affect homocysteine may be expected to influence the incidence of congenital heart problems. This was demonstrated when a functional variant in methionine synthase reductase intron-1 significantly increased the risk of congenital heart disease in the Han Chinese population (9).

Fetal Cardiology

Fetal cardiology remains a cornerstone of congenital heart practice. The paper by Marek et al. (10) offered a unique overview of prenatal diagnosis in the Czech republic, which by virtue of the strict organisation of the health service enabled a comprehensive national registry to develop over two decades. There were some particular successes and in recent years antenatal diagnosis of hypoplastic left heart reached 95.8%, whereas transposition was diagnosed in only 25.6% of cases.

Whether the antenatal development of the cardiac chambers is dependent on flow is debated, but an elegant paper by Stressig et al. from Bonn (11) demonstrated that preferential flow to the right heart in the setting of a diaphragmatic hernia does impair left heart development.

Isolated fetal atrioventricular block was reviewed in a retrospective European study of 175 cases (12). Risk factors for poor outcome were gestation <20 weeks, ventricular rate <50/min, hydrops and impaired ventricular function. No significant effect of treatment with corticosteroids was seen. In a multicentre French study (13), 141 patients with non-immune atrioventricular block, diagnosed in utero or up to age 15 years, were followed up long

term and showed surprisingly good outcomes, with no deaths or dilated cardiomyopathy at a mean follow-up of 11.6 ± 6.7 years.

Atrioventricular block can reflect prenatal exposure to maternal anti-SSA/Ro antibodies and the high mortality associated with cardiac neonatal lupus has been shown (14). In a non-randomised multicentre study of 20 fetuses exposed to maternal lupus antibodies (15) it was found that treatment with intravenous gamma globulin and steroids potentially improved the outcome for these children, with better than expected survival. However, a prospective study of 165 fetuses with exposure to anti-Ro/La antibody found that fetal atrioventricular prolongation did not predict progression to heart block so management based on the strategy of identifying and treating fetal atrioventricular prolongation was questioned (16).

Transplacental drug treatment for fetal tachyarrhythmias was reviewed in a multicentre study (17), which showed the superiority of flecainide and digoxin; however, the study was weakened by being non-randomised.

Cardiomyopathy, Heart Failure and Transplantation

Pre-participation screening for cardiomyopathy is gaining more attention in the media. An Italian study on the value of pre-participation screening of children with ECGs demonstrated that postpubertal persistence of T-wave inversion was associated with an increased risk of cardiomyopathy (18).

When to propose transplantation remains difficult in ambulatory patients. The risk of death and transplantation in paediatric dilated cardiomyopathy was reviewed in a multicentre database, and the authors showed that an increased left ventricular end-diastolic dimension was associated with increased risk of transplantation but not death (19). Work by Giardini et al. (20) has shown that metabolic exercise testing is useful in predicting prognosis, but the percentages of predicted values are better than absolute numbers. Transplantation for congenital heart disease is generally considered higher risk, although encouraging results were shown in a small adult congenital transplant series from the UK (21). An American database review of over a thousand transplants for adult congenital heart disease confirmed the high 30-day mortality, but better late survival after transplantation. Although heart transplants remain a precious resource, at present the results justify the continued expansion of adult congenital heart transplant programmes (22).

An international database showed that extracorporeal membrane oxygenation does not appear to be a reliable long-term circulatory support for children awaiting heart transplantation (23). Fortunately, other options of support exist, and Stiller et al. (24) provide a useful overview of mechanical cardiovascular support in infants and children.

The Single Ventricle

Patients with a single ventricle remain a great focus for congenital heart disease resources. Many controversies exist about

the management of these patients. ACE inhibitors are often used in this complex circulation, but the effects of their vasodilatation are unclear. Work in children with bidirectional cavopulmonary shunts demonstrated that enalaprilat did not increase total cardiac output but redistributed flow to the lower body, with a concomitant decrease in arterial oxygen saturation (25). The authors concluded that it is difficult to increase cardiac output in these patients and ACE inhibitors should be used with caution in those with borderline aortic saturations. This work fits rather well with the results of a randomised multicentre trial, which found administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function or heart failure severity (26). In a further analysis of their study population, the authors have also shown that the renin aldosterone genotype influences ventricular remodelling in infants with a single ventricle (27).

The late outcomes after the Fontan operation remain a concern. In some patients there is a progressive failure of the circulation over time, the underlying pathophysiology of which is not fully understood. In a review of the current evidence for alterations in the pulmonary vasculature in Fontan patients, the potential of treatments approved for pulmonary arterial hypertension which may provide benefits was discussed (28). Liver disease is now recognised as a serious problem late after a Fontan operation. Hepatic dysfunction and cirrhotic change were often seen in a series of Fontan patients (29). Hepatic complications were correlated with the duration of Fontan circulation. The authors concluded that these patients need regular evaluation of hepatic function, although some non-invasive hepatic fibrosis markers can be used effectively. At a recent consensus meeting on this problem the group recommended a prospective study protocol on the assessment of hepatic function 10 years after a Fontan operation (30).

The use of anticoagulation after a Fontan operation remains controversial. A multicentre randomised study of warfarin or heparin after a Fontan procedure was reported (31). A total of 111 patients were randomised. There was a similar, but very, incidence of thrombosis in both groups: 12/57 with aspirin and 13/54 in the warfarin group. Although there were no differences, the authors concluded that as the thrombosis rate was so high, alternative approaches should be considered.

Another Fontan controversy involves the use of fenestrations as although they may improve early surgical results, there is concern about late complications. The late results for fenestration of the systemic venous pathway at the time of the Fontan operation were reported in a multicentre retrospective non-randomised study (32). Of the 361 fenestrations, there were few deleterious later outcomes a mean of 8 ± 3 years after surgery. Saturations were 89% versus 95% in the fenestrated group.

Imaging

Three-dimensional echocardiography is developing rapidly and its application to congenital heart disease may be one of its key uses in future years (33). Other emerging imaging methods

include a new high-resolution ultrasound technique (34). The authors described the technique in adolescents after coarctation repair in early childhood and demonstrated increased preductal arterial intima media thickness, left ventricular mass and ascending aortic stiffness in adolescents. The more pronounced cardiovascular abnormalities after coarctation stent implantation were felt to be related to older patient age at the time of intervention.

Surgery

The Dutch Congenital Corvita (CONCOR) registry for adults with congenital heart disease was reviewed for the results of surgery in predominantly young adults with congenital heart disease (35). One-fifth required cardiovascular surgery during a 15-year period and in 40% the surgery was a reoperation. Men with congenital heart disease had a higher chance of undergoing surgery in adulthood and had a consistently worse long-term survival after reoperations in adulthood than women.

Detailed functional outcomes 8.1 years (range 2.0-14.0) after the Ross operation were reported in 45 subjects (aged 24.6 years, range 16.9-52.2 years) who underwent the Ross procedure between 1994 and 2006. Cardiovascular magnetic resonance imaging, echocardiography and cardiopulmonary exercise testing were used (36). The authors demonstrated minor autograft and homograft dysfunction in the majority of patients after the Ross procedure, associated with good ventricular function and exercise capacity. Late survival was compared in a study of 918 Ross patients and 406 mechanical valve patients 18-60 years of age who survived an elective procedure (1994-2008). With the use of propensity score matching, late survival was compared between the two groups (37). In comparable patients, there was no late survival difference in the first post-operative decade between the Ross procedure and mechanical aortic valve implantation with optimal anticoagulation self-management. The authors demonstrated that survival in these selected young adult patients was excellent, perhaps as a result of highly specialised anticoagulation self-management, better timing of surgery and improved patient selection in recent years. Despite the advent of the Ross operation, aortic valve surgery in children remains a complex and difficult area and a useful overview was provided by d'Udekem (38).

In a report of neurodevelopmental risk from surgery (39), neuropsychological and structural brain imaging assessments in children 16 years of age with transposition of the great arteries who underwent the arterial switch operation as infants were reviewed. Children were randomly assigned to total circulatory arrest or continuous low-flow cardiopulmonary bypass but few significant differences between the treatment group were found. However, adolescents with transposition of the great arteries who have undergone the arterial switch operation are at increased neurodevelopmental risk. The authors consider that children with congenital heart disease may benefit from ongoing surveillance to identify emerging difficulties.

Tetralogy of Fallot

A study using speckle tracking data in patients with corrected tetralogy of Fallot demonstrated that right ventricular outlet deformation is delayed, causing a reduction in right ventricular time delay which is significantly related to impairment in right ventricular performance (40). Late right heart failure is a serious problem in tetralogy and congenitally corrected transposition. In a study of 40 of these patients, with myocardial contrast echocardiography it was found that right ventricular myocardial microvascular density of the septal wall in patients with hypertrophy due to pressure and/or volume overload is reduced. The authors considered that this may be related to a reduced myocardial perfusion reserve and impaired right ventricular systolic function (41). A report on the impact of restrictive physiology on right ventricular function after repair of tetralogy found that diastolic right ventricular stiffness was increased (42). However, the lusitropic response to β adrenergic agents was abnormal regardless of restrictive physiology. In an investigation of 29 asymptomatic children with repaired tetralogy (43), despite moderate right ventricular dilatation and right bundle branch block compared with controls, the authors demonstrated neither right ventricular nor left ventricular dyssynchrony at rest but exercise induced mechanical dyssynchrony. This was unrelated to QRS duration, ventricular volumes and function, or peak oxygen consumption. In a study of repaired adult tetralogy, left ventricular longitudinal dysfunction was associated with greater risk of sudden cardiac death or life-threatening arrhythmias (44). The authors conclude that in combination with echocardiographic right heart variables, these measures provided important outcome information for estimating prognosis.

Pulmonary Hypertension

Further evidence of the benefits of pulmonary vasodilators in Eisenmenger syndrome was provided in a prospective open-label study of sildenafil in 84 patients (45). Twelve months of oral sildenafil treatment was well tolerated and appeared to improve exercise capacity, systemic arterial oxygen saturation and haemodynamic parameters in patients with Eisenmenger syndrome. The importance of pulmonary vasoreactivity as an independent predictor of outcome in 38 patients with Eisenmenger receiving bosentan was reported (46).

A unique national patient cohort of childhood pulmonary hypertension was reported from the UK (47). The authors showed, for the first time, that the incidence of pulmonary hypertension is lower in children than adults and that the clinical features can be different. Most children present with clinical evidence of advanced disease, and clinical status at presentation is predictive of outcome. This 7-year experience confirmed the significant improvement in survival over historical controls. The same group also reported a new CT approach to prognosis (48). They found that fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension. The need for paediatric drug development for pulmonary hyperten-

sion was emphasised by Barst (49). A study of patients with Eisenmenger syndrome ($n=181$, age 36.9 ± 12.1 years, 31% with Down's syndrome), in whom B-type natriuretic peptide (BNP) concentrations were measured as part of routine clinical care, found they predicted outcome (50). In addition, the authors speculated that disease-targeting treatments may help to reduce BNP concentrations in this population, while treatment-naïve patients have static or rising BNP concentrations. This topic was discussed in more detail in an editorial by D'Alto (51).

Arterial Abnormalities in Congenital Heart Disease

While aortic wall abnormalities have been described in inherited connective tissue disorders such as Marfan syndrome and bicuspid aortic valve disease (52, 53), recent reports indicate similar aortic involvement in classical congenital heart disease entities such as coarctation of the aorta, tetralogy of Fallot and transposition of the great arteries; MRI is central in defining the problem (54). Pulmonary artery dilatation is seen with pulmonary valve abnormalities and connective tissue disease, but also occurs in association with bicuspid aortic valve, in the absence of a pulmonary valve abnormality, suggesting a primary vessel wall pathology predisposing to arterial dilatation (55).

