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Integrated Clinical, Multimodality Imaging, and Electrophysiological Markers for Improved Prediction of Sudden Cardiac Death in Hypertrophic Cardiomyopathy

LETTER TO THE EDITOR

To the Editor,

I read with great interest the recent article by Balaban et al[1] which evaluates the role of the Index of Cardiac Electrophysiological Balance (ICEB) and its corrected variant (ICEBc) in predicting ventricular arrhythmias in patients with hypertrophic cardiomyopathy (HCM). The study provides valuable evidence that ICEB and ICEBc outperform conventional electrocardiographic markers and improve the discriminative capacity of the ESC SCD risk score, with the Base+ICEB model achieving the highest AUC (0.79). This finding is particularly remarkable given the ongoing limitations of current guideline-based risk models, which predominantly rely on structural parameters and may inadequately capture electrophysiological instability. Updated guidelines continue to emphasize clinical and imaging variables, while electrophysiological indices remain underrepresented.[2,3]

We would like to highlight several points that may further strengthen the interpretation and future applicability of these findings. First, although ICEB appears promising as an integrated marker of depolarization–repolarization balance, its mechanistic link with myocardial substrate remains incompletely defined. As myocardial fibrosis is a central determinant of arrhythmogenesis in HCM,[4] the lack of direct correlation between ICEB and late gadolinium enhancement limits pathophysiological interpretation. Future studies integrating electrocardiographic indices with cardiac magnetic resonance imaging parameters may clarify this relationship. Moreover, the study does not provide subgroup analyses according to HCM phenotypes (e.g., obstructive vs non-obstructive, apical vs septal, fibrosis burden). This is a significant limitation because electrophysiological properties and arrhythmic risk vary substantially across phenotypes. Moreover, although patients with prior septal reduction therapy were excluded, there is no detailed characterization of LVOT gradient severity distribution, and structural phenotype heterogeneity. This limits the generalizability of ICEB findings across the HCM spectrum. Second, the retrospective single-center design and relatively small sample size limit generalizability. In addition, the high prevalence of ICD implantation in arrhythmic groups introduces potential selection and detection biases, as device-based arrhythmia detection may overestimate clinical event rates. Prior large cohort studies have demonstrated that risk prediction models require robust external validation across diverse populations.[5] Additionally, a critical confounder is the markedly lower beta-blocker use in arrhythmic groups (LTA 66.7%, NSVT 75.9%) compared to controls (98.1%, $P < .001$). This finding is not discussed, despite its clear electrophysiological implications: beta-blockers influence heart rate, QT dynamics, and arrhythmia burden; reduced use in LTA/NSVT groups may reflect treatment bias or intolerance, but could also contribute to arrhythmogenesis; and failure to adjust for or discuss this variable introduces potential confounding in the association between ICEB and arrhythmic outcomes. Third, although ICEB improved AUC numerically, the lack of statistically significant superiority by DeLong testing raises questions regarding its incremental clinical utility. In this

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context, complementary metrics such as net reclassification improvement and decision curve analysis would provide more clinically meaningful insights into whether ICEB meaningfully alters ICD decision-making.[6] The authors should report the proportion of patients reclassified across ESC SCD risk categories after incorporating ICEB, particularly the percentage shifting from the gray zone to the high-risk group, to better demonstrate clinical utility beyond AUC improvement. Fourth, measurement reproducibility is an important consideration. The absence of intra- and interobserver variability analysis is a limitation, particularly given that ECG-derived indices may be subject to measurement variability. Standardization or automated digital ECG analysis may enhance reliability and facilitate broader clinical implementation. Furthermore, the absence of statistically significant differences in QT and QTc intervals among the LTA, NSVT, and control groups raises an important mechanistic question. Given that ICEB is mathematically derived from QT and QRS (QT/QRS), the observed difference in ICEB appears to be primarily driven by changes in QRS duration rather than repolarization itself. Indeed, QRS duration was significantly prolonged in arrhythmic groups, while QT remained unchanged. This suggests that ICEB in this cohort may reflect depolarization abnormalities (conduction delay) rather than true repolarization heterogeneity. Therefore, the interpretation of ICEB as a "repolarization marker" may be overstated and should be reconsidered or more cautiously framed. Finally, the integration of ICEB with emerging risk modifiers, including genotype and advanced imaging, represents an important future direction.[7,8] Genotype–phenotype correlations and multimodal risk assessment models are increasingly recognized as essential components of precision medicine in HCM.[7,9]

In conclusion, this study contributes meaningfully to the evolving field of SCD risk stratification in HCM. The ICEB and ICEBc represent promising electrophysiological markers that may complement existing SCD risk models, particularly in intermediate-risk patients. However, their clinical applicability requires validation in larger, prospective, multicenter studies incorporating multimodal risk parameters. We congratulate the authors on their innovative work and look forward to further research that will define the role of these indices in clinical practice.

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REFERENCES

1. Balaban İ, Tanyeri S, Karaduman A, et al. Electrophysiological markers in hypertrophic cardiomyopathy: enhancing sudden cardiac death risk prediction with index of cardiac electrophysiological balance and its corrected variant. *Anatol J Cardiol*. 2025. [CrossRef]
2. Ommen SR, Ho CY, Asif IM, et al. 2024 AHA/ACC/AMSSM/HRS/PACES/SCMR guideline for the management of hypertrophic cardiomyopathy: A report of the American Heart Association/American College of Cardiology joint committee on clinical practice guidelines. *Circulation*. 2024;149(23):e1239-e1311. [CrossRef]
3. Maron MS, Rowin EJ, Wessler BS, et al. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4(7):644-657. [CrossRef]
4. Mentias A, Raeisi-Giglou P, Smedira NG, et al. Late gadolinium enhancement in patients with hypertrophic cardiomyopathy and preserved systolic function. *J Am Coll Cardiol*. 2018;72(8):857-870. [CrossRef]
5. O'Mahony C, Jichi F, Pavlou M, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *Eur Heart J*. 2013;35(30):2010-2020. [CrossRef]
6. Pencina MJ, D'Agostino RB, Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011/01/05;30(1):11-21. [CrossRef]
7. Babur Güler G, Güler A, Tanboğa İH, et al. Phenotypic, epidemiologic, and imaging features of hypertrophic cardiomyopathy: a single-center experience. *Anatol J Cardiol*. 2026. [CrossRef]
8. Kalenderoğlu K, Hayıroğlu Mİ, Pay L, et al. The long-term mortality predictors in hypertrophic cardiomyopathy patients with low risk of sudden cardiac death. *Turk Kardiyol Dern Ars*. 2025;53(5):312-318. [CrossRef].
9. Tower-Rader A, Desai MY. Phenotype-genotype correlation in hypertrophic cardiomyopathy: less signal, more noise? *Circ Cardiovasc Imaging*. 2017;10(2):e006066. [CrossRef]