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Reply to the Letter to the Editor: "Integrated Clinical, Multimodality Imaging, and Electrophysiological Markers for Improved Prediction of Sudden Cardiac Death in Hypertrophic Cardiomyopathy"

LETTER TO THE EDITOR
REPLY

To the Editor,

We thank the authors[1] for their interest in our study[2] and for their thoughtful comments. We appreciate the opportunity to further clarify several points raised in their letter. However, we believe that some of the interpretations presented may not fully reflect the scope and methodological framework of our study.

First, the absence of a direct correlation between Index of Cardiac Electrophysiological Balance (ICEB) and myocardial fibrosis assessed by late gadolinium enhancement (LGE) is emphasized as a mechanistic limitation. However, our study was not designed to validate a structural surrogate but rather to evaluate the predictive value of a simple and clinically accessible electrophysiological index. The ICEB reflects the integrated balance between depolarization and repolarization processes, and therefore, a direct one-to-one relationship with a single structural parameter is not necessarily expected. Arrhythmogenesis in hypertrophic cardiomyopathy (HCM) is multifactorial, and the lack of cardiovascular magnetic resonance data should be interpreted as a scope-related limitation rather than a conceptual shortcoming.

Second, the absence of phenotype-based subgroup analyses has been highlighted as a concern. It should be noted that, in studies with relatively limited sample sizes, extensive subgroup analyses may compromise statistical power and model stability, increasing the risk of spurious findings. Our study was designed to assess the overall predictive performance of ICEB in a heterogeneous, real-world HCM population, which we believe enhances its clinical relevance.

Third, the potential confounding effect of beta-blocker use requires careful interpretation. In HCM, pharmacological therapy is typically not randomly distributed but rather guided by clinical characteristics, including symptom burden and arrhythmic risk. Therefore, differences in beta-blocker use may reflect underlying disease severity rather than act as an independent source of bias. Moreover, if beta-blockers were the primary determinant of ICEB variation, a more consistent and uniform effect across electrocardiographic parameters would be expected, which was not observed in our study.

Fourth, the clinical relevance of the observed improvement in the area under the curve should not be evaluated solely based on statistical comparisons such as the DeLong test. In risk prediction, even modest improvements may have meaningful clinical implications, particularly in intermediate-risk patients where decision-making is often challenging. Importantly, ICEB is a simple, cost-free, and widely available parameter, making its integration into existing models highly feasible in routine clinical practice.

Fifth, the suggestion that ICEB primarily reflects QRS prolongation rather than repolarization abnormalities may represent an incomplete interpretation. The

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ICEB is inherently a composite index derived from both depolarization and repolarization components. The contribution of QRS duration does not diminish its value; rather, it highlights the integrated electrophysiological information captured by the index. Conduction abnormalities themselves are well-recognized contributors to arrhythmogenesis in HCM, and therefore, this finding supports—rather than weakens—the physiological relevance of ICEB.

Finally, we acknowledge that our study is retrospective and single-center in design, as clearly stated. Such studies play an important role in hypothesis generation. The consistency of our findings with established electrophysiological principles supports their biological plausibility, while the simplicity of ICEB enhances its potential for clinical application.

In conclusion, while we appreciate the authors' perspective, we believe that several of the concerns raised reflect expectations beyond the intended scope of our study. Our findings suggest that ICEB is a simple, accessible, and clinically meaningful marker that may provide incremental value in arrhythmic risk stratification in HCM. Future studies incorporating multimodal approaches are certainly warranted; however, these should be viewed as complementary rather than prerequisites to recognizing the utility of practical electrophysiological indices such as ICEB.

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