Catheter Intervention

With the increased use of interventional cardiological procedures in the young it is clearly important to consider radiation exposure. Data from Italy raised a concern that children with congenital heart disease are exposed to a significant cumulative dose of radiation (56). Indirect cancer risk estimations and direct DNA studies showed that children with congenital heart disease are exposed to a significant radiation dose and emphasised the need for strict radiation dose optimisation in children. The accompanying editorial from Hoffmann and Bremerich expanded on the risks (57).

New developments in catheterisation techniques continue. A prospective, randomised, multicentre, investigational device exemption trial in America compared the use of cutting balloons with high-pressure balloons in treating pulmonary artery stenosis. The authors found a greater efficacy for cutting balloons and a similar safety profile (58). Data from the UK on over 100 stent procedures for coarctation from a single centre (59), demonstrated that stenting for aortic coarctation and re-coarctation is effective with low-immediate complication rates. Postprocedural aneurysm was rare and stent fractures were not seen with the newer-generation stents. The optimal method of follow-up of these patients is unclear with both CT and MRI considered useful (60). A multicentre observational study from the USA reported data from 350 children with native coarctation >10 kg (61). There were 217 stents, 61 balloon angioplasties and 72 surgical procedures. Stenting and surgery were better than balloon angioplasties in reducing upper limb to lower limb blood pressure gradient at short-term follow-up and had better inte-

grated aortic arch imaging outcomes. Stent patients had the shortest stay and the lowest complication rate, although they were more likely to require a planned intervention. The authors cautioned over interpretation of the results as the study was not randomised. Balloon angioplasty for aortic arch obstruction is commonly needed after the Norwood procedure, and results from a retrospective review (62) reported that only 58% of those having an initial balloon angioplasty were free from arch reintervention at 5 years, with the greatest risk of reintervention in those <3 months at initial intervention and those with less successful initial results.

Roberts et al. (63) report multicentre experience of successful percutaneous tricuspid valve replacement using the Melody valve in 15 patients. All patients had a prior bioprosthetic valve or conduit in place and had developed significant stenosis or regurgitation. Encouraging results were reported with the Edwards SAPIEN transcatheter valve for conduit failure in the pulmonary position in 36 patients from four centres (64). Helpful images of this device were published by Lauten et al. (65) The outcomes of pre-stenting 1 year after using the Melody valve in the pulmonary position (66) were reported in 65 patients. The early haemodynamic results were sustained at 1 year, but there was no evidence of further positive functional remodelling after the immediate acute effects.

The strategies surrounding cardiac pacing in infants and children are often debated. A recent multicentre study showed that left ventricular pacing was associated with better systolic function than right ventricular pacing (67), and a useful review put the problems of pacing in children into context (68).

Adult Congenital Heart Disease

The expanding population of adults with congenital heart disease is reflected in the increasing numbers of publications in this field. The emerging burden of hospital admissions of adults with congenital heart disease was described using a Dutch national registry (69). During 28 990 patient-years, 2908 patients (50%) were admitted to hospital. Median age at admission was 39 years (range 18-86). Admission rates were at least two times higher than in the general population, and most marked in the older-age groups. With the ageing of this population, the authors advocate timely preparation of healthcare resources.

A paper from Toronto described the respiratory and skeletal muscle weakness in adults with congenital heart disease which resembles that seen in older adults with advanced heart failure (70). The importance of this shift in focus in the mechanisms of reduced exercise tolerance in congenital heart disease is further discussed in the editorial by Giardini (71). Biomarkers may also have an important role in assessment of these patients. The relationship of systemic right ventricular function to ECG and NT-proBNP levels in adults late after the Senning or Mustard procedure was investigated (72). Circulating NT-proBNP levels and several surface ECG parameters were shown to constitute surrogate markers of systemic right ventricular function and

provide additional information on heart failure status. Although paediatricians are well aware of the association of Down's syndrome and congenital heart disease, information from the Netherlands documented that 17% of patients with Down's syndrome living in residential centres had undiagnosed congenital heart disease. Thirty-one centres and 1158 patients were included in the first stage of the study (73). The authors recommend cardiac screening in older patients with Down's syndrome, for whom new therapeutic options are available, and for prevention of cardiac complications in old age.

Stroke was a major cause of morbidity in adult congenital heart disease in a retrospective analysis of aggregated European and Canadian databases (74) with a total of 23 153 patients aged 16-91 years (mean 36.4). Among them, 458 patients (2.0%) had one or more cerebrovascular accident. The highest prevalence was in cyanotic lesions 50/215 (23.3%).

A meta-analysis and systematic review of atrial septal defect closure identified 26 studies including 1841 patients who underwent surgical closure and 945 who underwent percutaneous closure (75). Meta-analysis using a random effects model demonstrated a reduction in the prevalence of atrial tachyarrhythmias after atrial septal defect closure [OR=0.66 (95% CI 0.57 to 0.77)]. This effect was demonstrated after both percutaneous and surgical closure. Immediate (<30 days) and mid-term (30 days-5 years) follow-up also showed a reduction in the prevalence of atrial tachyarrhythmias.

Inuzuka et al. reviewed data of 1375 consecutive adult patients with congenital heart disease (age 33±13 years) who underwent cardiopulmonary exercise testing at a single centre over a period of 10 years (76). They showed that cardiopulmonary exercise testing provides strong prognostic information in adult patients with congenital heart disease. However, they considered prognostication should be approached differently, depending on the presence of cyanosis, use of rate-lowering drugs and achieved level of exercise.

Pregnancy and Congenital Heart Disease

Heart disease has become the major factor in maternal mortality during pregnancy in developed countries. The increasing number of women with congenital heart disease surviving to adult life has made care in pregnancy for this group an important area of obstetric cardiology. The care needed for this vulnerable group has been highlighted (77). The outcomes of 405 pregnancies of women with congenital heart disease were investigated and late cardiac events investigated (78). While adverse events during pregnancy are well known, the problem of late cardiac events after pregnancy is less well known. The authors found pre-pregnancy maternal characteristics can help to identify women at increased risk for late cardiac events. Adverse cardiac events during pregnancy were also important and are associated with an increased risk of late cardiac events. Opatowsky et al. (79) used the US national registry of hospital admissions to assess annual deliveries for women with congenital

heart disease. These increased 34.9% from 1998 to 2007 compared with an increase of 21.3% in the general population. Women with congenital heart disease were more likely to sustain a cardiovascular event (4042/100 000 vs 278/100000 deliveries); arrhythmia was the most common cardiovascular event. Death occurred in 150/100000 patients with congenital heart disease compared with 8.2/100000 patients without. Complex disease was associated with greater odds of having an adverse cardiovascular event than simple congenital heart disease (8158/100000 vs 3166/100000, multivariable OR=2.0, 95% CI 1.4 to 3.0).

Lui et al. (80) investigated heart rate response during exercise and pregnancy outcome in women with congenital heart disease. Peak heart rate, percentage of maximum age predicted heart rate and chronotropic index were associated with a cardiac event. Neonatal events occurred in 20%. Peak oxygen consumption was not associated with an adverse pregnancy outcome. The authors concluded that an abnormal chronotropic response correlates with adverse pregnancy outcomes in women with congenital heart disease and should be considered in refining risk stratification schemes.

Global Burden of Cardiovascular Disease

Congenital heart disease in developing countries is clearly important as the great majority of patients are born there. A concerning finding from New Delhi (81) is that female gender is an important determinant of non-compliance with paediatric cardiac surgery. Their prospective study of 405 cases included in-depth interviews. They concluded that deep-seated social factors underlie this gender bias. An interesting overview of this problem is given by Daljit Singh and colleagues (82). In a developed country (Taiwan) an investigation of 289 patients with adult congenital heart disease found that female gender was associated with poor physical and psychological quality of life (83). The common denominators for quality of life were primarily personality trait, psychological distress and family support, but interestingly, not disease severity.

A patent ductus is an easily treatable lesion but, if untreated, large ducts can lead to pulmonary vascular disease. Late presentation in developing countries means that many patients have a level of pulmonary hypertension that could make intervention dangerous. The results from a study in Mexico (84) are important and encouraging. They reported 168 patients with isolated patent ductus arteriosus (PDA) and pulmonary artery systolic pressure ≥ 50 mm Hg. Mean age was 10.3 ± 14.3 years (median 3.9), PDA diameter was 6.4 ± 2.9 mm (median 5.9), pulmonary artery systolic pressure was 63.5 ± 16.2 mm Hg (median 60). The overall success rate was 98.2%. Follow-up in 145 (86.3%) cases for 37.1 ± 24 months (median 34.1) showed further decrease of the pulmonary pressure to 30.1 ± 7.7 mm Hg ($p < 0.0001$). The authors have shown that in selected cases percutaneous treatment of hypertensive ductus is safe and effective and that pulmonary pressures decrease immediately and continue to fall with time.

Images of Congenital Heart Disease

Perhaps one of the most alluring aspects of congenital heart disease is the aesthetics of the abnormalities. This lends itself to imaging, and congenital heart images brighten up the pages of many major cardiac journals. Therefore it seems appropriate to end this Almanac with reference to some of the more stunning images that reflect the key areas in congenital heart disease that were discussed above, including intervention (85-91), fetal and neonatal (92-95), heart failure and mechanical support (96), adolescent and adult congenital heart disease (97, 98), advanced imaging with MRI and CT (99, 100) and unusual morphology (101-107). All of which are well worth a look to brighten up a night catching up on the cardiac journals.

Contributors MB and ND carried out the literature review; MB wrote the first draft of the manuscript, which was revised and approved by both authors.

Competing interest: None.

Provenance and peer review Commissioned; internally peer reviewed.

References

1. Dolk H, Loane M, Garne E; European Surveillance of Congenital Anomalies (EUROCAT) Working Group. Congenital heart defects in Europe: prevalence and perinatal mortality, 2000 to 2005. *Circulation* 2011; 123: 841-9. [\[CrossRef\]](#)
2. Van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011; 58: 2241-7. [\[CrossRef\]](#)
3. Tararbit K, Houyel L, Bonnet D, et al. Risk of congenital heart defects associated with assisted reproductive technologies: a population-based evaluation. *Eur Heart J* 2011; 32: 500-8. [\[CrossRef\]](#)
4. Van Engelen K, Topf A, Keavney BD, et al. 22q11.2 Deletion Syndrome is underrecognised in adult patients with tetralogy of Fallot and pulmonary atresia. *Heart* 2010; 96: 621-4. [\[CrossRef\]](#)
5. Griffin HR, To'p'f A, Glen E, et al. Systematic survey of variants in TBX1 in nonsyndromic tetralogy of Fallot identifies a novel 57 base pair deletion that reduces transcriptional activity but finds no evidence for association with common variants. *Heart* 2010; 96: 1651-5. [\[CrossRef\]](#)
6. Caleshu C, Day S, Rehm HL, et al. Use and interpretation of genetic tests in cardiovascular genetics. *Heart* 2010; 96: 1669-75. [\[CrossRef\]](#)
7. De Luca A, Sarkozy A, Consoli F, et al. Familial transposition of the great arteries caused by multiple mutations in laterality genes. *Heart* 2010; 96: 673-7. [\[CrossRef\]](#)
8. Keavney B. Left, right: a step forward in understanding transposition of the great arteries. *Heart* 2010; 96: 653-5. [\[CrossRef\]](#)
9. Zhao JY, Yang XY, Gong XH, et al. Functional variant in methionine synthase reductase intron-1 significantly increases the risk of congenital heart disease in the Han Chinese population. *Circulation* 2012; 125: 482-90. [\[CrossRef\]](#)
10. Marek J, Tomek V, Skovra'nek J, et al. Prenatal ultrasound screening of congenital heart disease in an unselected national population: a 21-year experience. *Heart* 2011; 97: 124-30. [\[CrossRef\]](#)
11. Stressig R, Fimmers R, Eising K, et al. Preferential streaming of the ductus venosus and inferior caval vein towards the right heart is

- associated with left heart underdevelopment in human fetuses with left-sided diaphragmatic hernia. *Heart* 2010; 96: 1564-8. [\[CrossRef\]](#)
12. Eliasson H, Sonesson SE, Sharland G, et al; Fetal working group of the European association of pediatric cardiology. Isolated atrioventricular block in the fetus: a retrospective, multinational, multicenter study of 175 patients. *Circulation* 2011; 124: 1919-26. [\[CrossRef\]](#)
13. Baruteau AE, Fouchard S, Behaghel A, et al. Characteristics and long-term outcome of non-immune isolated atrioventricular block diagnosed in utero or early childhood: a multicentre study. *Eur Heart J* 2012; 33: 622-9. [\[CrossRef\]](#)
14. Izmirli PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. *Circulation* 2011; 124: 1927-35. [\[CrossRef\]](#)
15. Trucco SM, Jaeggi E, Cuneo B, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. *J Am Coll Cardiol* 2011; 57: 715-23. [\[CrossRef\]](#)
16. Jaeggi ET, Silverman ED, Laskin C, et al. Prolongation of the atrioventricular conduction in fetuses exposed to maternal anti-Ro/SSA and anti-La/SSB antibodies did not predict progressive heart block. A prospective observational study on the effects of maternal antibodies on 165 fetuses. *J Am Coll Cardiol* 2011; 57: 1487-92. [\[CrossRef\]](#)
17. Jaeggi ET, Carvalho JS, De Groot E, et al. Comparison of transplacental treatment of fetal supraventricular tachyarrhythmias with digoxin, flecainide, and sotalol: results of a nonrandomized multicenter study. *Circulation* 2011; 124: 1747-54. [\[CrossRef\]](#)
18. Migliore F, Zorzi A, Michieli P, et al. Prevalence of cardiomyopathy in Italian asymptomatic children with electrocardiographic T-wave inversion at preparticipation screening. *Circulation* 2012; 125: 529-38. [\[CrossRef\]](#)
19. Alvarez JA, Orav EJ, Wilkinson JD, et al; Pediatric cardiomyopathy registry Investigators. Competing risks for death and cardiac transplantation in children with dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. *Circulation* 2011; 124: 814-23. [\[CrossRef\]](#)
20. Giardini A, Fenton M, Andrews RE, et al. Peak oxygen uptake correlates with survival without clinical deterioration in ambulatory children with dilated cardiomyopathy. *Circulation* 2011; 124: 1713-18. [\[CrossRef\]](#)
21. Irving C, Parry G, O'Sullivan J, et al. Cardiac transplantation in adults with congenital heart disease. *Heart* 2010; 96: 1217-22. [\[CrossRef\]](#)
22. Burch M. Is heart transplantation for adult congenital heart disease an appropriate use of a scarce resource? *Heart* 2010; 96: 1172-3. [\[CrossRef\]](#)
23. Almond CS, Singh TP, Gauvreau K, et al. Extracorporeal membrane oxygenation for bridge to heart transplantation among children in the United States: analysis of data from the organ procurement and transplant network and extracorporeal life support organization registry. *Circulation* 2011; 123: 2975-84. [\[CrossRef\]](#)
24. Stiller B, Benk C, Schlensak C. Congenital heart disease: mechanical cardiovascular support in infants and children. *Heart* 2011; 97: 596-602. [\[CrossRef\]](#)
25. Lee KJ, Yoo SJ, Holtby H, et al. Acute effects of the ACE inhibitor enalaprilat on the pulmonary, cerebral and systemic blood flow and resistance after the bidirectional cavopulmonary connection. *Heart* 2011; 97: 1343-8. [\[CrossRef\]](#)
26. Williams RV, Zak V, Ravishankar C, et al; Pediatric Heart Network Investigators. Factors affecting growth in infants with single ventricle physiology: a report from the Pediatric Heart Network Infant Single Ventricle Trial. *J Pediatr* 2011; 159: 1017-22. [\[CrossRef\]](#)
27. Mital S, Chung WK, Colan SD, et al; Pediatric Heart Network Investigators. Reninangiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. *Circulation* 2011; 123: 2353-62. [\[CrossRef\]](#)
28. Beghetti M. Fontan and the pulmonary circulation: a potential role for new pulmonary hypertension therapies. *Heart* 2010; 96: 911-16. [\[CrossRef\]](#)
29. Baek JS, Bae EJ, Ko JS, et al. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. *Heart* 2010; 96: 1750-5. [\[CrossRef\]](#)
30. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol*. Published Online First: 26 April 2012. doi:10.1007/s00246-012-0315-7. [\[CrossRef\]](#)
31. Monagle P, Cochrane A, Roberts R, et al. A multicenter, randomized trial comparing heparin/warfarin and acetylsalicylic acid as primary thromboprophylaxis for 2 years after the Fontan procedure in children. Fontan Anticoagulation Study Group. *J Am Coll Cardiol* 2011; 58: 645-51. [\[CrossRef\]](#)
32. Atz AM, Trivison TG, McCrindle BW, et al; Pediatric Heart Network Investigators. Late status of Fontan patients with persistent surgical fenestration. *J Am Coll Cardiol* 2011; 57: 2437-43. [\[CrossRef\]](#)
33. Vettukattil JJ. Three dimensional echocardiography in congenital heart disease. *Heart* 2012; 98: 79-88. [\[CrossRef\]](#)
34. Sarkola T, Redington AN, Slorach C, et al. Assessment of vascular phenotype using a novel very-high-resolution ultrasound technique in adolescents after aortic coarctation repair and/or stent implantation: relationship to central haemodynamics and left ventricular mass. *Heart* 2011; 97: 1788-93. [\[CrossRef\]](#)
35. Zomer AC, Verheugt CL, Vaartjes I, et al. Surgery in adults with congenital heart disease. *Circulation* 2011; 124: 2195-201. [\[CrossRef\]](#)
36. Puranik R, Tsang VT, Broadley A, et al. Functional outcomes after the Ross (pulmonary autograft) procedure assessed with magnetic resonance imaging and cardiopulmonary exercise testing. *Heart* 2010; 96: 304-8. [\[CrossRef\]](#)
37. Mokhes MM, Kortke H, Stierle U, et al. Survival comparison of the Ross procedure and mechanical valve replacement with optimal self-management anticoagulation therapy: propensity-matched cohort study. *Circulation* 2011; 123: 31-8. [\[CrossRef\]](#)
38. d'Udekem Y. Aortic valve surgery in children. *Heart* 2011; 97: 1182-9. [\[CrossRef\]](#)
39. Bellinger DC, Wypij D, Rivkin MJ, et al. Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging. *Circulation* 2011; 124: 1361-9. [\[CrossRef\]](#)
40. van der Hulst AE, Roest AA, Delgado V, et al. Relationship between temporal sequence of right ventricular deformation and right ventricular performance in patients with corrected tetralogy of Fallot. *Heart* 2011; 97: 231-6. [\[CrossRef\]](#)
41. Rutz T, de Marchi SF, Schwerzmann M, et al. Right ventricular absolute myocardial blood flow in complex congenital heart disease. *Heart* 2010; 96: 1056-62. [\[CrossRef\]](#)
42. Apitz C, Latus H, Binder W, et al. Impact of restrictive physiology on intrinsic diastolic right ventricular function and lusitropy in children and adolescents after repair of tetralogy of Fallot. *Heart* 2010; 96: 1837-41. [\[CrossRef\]](#)
43. Roche SL, Grosse-Wortmann L, Redington AN, et al. Exercise induces biventricular mechanical dyssynchrony in children with repaired tetralogy of Fallot. *Heart* 2010; 96: 2010-15. [\[CrossRef\]](#)
44. Diller GP, Kempny A, Liodakis E, et al. Left ventricular longitudinal function predicts life-threatening ventricular arrhythmia and death in

- adults with repaired tetralogy of Fallot. *Circulation* 2012; 125: 2444-6. [\[CrossRef\]](#)
45. Zhang ZN, Jiang X, Zhang R, et al. Oral sildenafil treatment for Eisenmenger syndrome: a prospective, open-label, multicentre study. *Heart* 2011; 97: 1876-81. [\[CrossRef\]](#)
46. D'Alto M, Romeo E, Argiento P, et al. Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. *Heart* 2010; 96: 1475-9. [\[CrossRef\]](#)
47. Moledina S, Hislop AA, Foster H, et al. Childhood idiopathic pulmonary arterial hypertension: a national cohort study. *Heart* 2010; 96: 1401-6. [\[CrossRef\]](#)
48. Moledina S, de Bruyn A, Schievano S, et al. Fractal branching quantifies vascular changes and predicts survival in pulmonary hypertension: a proof of principle study. *Heart* 2011; 97: 1245-9. [\[CrossRef\]](#)
49. Barst RJ. Children deserve the same rights we do: the need for paediatric pulmonary arterial hypertension clinical drug development. *Heart* 2010; 96: 1337-8. [\[CrossRef\]](#)
50. Diller GP, Alonso-Gonzalez R, Kempny A, et al. B-type natriuretic peptide concentrations in contemporary Eisenmenger syndrome patients: predictive value and response to disease targeting therapy. *Heart* 2012; 98: 736-42. [\[CrossRef\]](#)
51. D'Alto M. Brain natriuretic peptide, survival and response to targeting therapy: another piece in the complex puzzle of Eisenmenger syndrome. *Heart* 2012; 98: 681-2. [\[CrossRef\]](#)
52. Braverman AC. Aortic involvement in patients with a bicuspid aortic valve. *Heart* 2011; 97: 506-13. [\[CrossRef\]](#)
53. Benedetto U, Melina G, Takkenberg JJ, et al. Surgical management of aortic root disease in Marfan syndrome: a systematic review and meta-analysis. *Heart* 2011; 97: 955-8. [\[CrossRef\]](#)
54. Grotenhuis HB, de Roos A. Structure and function of the aorta in inherited and congenital heart disease and the role of MRI. *Heart* 2011; 97: 66-74. [\[CrossRef\]](#)
55. Kutty S, Kaul S, Danford CJ, et al. Main pulmonary artery dilation in association with congenital bicuspid aortic valve in the absence of pulmonary valve abnormality. *Heart* 2010; 96: 1756-61. [\[CrossRef\]](#)
56. Ait-Ali L, Andreassi MG, Foffa I, et al. Cumulative patient effective dose and acute radiation-induced chromosomal DNA damage in children with congenital heart disease. *Heart* 2010; 96: 269-74. [\[CrossRef\]](#)
57. Hoffmann A, Bremerich J. The danger of radiation exposure in the young. *Heart* 2010; 96: 251-2. [\[CrossRef\]](#)
58. Peng LF, Lock JE, Nugent AW, et al. Comparison of conventional and cutting balloon angioplasty for congenital and postoperative pulmonary vein stenosis in infants and young children. *Catheter Cardiovasc Interv* 2010; 75: 1084-90.
59. Chakrabarti S, Kenny D, Morgan G, et al. Balloon expandable stent implantation for native and recurrent coarctation of the aorta: prospective computed tomography assessment of stent integrity, aneurysm formation and stenosis relief. *Heart* 2010; 96: 1212-16. [\[CrossRef\]](#)
60. Rosenthal E, Bell A. Optimal imaging after coarctation stenting. *Heart* 2010; 96: 1169-71. [\[CrossRef\]](#)
61. Forbes TJ, Kim DW, Du W, et al. Comparison of surgical, stent, and balloon angioplasty treatment of native coarctation of the aorta: an observational study by the CCISC (Congenital Cardiovascular Interventional Study Consortium). *J Am Coll Cardiol* 2011; 58: 2664-74. [\[CrossRef\]](#)
62. Porras D, Brown DW, Marshall AC, et al. Factors associated with subsequent arch reintervention after initial balloon aortoplasty in patients with Norwood procedure and arch obstruction. *J Am Coll Cardiol* 2011; 58: 868-76. [\[CrossRef\]](#)
63. Roberts PA, Boudjemline Y, Cheatham JP, et al. Percutaneous tricuspid valve replacement in congenital and acquired heart disease. *J Am Coll Cardiol* 2011; 58: 117-22. [\[CrossRef\]](#)
64. Kenny D, Hijazi ZM, Kar S, et al. Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. *J Am Coll Cardiol* 2011; 58: 2248-56. [\[CrossRef\]](#)
65. Lauten A, Hoyme M, Figulla HR. Severe pulmonary regurgitation after tetralogy-of-Fallot repair: transcatheter treatment with the Edwards SAPIEN XT heart valve. *Heart* 2012; 98: 623-4. [\[CrossRef\]](#)
66. Nordmeyer J, Lurz P, Khambadkone S, et al. Pre-stenting with a bare metal stent before percutaneous pulmonary valve implantation: acute and 1-year outcomes. *Heart* 2011; 97: 118-23. [\[CrossRef\]](#)
67. van Geldorp IE, Delhaas T, Gebauer RA, et al. Impact of the permanent ventricular pacing site on left ventricular function in children: a retrospective multicentre survey. Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Paediatric Cardiology. *Heart* 2011; 97: 2051-5. [\[CrossRef\]](#)
68. McLeod KA. Cardiac pacing in infants and children. *Heart* 2010; 96: 1502-8. [\[CrossRef\]](#)
69. Verheugt CL, Uiterwaal CS, van der Velde ET, et al. The emerging burden of hospital admissions of adults with congenital heart disease. *Heart* 2010; 96: 872-8. [\[CrossRef\]](#)
70. Greutmann M, Le TL, Tobler D, et al. Generalised muscle weakness in young adults with congenital heart disease. *Heart* 2011; 97: 1164-8. [\[CrossRef\]](#)
71. Giardini A. Generalised myopathy in young adults with congenital heart disease. *Heart* 2011; 97: 1115-16. [\[CrossRef\]](#)
72. Plymen CM, Hughes ML, Picaut N, et al. The relationship of systemic right ventricular function to ECG parameters and NT-proBNP levels in adults with transposition of the great arteries late after Senning or Mustard surgery. *Heart* 2010; 96: 1569-73. [\[CrossRef\]](#)
73. Vis JC, de Bruin-Bon RH, Bouma BJ, et al. Congenital heart defects are underrecognised in adult patients with Down's syndrome. *Heart* 2010; 96: 1480-4. [\[CrossRef\]](#)
74. Hoffmann A, Chockalingam P, Balint OH, et al. Cerebrovascular accidents in adult patients with congenital heart disease. *Heart* 2010; 96: 1223-6. [\[CrossRef\]](#)
75. Vecht JA, Saso S, Rao C, et al. Atrial septal defect closure is associated with a reduced prevalence of atrial tachyarrhythmia in the short to medium term: a systematic review and meta-analysis. *Heart* 2010; 96: 1789-97. [\[CrossRef\]](#)
76. Inuzuka R, Diller GP, Borgia F, et al. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation* 2012; 125: 250-9. [\[CrossRef\]](#)
77. Kaleschke G, Baumgartner H. Pregnancy in congenital and valvular heart disease. *Heart* 2011; 97: 1803-9. [\[CrossRef\]](#)
78. Balint OH, Siu SC, Mason J, et al. Cardiac outcomes after pregnancy in women with congenital heart disease. *Heart* 2010; 96: 1656-61. [\[CrossRef\]](#)
79. Opatowsky AR, Siddiqi OK, D'Souza B, et al. Maternal cardiovascular events during childbirth among women with congenital heart disease. *Heart* 2012; 98: 145-51. [\[CrossRef\]](#)
80. Lui GK, Silversides CK, Khairy P, et al. Heart rate response during exercise and pregnancy outcome in women with congenital heart disease. Alliance for Adult Research in Congenital Cardiology (AARCC). *Circulation* 2011; 123: 242-8. [\[CrossRef\]](#)

81. Ramakrishnan S, Khera R, Jain S, et al. Gender differences in the utilisation of surgery for congenital heart disease in India. *Heart* 2011; 97: 1920-5. [\[CrossRef\]](#)
82. Singh D, Wander GS, Singh RJ. Gender equality in India for children with congenital heart disease: looking for answers. *Heart* 2011; 97: 1897-8. [\[CrossRef\]](#)
83. Chen CA, Liao SC, Wang JK, et al. Quality of life in adults with congenital heart disease: biopsychosocial determinants and sex-related differences. *Heart* 2011; 97: 38-43. [\[CrossRef\]](#)
84. Zabál C, García-Montes JA, Buendía 'a-Hernández A, et al. Percutaneous closure of hypertensive ductus arteriosus. *Heart* 2010; 96: 625-9. [\[CrossRef\]](#)
85. Mullens W, Dubois C, De Keyser J. Images in cardiology: coronary fistula: a rare case of right heart failure. *Heart* 2005; 91: 1329. [\[CrossRef\]](#)
86. Tzifa A, Razavi R. Test occlusion of Fontan fenestration: unique contribution of interventional MRI. *Heart* 2011; 97: 89. [\[CrossRef\]](#)
87. MacDonald ST, Arcidiacono C, Butera G. Fenestrated Amplatzer atrial septal defect occluder in an elderly patient with restrictive left ventricular physiology. *Heart* 2011; 97: 438. [\[CrossRef\]](#)
88. De Vlieger G, Budts W, Dubois CL. Images in cardiology: Horner syndrome after stenting of a coarctation of the aorta. *Heart* 2010; 96: 714. [\[CrossRef\]](#)
89. Mitchell G, Loo B, Morgan-Hughes G. Atrial septal defect closure device, a three-dimensional volume render. *Heart* 2010; 96: 1222. [\[CrossRef\]](#)
90. Bartel T, Bonaros N, Müller S. Device failure weeks to months after transcatheter closure of secundum type atrial septal defects. *Heart* 2010; 96: 1603. [\[CrossRef\]](#)
91. Deo SV, Burkhart HM, Ammash N, et al. Successful hybrid rescue of occluded pulmonary artery in pulmonary atresia. *Circulation* 2011; 123: 2431-3. [\[CrossRef\]](#)
92. Padalino MA, Vida VL, Bhattarai A, et al. Giant intramural left ventricular rhabdomyoma in a newborn. *Circulation* 2011; 124: 2275-7. [\[CrossRef\]](#)
93. Battista Danzi G, Salice P, Mosca F. Double aortic arch in neonates: optimal definition by means of contrast-enhanced helical CT scan. *Heart* 2011; 97: 950. [\[CrossRef\]](#)
94. Nagashima M, Higaki T, Kurata A. Ectopia cordis with right and left ventricular diverticula. *Heart* 2010; 96: 12. [\[CrossRef\]](#)
95. Sridharan S, Dedieu N, Marek J. Images in cardiology: power doppler three-dimensional visualisation of aortic arch interruption in fetal life. *Heart* 2010; 96: 15. [\[CrossRef\]](#)
96. Arendt K, Doll S, Mohr FW. Failing mustard circulation with secondary pulmonary hypertension: mechanical assist device to achieve reverse pulmonary vascular remodelling for subsequent heart transplantation. *Heart* 2010; 96: 14. [\[CrossRef\]](#)
97. Farahmand P, Redheuil A, Chauvaud S, et al. Images in cardiovascular medicine: septic pulmonary thromboemboli in an adolescent with tetralogy of Fallot. *Circulation* 2011; 123: 2164-6. [\[CrossRef\]](#)
98. Radojevic J, Redheuil A, Iserin L. Pulmonary atresia with intact ventricular septum and diastolic liver expansion. *Heart* 2011; 97: 1813-14. [\[CrossRef\]](#)
99. Gulati A, Gheta R, Chan CF, et al. Longitudinal follow-up of a right atrial appendage aneurysm by cardiac magnetic resonance imaging. *Circulation* 2011; 123: 2289-91. [\[CrossRef\]](#)
100. Fukui D, Kai H, Takeuchi T, et al. Longest survivor of pulmonary atresia with ventricular septal defect: well-developed major aortopulmonary collateral arteries demonstrated by multidetector computed tomography. *Circulation* 2011; 124: 2155-7. [\[CrossRef\]](#)
101. Defaye P, Kane A, Jacon P. An unusual connection of the right and left inferior pulmonary veins in the left atrium via a common ostium. *Heart* 2010; 96: 1951. [\[CrossRef\]](#)
102. Lee MS, Pande RL, Rao B, et al. Cerebral abscess due to persistent left superior vena cava draining into the left atrium. *Circulation* 2011; 124: 2362-4. [\[CrossRef\]](#)
103. Chaowu Y, Xin S, Shihua Z, et al. Complete transposition of the atrioventricular valves associated with left ventricular apical hypoplasia. *Circulation* 2011; 124: e538-9. [\[CrossRef\]](#)
104. Cheng ST, Lan CC. Obstructive sleep apnoea syndrome related to double aortic arch. *Heart* 2011; 97: 1456-7. [\[CrossRef\]](#)
105. Jayan JP, Vijayalakshmi IB, Narasimhan C. Images in cardiology: a rare anomaly: 'hemitruncus'. *Heart* 2011; 97: 12.
106. Jang SW, Rho TH, Kim JH. Membranous interventricular septal aneurysm resulted in complete atrioventricular block. *Heart* 2010; 96: 244. [\[CrossRef\]](#)
107. Salahuddin S, Ramakrishnan S, Bhargava B. Classic supraaortic aortic stenosis. *Heart* 2010; 96: 1808. [\[CrossRef\]](#)

Prof. Dr. A. Mithat Özer'in ardından

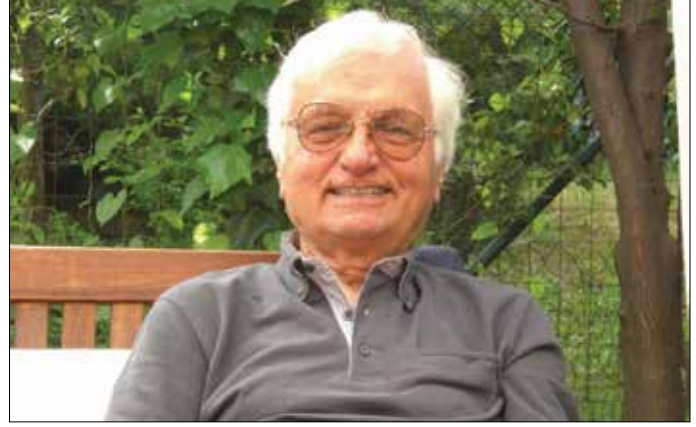
In memoriam of Prof. Dr. A. Mithat Özer

Prof. Dr. Ahmet Mithat Özer'i 16 Mart 2013 tarihinde kaybettik.

Prof. Dr. A. Mithat Özer 1928 yılında Manisa da doğmuştur. 1953'te İstanbul Tıp Fakültesini bitirdikten sonra kısa bir süre Manisa, Akhisar Gölarmara da serbest hekimlik ve belediye başkanlığı yaptıktan sonra, İstanbul Haydarpaşa Numune hastanesinde iç hastalıkları kliniğinde asistan olmuş ve 1960 yılında uzman unvanını almıştır. 1960-67 yılları arasında Almanya'da çalışmış ve orada kardiyoloji uzmanı olmuştur.

Ege Üniversitesi İç hastalıkları kliniği kardiyoloji biriminde 1967 yılında çalışmaya başlamıştır. 1973-74 yıllarında Şikago Üniversitesinde kardiyoloji kliniği çalışmıştır. 1978 yılında Ege Üniversitesinin ikinci tıp fakültesi olan İzmir Tıp Fakültesine geçmiş, burada İç hastalıkları ana bilim dalı başkanlığı ve dekan yardımcılığı görevinde bulunmuştur. 1982 yılında yeni kurulan 9 Eylül Üniversitesinde, 1993 yılına kadar büyük emeklerle kurduğu Kardiyoloji ana bilim dalı başkanlığını sürdürmüştür. Son yıllarını İstanbul da serbest hekimlik yaparak geçirmiştir. 16 Mart günü İstanbul Tıp Fakültesinde yapılacak altmışıncı yıl mezunlar törenine katılmak için evinden ayrılmış bindiği tramvayda fenalaşarak orada vefat etmiştir.

Prof. Dr. Özer gerek Ege Üniversitesinde ve gerekse 9 Eylül Üniversitesinde pek çok kardiyoloğun yetişmesinde emeği geçen, kurucuları arasında olduğu 9 Eylül Üniversitesi Tıp Fakültesinin gelişmesinde büyük katkıları olan bir hoca idi. Pek



çok araştırmada görev almış ulusal ve uluslararası yayınlarda bulunmuştur. Ayrıca İzmir de kurulan ve Türkiye'deki pek çok hocanın katıldığı "Hipertansiyonla Mücadele derneği" nin kurucusu ve ilk başkanı idi.

Yaptığı başarılı işlerinin yanında mütevazı, uzlaştııcı, sevecen kişiliği ile, Türk Kardiyoloji camiasında unutulmazlar arasında yerini alacaktır.

Prof. Dr. İstemi Nalbantgil
Ege Üniversitesi Tıp Fakültesi,
Kardiyoloji Anabilim Dalı, Emekli Öğretim Üyesi İzmir-Türkiye





GELECEK SAYI (HAZİRAN 2013)
FORTHCOMING ISSUE (JUNE 2013)



ÖZGÜN ARAŞTIRMALAR / ORIGINAL INVESTIGATIONS

Increased apolipoprotein A-I levels mediate the development of prehypertension among Turks
Artmış apolipoprotein A-I düzeyleri prehipertansiyon gelişmesine Türk yetişkinlerinde aracılık etmektedir
Altan Onat, Günay Can, Ender Örnek, Gökhan Çiçek, Sani N. Murat, Hüsnüye Yüksel, İstanbul, Ankara-Turkey

A new index (CHOLINDEX) in detecting coronary artery disease risk
Koroner arter hastalığı riskini belirlemede yeni bir index (CHOLINDEX)
Onur Akpınar, Abdi Bozkurt, Esmeray Acartürk, Gülşah Şeydaoğlu, Adana-Turkey

Epicardial adipose tissue is independently associated with increased left ventricular mass in untreated hypertensive patients: an observational study
Epikardiyal adipöz doku tedavi edilmemiş hipertansif hastalarda artmış sol ventrikül kitlesi ile bağımsız ilişkilidir: Gözlemsel bir çalışma
Turan Erdoğan, Mustafa Çetin, Sinan Altan Kocaman, Murtaza Emre Durakoğlugil, Elif Ergül, Yavuz Uğurlu, Aytun Çanga, Rize-Turkey

Subclinical left ventricular systolic dysfunction in patients with mild-to-moderate rheumatic mitral stenosis and normal left ventricular ejection fraction: an observational study
Hafif orta derecede romatizmal mitral kapak darlığı ve normal sol ventrikül ejeksiyon fraksiyonu olan hastalarda subklinik sol ventrikül sistolik disfonksiyonu: Bir gözlemsel çalışma
Özlem Yıldırım Türk, Fatma Funda Helvacioğlu, Yelda Tayyareci, Selen Yurdakul, Saide Aytekin, İstanbul-Turkey

Editorial Comment/Editöryel Yorum: Mitral stenosis-beyond valvular disease
Mitral stenosis-kapak hastalığı ötesinde
Marina Leitman, Zvi Vered-Israel

Role of electrocardiographic changes in discriminating acute or chronic right ventricular pressure overload
Elektrokardiyografik değişikliklerin sağ ventrikül basınç yüklenmesini akut veya kronik olarak ayırt etmedeki rolü
Mehmet Mustafa Can, Olcay Özveren, Murat Biteker, Cihan Şengül, Ömer Uz, Zafer Işılak, Ata Kırılmaz, İstanbul-Turkey

Atrial Fibrillation in Turkey: Epidemiologic Registry (AFTER) study design
Türkiye'de Atrial Fibrilasyon: Epidemiyolojik Kayıt (AFTER) çalışması dizaynı
Faruk Ertaş, Hasan Kaya, Murat Yüksel, Mehmet Serdar Soyding, Sait Alan, Mehmet Sıddık Ülgen, Diyarbakır-Turkey

Role of electrocardiographic changes in discriminating acute or chronic right ventricular pressure overload
Elektrokardiyografik değişikliklerin sağ ventrikül basınç yüklenmesini akut veya kronik olarak ayırt etmedeki rolü
Mehmet Mustafa Can, Olcay Özveren, Murat Biteker, Cihan Şengül, Ömer Uz, Zafer Işılak, Ata Kırılmaz, İstanbul-Turkey

The role of tenascin-C and oxidative stress in rheumatic and congenital heart valve diseases: an observational study
Tenascin-C ve oksidatif stresin romatizmal ve konjenital kalp kapak hastalığındaki rolü: Gözlemsel bir çalışma
Zehra Karataş, Tamer Baysal, Fatih Sap, Hakan Altın, Hümeysra Çiçekler, Konya-Turkey

Relationship of paraoxonase-1, malondialdehyde and mean platelet volume with markers of atherosclerosis in familial Mediterranean fever: an observational study
Ailevi Akdeniz ateşinde paraoksonaz-1, malondialdehit ve ortalama trombosit hacmi ile ateroskleroz belirteçlerinin ilişkisi: Gözlemsel bir çalışma
Özlem Karakurt Antürk, Kemal Üreten, Münevver Sarı, Nuray Yazihan, Ezgi Ermiş, İmge Ergüder, Balıkesir, Ankara, Şanlıurfa-Turkey

Thyroid functions after contrast agent administration for coronary angiography: a prospective observational study in euthyroid patients
Koroner anjiyografi amacıyla kontrast madde verildikten sonra tiroid fonksiyonları: Ötiroid hastalarda prospektif bir gözlemsel çalışma
Sevil Özkan, Aslıhan Semiz Oysu, Kadir Kayataş, Refik Demirtunç, Mehmet Eren, Hatice Uslu, Yüksel Altuntaş, İstanbul-Turkey

DERLEMELER / REVIEWS

Aspirin resistance: Where are we now?

Aspirin direnci: Şimdi biz neredeyiz?

Okay Abacı, Kadriye Orta Kılıçkesmez, İstanbul-Turkey

Kardiyak bilgisayarlı tomografi ve radyasyon

Cardiac computed tomography and radiation

Burak Sezenöz, Asife Şahinarslan, Ankara-Turkey

EĞİTİM / EDUCATION

Anticoagulation for non-valvular atrial fibrillation: new anticoagulant agents

Non-valvüler atriyal fibrilasyonda antikoagülasyon: Yeni antikoagülen ilaçlar

Alper Kepez, Okan Erdoğan, İstanbul-Turkey

BİLİMSEL MEKTUP / SCIENTIFIC LETTER

Characterization of the day-night fluctuations of serum melatonin in young boys and girls with different body mass indexes within normal range according to World Health Organization Classification

Dünya Sağlık Örgütüne göre normal aralıkta, değişik vücut kitle indekslerine sahip genç erkek ve kızlardaki gündüz-gece serum melatonin dalgalanmalarının karakteristikleri

Mustafa Yıldız, Banu Şahin Yıldız, Alparslan Şahin, İstanbul-Turkey

OLGU SUNUMLARI / CASE REPORTS

Coronary venous angioplasty to a ring- like stricture preventing left ventricular lead insertion

Sol ventrikül lead implantasyonunu önleyen striktüre uygulanan koroner venöz anjiyoplasti

Ali Deniz, Oğuz Akkuş, Mehmet Kanadaşı, Mesut Demir, Adana-Turkey

Electroanatomic mapping guided radiofrequency ablation of multifocal atrial tachycardia in a child

Multifokal atriyal taşikardi'li bir çocuğun elektroanatomik haritalama sistemi eşliğinde radyofrekans kateter ablasyonu

Tevfik Demir, Yakup Ergül, Celal Akdeniz, Volkan Tuzcu, Eskişehir, İstanbul-Turkey

Percutaneous right internal jugular venous cannulation in minimally invasive cardiac surgery

Minimal invaziv kalp cerrahisinde perkütan sağ internal juguler venöz kanülasyon

Emrah Şişli, Ali Aycan Kavala, Gökçen Özserim, Öztekin Oto, Hatay, İstanbul, İzmir-Turkey

Suspected endocarditis after CoreValve® implantation: a word of caution

CoreValve® implantasyonu sonrası ortaya çıkan şüpheli endokarditis: Değinilmesi gereken bir uyarı

İlkay Bozdağ-Turan, Stephan Kische, Giuseppe D'Ancona, Cristopher A. Nienaber, Hüseyin İnce, Rostock-Germany

A favorable outcome of a post-myocardial infarction ventricular septal rupture

Miyokart enfarktüsü sonrası ventriküler septal rüptürün olumlu sonucu

Paloma Manea, Rodica Ghiuru, Flavia Cociorva, Mircea Balasanian, Grigore Tinica, Romania

EDİTÖRE MEKTUPLAR / LETTERS TO THE EDITOR

Color M-mode propagation velocity as a valuable but neglected parameter

Değerli fakat gözardı edilen bir parametre olarak renkli M-mode akım yayılma hızı

Sait Demirkol, Şevket Balta, Mustafa Çakar, Ankara-Turkey

Effect of systemic inflammation in the cardiac surgery performed on elderly

Yaşlılarda yapılan açık kalp cerrahisinde sistemik enflamasyonun etkisi

Orhan Gökalp, Serkan Yazman, Barçın Özcecm, Ali Gürbüz, İzmir-Turkey; Lefkoşe-Cyprus

Thrombus aspiration may decrease bleeding risk in the early postoperative myocardial infarction treated with percutaneous intervention

Perkütan girişim ile tedavi edilen erken dönem postoperatif miyokart enfarktüsünde trombüs aspirasyonu kanama riskini azaltabilir

Ahmet Karabulut, İstanbul-Turkey

A new piece of puzzle: inflammation in the prediction of recurrence after successful electrical cardioversion in patients with nonvalvular atrial fibrillation

Bulmacanın yeni bir parçası: Nonvalvüler atriyal fibrilasyon hastalarında başarılı elektriksel kardiyoversiyon sonrası nöksü öngörmede enflamasyonun rolü

Şevket Balta, Murat Ünlü, Sait Demirkol, Turgay Çelik, Ankara-Turkey

Importance of multislice computed tomography angiography for the diagnosis and evaluation of silent coronary ischemia and asymptomatic acute myocardial infarction: long-term follow-up of three cases

Sessiz koroner iskemisinin ve semptomsuz akut miyokart enfarktüsünün tanısında ve değerlendirilmesinde çok kesitli bilgisayarlı koroner kalp tomografisinin önemi: Uzun dönem takip edilmiş üç olgu

Faruk Erzençin, Ramime Özel, Mustafa Özcan, Hüseyin Oflaz, İstanbul-Turkey

Long-life oral anticoagulant therapy and rupture of corpus luteum

Yaşam boyu oral antikoagülan tedavisi ve korpus luteum rüptürü

Ali Akdemir, Ahmet Mete Ergenoğlu, Ahmet Özgür Yeniel, Levent Akman, İzmir-Turkey

The effects of flight on the electrocardiogram

Uçusun elektrokardiyogram üzerindeki etkileri

Mehmet Gül, Hüseyin Uyarel, Musa Salmanoğlu, Murat Uğur, Hüseyin Aksu, İstanbul, Amasya-Turkey

Percutaneous pulmonary valve implantation; first experiences from Turkey

Perkütan pulmoner kapak implantasyonu; Türkiye'den ilk deneyimler

Ender Ödemiş, Alper Güzeltaş, Murat Saygı, İhsan Bakır, İstanbul-Turkey

Extent of angiographic coronary artery disease in khat users

Khat kullanıcılarında koroner arter hastalığının anjiyografik yaygınlığı

Abdul-Kafi Shujaa, Wail Nammas, Sanaa-Yemen; Cairo-Egypt

TANISAL BİLMECE / DIAGNOSTIC PUZZLE

An interesting diastolic jet in left ventricle

Sol ventrikülde ilginç bir diyastolik jet

Onur Taşar, Sedat Kalkan, Taylan Akgün, Cevat Kırmacı, İstanbul-Turkey

E-SAYFA ÖZGÜN GÖRÜNTÜLER / E-PAGE ORIGINAL IMAGES

Giant septal hypertrophic cardiomyopathy

Dev septal hipertrofik kardiyomiyopati

Zafer Işılak, Murat Yalçın, Alptuğ Tokatlı, Mehmet Uzun, İstanbul-Turkey

Unusual case with venous channels connecting the left and the right brachiocephalic veins

Sol ve sağ brakiosefalik venleri bağlayan venöz kanalları olan olağandışı vaka

Mutlu Çağan Sümerkan, Serkan Bulur, Mehmet Ağırbaşı, Düzce-Turkey

Percutaneous closure of second secundum atrial septal defect under three-dimensional transesophageal echocardiography guidance

Üç boyutlu transözofajiyal ekokardiyografi rehberliğinde ikinci sekundum atriyal septal defektin perkütan kapatılması

Sait Demirkol, Cem Barçın, Şevket Balta, Murat Ünlü, Ankara-Turkey

Self-inflicted sewing needle in the heart

Kalpde dikiş iğnesi

Ahmet Elibol, Sabit Sarıkaya, Taylan Adademir, Kaan Kırallı, İstanbul-Turkey

The importance of prominent crista terminalis after cardiac surgery

Kalp cerrahisi sonrasında belirgin krista terminalisin önemi

Azin Alizadeasl, Anita Sadeghpour, Majid Kyavar, Tabriz-Iran

Coexistence of accessory mitral papillary muscle and ventricular septal defect

Aksesuar mitral papiller kas ve ventriküler septal defekt birlikteliği

A 21-year-old female patient presented with a complaint of exertional dyspnea. On cardiac examination, a grade 3/6 pansystolic murmur was heard over the mesocardiac region. ECG revealed sinus rhythm and left ventricular hypertrophy with left axis deviation evident in lateral chest derivations. Transthoracic echocardiography (TTE) demonstrated a left ventricular ejection fraction of 65% and a perimembranous ventricular septal defect (VSD) jet with a 120 mmHg maximal gradient obtained by the continuous wave Doppler. Right ventricular chamber size was normal and the calculated Qp/Qs ratio was 1.6. Apical four chamber and apical short axis views showed an accessory mitral papillary muscle with its chordae located parallel to the interventricular septum extending to the anterior mitral leaflet. There was no mitral regurgitation or stenosis, nor an evident stenosis of the left ventricular outflow tract (LVOT) (Fig. 1-3 and Video 1, 2. See corresponding video/movie images at www.anakarder.com). A subsequent real-time three-dimensional transesophageal echocardiography (TEE) revealed the presence of an accessory mitral papillary muscle and an associated chordae extending from the anterolateral papillary muscle parallel to the interventricular septum to the edge of the anterior mitral leaflet in the LVOT and a perimembranous VSD (Fig. 4, 5 and Video 3, 4. See corresponding video/movie images at www.anakarder.com). For comprehensive evaluation of the anatomy, a cardiac magnetic resonance imaging was also performed. Vertical long and short-axis images confirmed the diagnosis of the accessory papillary muscle originating from anterolateral papillary muscle and perimembranous VSD (Fig. 6, Video 5. See corresponding video/movie images at www.anakarder.com). The patient was scheduled to an elective surgical operation.

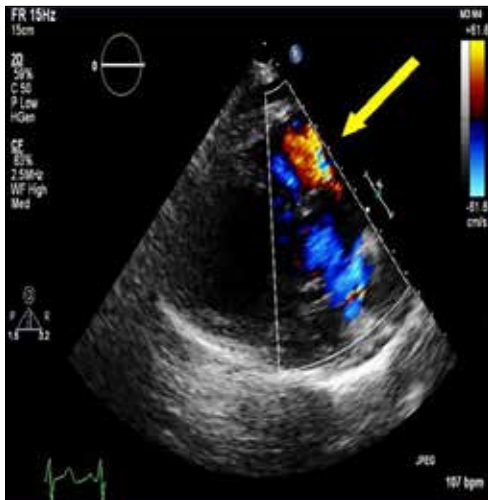


Figure 1. TTE in the parasternal long- axis and apical four- chamber views. Color Doppler imaging demonstrating the perimembranous VSD, and two-dimensional echocardiogram showing the accessory papillary muscle across the LVOT

LVOT - left ventricular outflow tract, TTE - transthoracic echocardiography, VSD - ventricular septal defect

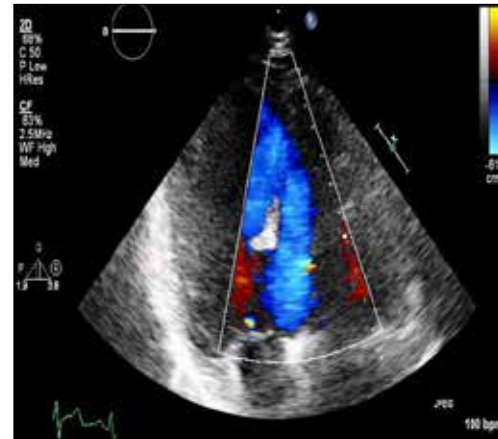


Figure 2. TTE in the parasternal long- axis and apical four- chamber views. Color Doppler imaging demonstrating the perimembranous VSD, and two-dimensional echocardiogram showing the accessory papillary muscle across the LVOT

LVOT - left ventricular outflow tract, TTE - transthoracic echocardiography, VSD - ventricular septal defect

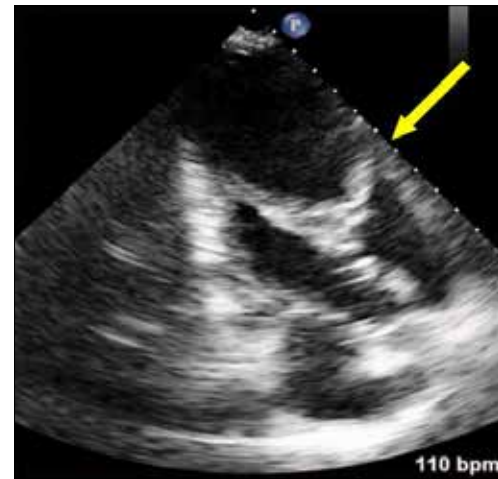


Figure 3. TTE in the modified two-chamber view. The accessory papillary muscle originating from the anterolateral papillary muscle is seen

TTE - transthoracic echocardiography



Figure 4. TEE demonstrating the perimembranous VSD

TEE - transesophageal echocardiography, VSD - ventricular septal defect

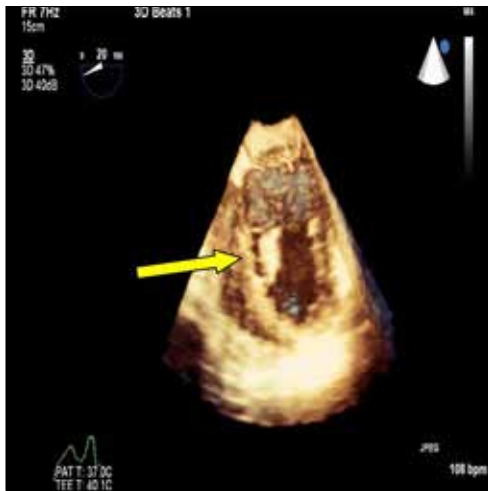


Figure 5. Real-time three-dimensional TEE demonstrating the accessory papillary muscle extending from the interventricular septum to the LVOT

LVOT - left ventricular outflow tract, TEE - transesophageal echocardiography



Figure 6. Cardiac MRI in the vertical axis showing the accessory papillary muscle

MRI - magnetic resonance imaging

Zafer Işılak, Onur Sinan Deveci, Murat Yalçın, Mehmet İncedayı*
Departments of Cardiology and *Radiology, Gülhane Military
Medical Academy, Haydarpaşa Hospital, İstanbul-Turkey

Video 1. TTE in the parasternal long-axis color-Doppler imaging demonstrating shows the perimembraneous VSD

LVOT - left ventricular outflow tract, TTE - transthoracic echocardiography, VSD - ventricular septal defect

Video 2. TTE in apical four-chamber color-Doppler imaging demonstrating shows the accessory papillary muscle across the LVOT

LVOT - left ventricular outflow tract, TTE - transthoracic echocardiography

Video 3. TEE shows demonstrating the perimembraneous VSD

TEE - transesophageal echocardiography, VSD - ventricular septal defect

Video 4. Real-time three dimension TEE demonstrating the accessory papillary muscle extending from the interventricular septum to the LVOT

LVOT - left ventricular outflow tract, TEE - transesophageal echocardiography

Video 5. Cardiac MRI in the vertical axis showing the accessory papillary muscle

MRI - magnetic resonance imaging

Address for Correspondence/Yazışma Adresi: Dr. Zafer Işılak,
Gülhane Askeri Tıp Akademisi, Haydarpaşa Hastanesi, Kardiyoloji Bölümü,
Tıbbiye Cad. 34668 Üsküdar, İstanbul-Türkiye
Phone: +90 216 542 34 80 Fax: +90 216 348 78 80
E-mail: drzaferisilak@gmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.092

All-in-one case: constrictive pericarditis, secundum atrial septal defect, persistent left superior vena cava and anomalous drainage of hemiazygos vein to coronary sinus

Hepsi bir vakada: Konstrüktif perikardit, sekundum atriyal septal defekt, persistan sol süperiyör vena kava ve hemiazigos venin koroner sinüse açılması

We present a 31-year-old female with history of constrictive pericarditis operation due to childhood tuberculosis who complained of breathlessness and swelling (Fig. 1A). We diagnosed secundum atrial septal defect (ASD) and dilated coronary sinus (CS) in her control echocardiography (Fig. 1B). Contrast echocardiography via left brachial venous injection revealed persistent left superior vena cava (PLSVC). To evaluate the heart and the pericardium, contrast enhanced multislice computerized tomography was performed via left brachial venous injection. Volume rendered images showed PLSVC and hemiazygos vein anomalous drainage to CS were diagnosed (Fig. 2A, B). There were no abnormal shunts from PLSVC and hemiazygos vein to other cardiac areas. Vena cava inferior (VCI) was right-sided and draining to

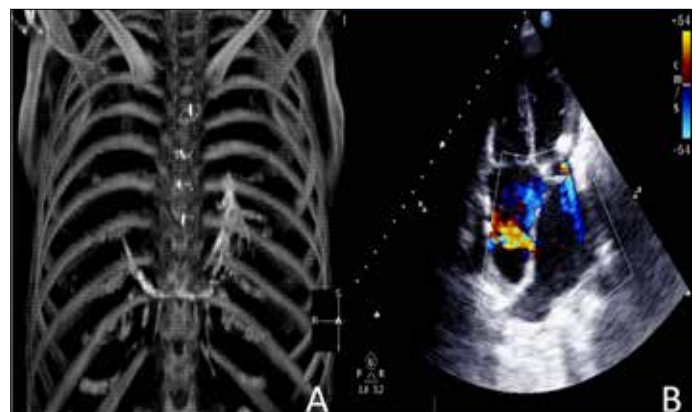


Figure 1. A) Multislice CT angiogram, three-dimensional bone-window image of pericardial calcification, B) Color Doppler echocardiography showing secundum atrial septal defect

CT - computerized tomography

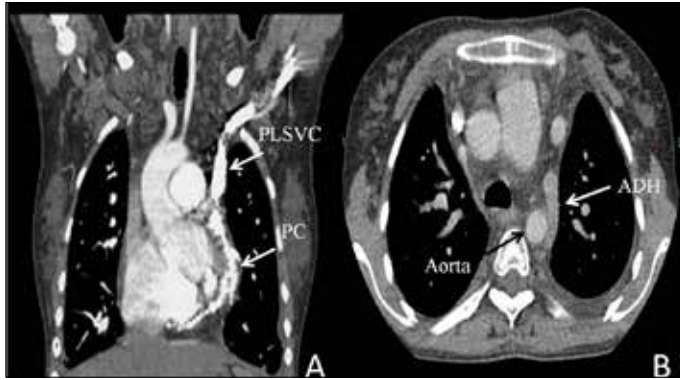


Figure 2. A) Multislice CT angiogram, vascular-window image of PLSVC and pericardial calcification, B) Multislice CT angiogram, vascular-window image of anomalous drainage of hemiazygos (ADH)
CT - computerized tomography, PLSVC - persistent left superior vena cava

the right atrium. In her right and left ventricular (RV-LV) catheterization, RV and LV pressure curve showed signs of dip and plateau (square root) indicating constrictive pericarditis. RV and LV end-diastolic pressure (EDP) were measured as of 35 and 40 mmHg consecutively. Because of symptoms, severe calcification in the pericardium (Fig. 1A-2A) and high end-diastolic pressure, redo-operation was planned. Although there are different combinations of this conditions, we have not found all in one case in the literature.

Abdurrahman Tasal, Osman Sönmez, Ercan Erdoğan, Ömer Göktekin
Department of Cardiology, Faculty of Medicine, Bezmialem Vakıf University, İstanbul-Turkey

Address for Correspondence/Yazışma Adresi: Dr. Abdurrahman Tasal, Bezmialem Vakıf Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Fatih, İstanbul-Türkiye
Phone: +90 212 453 18 00 Fax: +90 212 621 75 80
E-mail: tasal01@hotmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.093

Severe pulmonary vein stenosis due to invasion of metastatic lung cancer

Metastatik akciğer kanseri invazyonuna bağlı gelişen ciddi pulmoner ven darlığı

A 40-year-old-woman presented to the emergency department with dyspnea and hemoptysis. She had been complaining of dyspnea and hemoptysis for about eleven months. On admission, she had dyspnea (class IV according to the New York Heart Association) and respiratory rate of 28 breaths/min, regular pulse rate of 110 beats/min. The electrocardiogram showed sinus tachycardia and chest radiography revealed left sided pleural effusion (Fig. 1A). Transthoracic echocardiography revealed a turbulent flow in the upper left pulmonary vein in the entrance of left atrium on apical long-axis position (Fig. 2A). No other cardiac structural abnormalities were found on transthoracic echocardiography but estimated pulmonary artery systolic pressure was 70 mmHg. Transesophageal echocardiography and

multislice computed tomography (MSCT) revealed severe obstruction in the anastomotic site of left upper pulmonary venous confluence to the left atrium (Fig.1B) and invasion of the wall of the left atrium. Pulmonary vein stenosis was diagnosed by spectral Doppler interrogation of the pulmonary veins (continuous, turbulent flow with calculated mean gradient up to 36 mm Hg) (Fig. 2B, 1C). MSCT also revealed a small mass in the middle lobe of the lung and metastatic invasion of left upper pulmonary vein (Fig. 1D). For further staging and therapeutic evaluation patient was sent to a hospital of respiratory and oncology center.

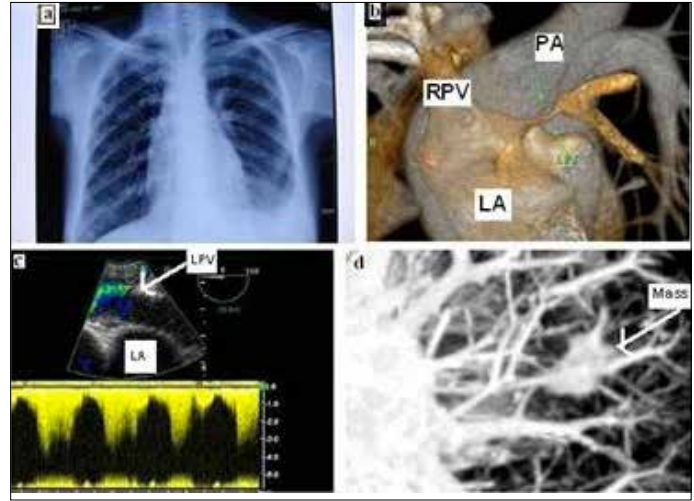


Figure 1. A) Chest radiography view of left sided pleural effusion, B) Computed tomography view of stenosis of upper left pulmonary vein of left atrial wall, C) 2D transesophageal echocardiography apical four-chamber view of high pulmonary venous gradient (36 mmHg), D) Computed tomography; view of a mass in the middle lobe

LA - left atrium, LPV - left pulmonary vein, PA - pulmonary artery, RPV - right pulmonary vein

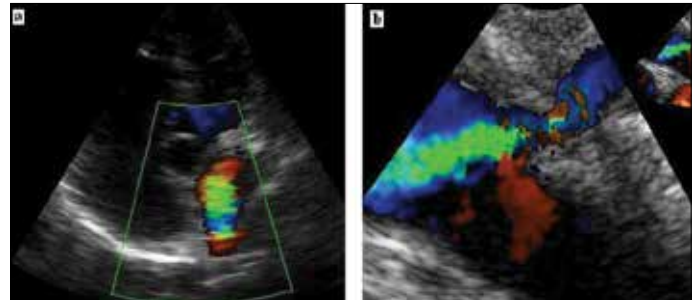


Figure 2. A) 2D transthoracic echocardiographic apical four-chamber view of a color imaging turbulent flow in upper left pulmonary vein in entrance of left atrium. B) 2D transesophageal echocardiography apical four-chamber view of obstruction of left upper pulmonary vein

LA - left atrium, LUPV - left upper pulmonary vein, LV - left ventricle, RA - right atrium, RV - right ventricle

Mehmet Mustafa Can
Clinic of Cardiology, Malatya State Hospital, Malatya-Turkey

Address for Correspondence/Yazışma Adresi: Dr. Mehmet Mustafa Can, Bağcılar Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul-Türkiye
Phone: +90 212 440 40 00 E-mail: mehmetmustafacan@yahoo.com
Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.094

Free-floating intra-aortic thrombus causing coronary artery occlusion: appearance in ECG-gated computed tomography with cine-images 🎬

Sine-görüntüleri ile EKG-gated BT'de koroner arter tıkanmasına neden olan intra-aortik serbest-yüzen trombüs

A 36-year-old man who admitted to emergency service with chest pain referred to our clinic for coronary artery computed tomography (CT) examination. There was no family history of ischemic heart disease. Electrocardiographic examination was normal. Echocardiography examination showed suspect hypokinesis in apical region.

Contrast-enhanced CT depicted approximately 1 cm long distal left anterior descending artery (LAD) occlusion (Fig. 1). Proximal 2/3 segments of LAD and other coronary arteries were normal and free of even minor atherosclerotic plaques. CT examination also showed perfusion defect and hypokinesis in left ventricular apical region (Fig. 2, Video 1. See corresponding video/movie images at www.anakarder.com). When evaluating extra-cardiac structures we saw a pedunculated mass in the ascending aorta, which was attached to medial wall of aorta with a thin stalk (Fig. 3). Cine images showed that the mass is highly mobile (Video 2, 3. See corresponding video/movie images at www.anakarder.com). Intra-aortic thrombus was thought in the first order differential diagnosis.

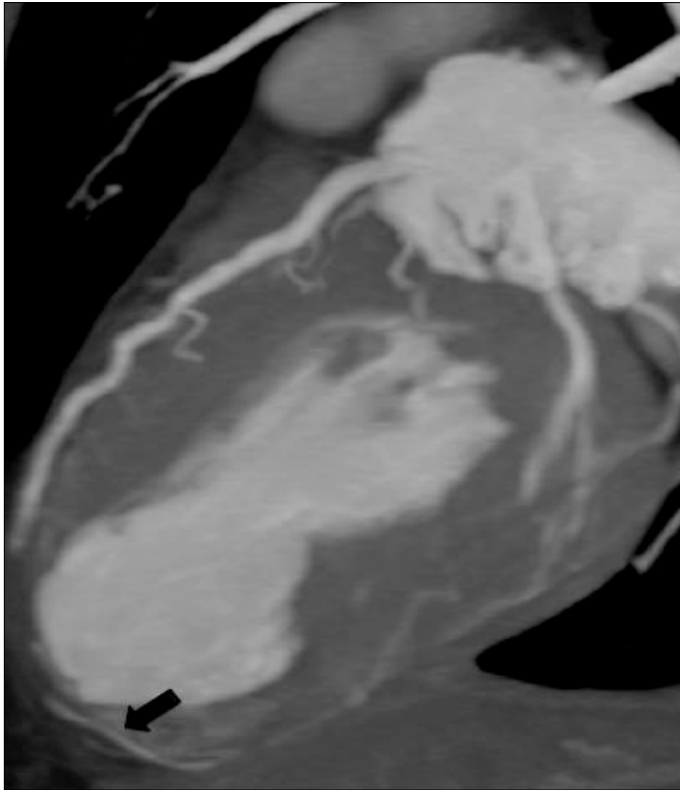


Figure 1. Contrast-enhanced ECG-gated multi-slice spiral computed tomography MIP image, diastolic phase shows segmental distal LAD occlusion. Distal to occlusion there is retrograde/collateral filling (arrow). Note that proximal and mid segment of LAD is free of arteriosclerosis
ECG - electrocardiogram, LAD - left anterior descending artery

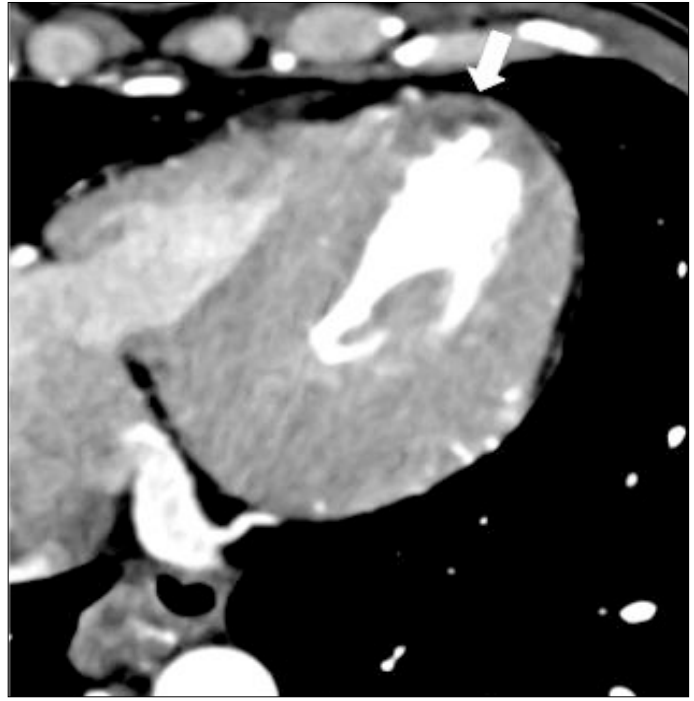


Figure 2. Axial image demonstrates hypodense left ventricular apex (arrow) relative to normal perfused myocardium

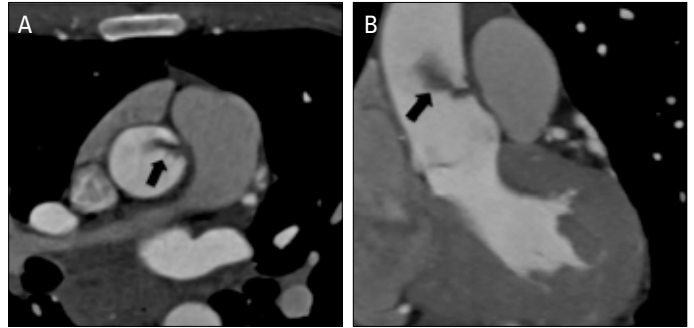


Figure 3. Axial (A) and oblique sagittal (B) images demonstrate a well-defined, pedunculated, spherical mass (arrows) located in ascending aorta slightly above the left coronary sinus

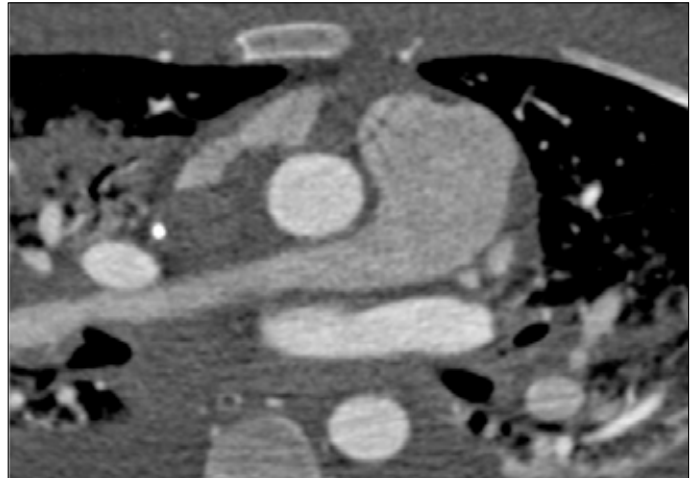


Figure 4. Axial image (approximately the same level with figure 3) shows that the mass in ascending aorta no more exists. Bilateral pleural effusion and consolidation in the middle lobe is seen after heart attack

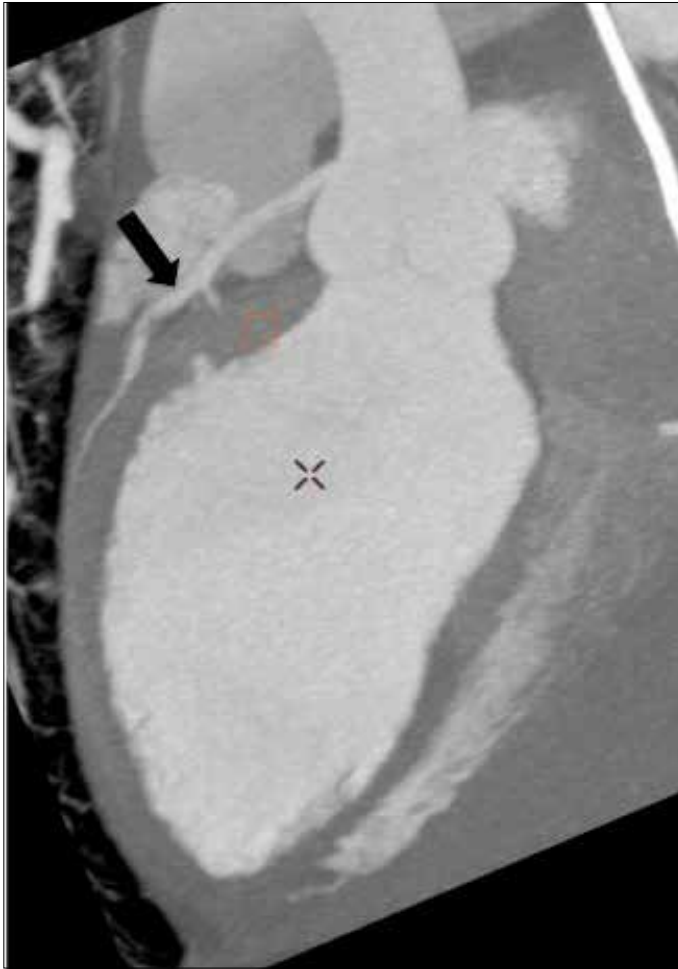


Figure 5. Contrast-enhanced ECG-gated multislice spiral computed tomography MIP image, demonstrates more proximal LAD (arrow) occlusion after disappearance of aortic mass

ECG - electrocardiogram, LAD - left anterior descending artery

Twelve days later control CT examination showed that ascending aorta and thoracic aorta were free of thrombus (Fig. 4). CT examination showed a new thrombus in the proximal segment of LAD (Fig. 5), which caused enlargement of perfusion defect effecting both apical and septal wall of left ventricle. There was severe hypokinesia in the mid and septal part of left ventricle consisted with LAD territory (Video 4. See corresponding video/movie images at www.anakarder.com).

Although there was no histopathology diagnosis of the mobile aortic mass, it is highly probable that it was an intra-aortic thrombus, which was broken away, causing a new more proximal embolus in LAD.

Terman Gümüş, Sergin Akpek, Genco Yücel
Clinic of Radiology and Cardiology of, VKV American Hospital,
İstanbul-Turkey

Video 1. Cine-image two-chamber view shows akinesia in the left ventricle apex

Video 2. Cine-image shows, mobile mass attached to the wall of proximal ascending aorta with a thin stalk

Video 3. Cine-image shows the relation of the mass with left coronary artery, aortic valves. Note the mass is very mobile which may predict its potential to break away

Video 4. Four-chamber cine-image shows akinesia in the mid-septal region as well as apex. Apex and septum show hypodense subendocardium consisted with hypoperfusion

Address for Correspondence/Yazışma Adresi: Dr. Terman Gümüş,
Amerikan Hastanesi, Güzelbahçe Sokak No: 20 Nişantaşı, İstanbul- Türkiye
Phone: +90 212 444 37 77 Fax: +90 212 311 21 90
E-mail: termang@gmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.095

Interventricular septal cardiac hydatid cyst mimicking hypertrophic cardiomyopathy

*Hipertrofik kardiyomiyopatiyi taklit eden
interventriküler septal kist hidatik*

A 27-year-old, male patient with nonobstructive hypertrophic cardiomyopathy was admitted to our clinic with exertional dyspnea. Physical examination and routine laboratory tests were normal. Transthoracic echocardiography revealed asymmetric septal hypertrophy (29 mm) with-

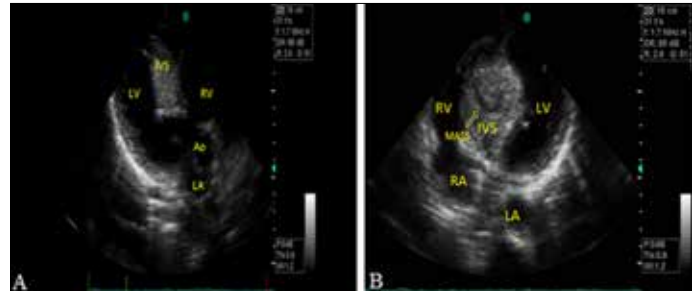


Figure 1. A) Asymmetric septal hypertrophy was evident in transthoracic echocardiography. B) A mass surrounded by a hyperechogenic calcified membrane, containing a water-like fluid (arrow) was demonstrated by transthoracic echocardiography

Ao - aorta, IVS - interventricular septum, LA - left atrium, LV - left ventricle, RA - right atrium
RV - right ventricle

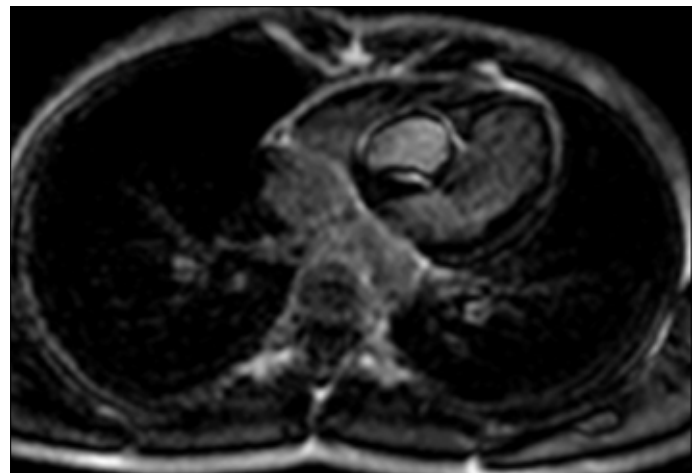


Figure 2. A cystic mass localized in the interventricular septum was demonstrated on cardiac magnetic resonance imaging

out gradient in the left ventricular outflow tract (Fig.1 A). A cystic structure encircled by a hyperechogenic calcified membrane compatible with cardiac hydatid cyst was demonstrated in apical four -chamber view (Fig. 1B). A cystic mass localized in the interventricular septum was demonstrated in cardiac magnetic resonance imaging (Fig. 2, Video 1. See corresponding video movie images at www.anakarder.com). Patient was operated with the diagnosis of cardiac mass of unknown origin. Histopathological examination of surgery specimen revealed diagnosis of hydatid cyst. Hydatid cyst rarely involves heart and particularly interventricular septum. The diagnosis of hydatid cyst of the interventricular septum is difficult because of clinical and radiographic findings may be lacking or nonspecific.

Turhan Turan, Abdulkadir Çakmak¹, Mustafa Çapraz², Ahmet Çağrı Aykan³
Clinic of Cardiology, Akçaabat State Hospital, Trabzon- Turkey
Clinic of ¹Cardiology and ²Internal Medicine, Amasya Sabuncuoğlu

Serefettin State Hospital, Amasya- Turkey

³Clinic of Cardiology, Ahi Evren Thoracic and Cardiovascular Center, Trabzon- Turkey

Video 1. A cystic mass localized in the interventricular septum was demonstrated on cardiac magnetic resonance imaging

Address for Correspondence/Yazışma Adresi: Dr. Turhan Turan,
Akcaabat Haçkalı Baba Devlet Hastanesi, Kardiyoloji Kliniği Trabzon- Türkiye
Phone: +90 506 505 26 00
E-mail: drtt61@gmail.com

Available Online Date/Çevrimiçi Yayın Tarihi: 21.02.2013

©Telif Hakkı 2013 AVES Yayıncılık Ltd. Şti. - Makale metnine www.anakarder.com web sayfasından ulaşılabilir.

©Copyright 2013 by AVES Yayıncılık Ltd. - Available online at www.anakarder.com
doi:10.5152/akd.2013.096