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Electrophysiological Markers in Hypertrophic Cardiomyopathy: Enhancing Sudden Cardiac Death Risk Prediction with Index of Cardiac Electrophysiological Balance and Its Corrected Variant

ABSTRACT

Background: Hypertrophic cardiomyopathy (HCM) is characterized by asymmetric left ventricular hypertrophy and myocardial fibrosis, which significantly increases the risk of sudden cardiac death (SCD). Existing risk stratification models are limited in predicting SCD risk in patients within the "gray zone"—those with intermediate risk. This study investigates the prognostic utility of the Index of Cardiac Electrophysiological Balance (ICEB) and its corrected variant (ICEBc) in predicting ventricular arrhythmias (VAs) in HCM. To evaluate the predictive value of ICEB and ICEBc for Life-Threatening Arrhythmias (LTA) and non-sustained ventricular tachycardia (NSVT) in HCM and compare their performance with traditional repolarization parameters and the European Society of Cardiology (ESC) SCD Risk Score.

Methods: A retrospective observational study was conducted at a single center, including 127 HCM patients categorized into 3 groups: LTA (n = 45), NSVT (n = 29), and control (n = 53). Electrocardiographic parameters, including ICEB, ICEBc, Tp-e interval, Tp-e/QTc ratio, and QRS-T angle were measured. Multiple logistic regression and receiver operating characteristic (ROC) curve analyses were performed to identify independent predictors of VAs.

Results: The ICEB and ICEBc were significantly lower in LTA and NSVT groups compared to the control group ($P < .001$), indicating increased arrhythmogenic risk. The ROC curve analysis showed that ICEB and ICEBc had superior predictive power for LTA and NSVT compared to traditional markers and the ESC SCD Risk Score, with the highest area under the curve (AUC) for the Base + ICEB Model (AUC = 0.79).

Conclusion: The ICEB and ICEBc are robust markers of repolarization heterogeneity and effective predictors of VAs in HCM patients. Their integration into existing risk stratification models could enhance predictive accuracy, particularly for gray zone patients.

Keywords: Hypertrophic cardiomyopathy, Index of Cardiac Electrophysiological Balance, life-threatening arrhythmias, risk stratification, sudden cardiac death, ventricular arrhythmias

ORIGINAL INVESTIGATION

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INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder characterized by asymmetric left ventricular hypertrophy and myocardial fibrosis, significantly increasing the risk of sudden cardiac death (SCD).[1] Although implantable cardioverter-defibrillators (ICDs) are recommended for SCD prevention, accurately identifying high-risk patients remains challenging.[2] Traditional risk stratification models, such as those recommended by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA), primarily rely on structural parameters like maximal left ventricular wall thickness and family history of SCD.[3] However, these models inadequately account for electrical instabilities, particularly in patients within the "gray zone"—those with intermediate SCD risk who do not clearly meet ICD implantation criteria but may still be at significant risk.[4] This limitation contributes to clinical uncertainty,

potentially leading to either unnecessary ICD placements or underestimation of SCD risk.[4]

Recent studies highlight the insufficiency of conventional models in stratifying patients in the gray zone, emphasizing the need for advanced tools that assess both structural and electrical heterogeneity in HCM.[5] Electrical instability, due to heterogeneous myocardial fibrosis and abnormal repolarization, plays a critical role in HCM's arrhythmogenic potential. Consequently, integrating advanced electrophysiological parameters could improve SCD risk prediction. The 2019 Enhanced ACC/AHA strategy incorporated additional clinical and electrocardiographic parameters, enhancing predictive accuracy.[6] However, even this advanced approach struggles to accurately assess gray zone patients, underscoring the need for innovative markers that more precisely evaluate electrophysiological stability.

New electrocardiographic markers, including the Index of Cardiac Electrophysiological Balance (ICEB) and its heart rate-corrected version (ICEBc), have been developed to address these limitations. The ICEB evaluates the balance between ventricular depolarization (QRS duration) and repolarization (QT interval), providing a more comprehensive assessment of electrical stability. The ICEBc offers improved risk prediction by adjusting for heart rate variability.[7,8] These parameters are particularly relevant in HCM, where myocardial fibrosis and electrical heterogeneity increase the risk of reentrant ventricular arrhythmias (VAs). Unlike traditional parameters, ICEB and ICEBc provide an integrated evaluation of depolarization and repolarization dynamics, offering a more accurate representation of myocardial electrical stability.

Traditional parameters like the Tp-e interval, Tp-e/QTc ratio, and QRS-T angle are widely used to assess repolarization heterogeneity but fail to provide a holistic view of electrophysiological balance.[9-11] In contrast, ICEB and ICEBc offer a more nuanced assessment by quantifying the dynamic interaction between ventricular depolarization and repolarization, thus more accurately reflecting myocardial electrical stability.

HIGHLIGHTS

- European Society of Cardiology (ESC) sudden cardiac death (SCD) risk score is insufficient to predict the SCD risk, particularly in patients within the "gray zone"—those with intermediate SCD risk.
- Index of Cardiac Electrophysiological Balance (ICEB) shows an inverse correlation with Life-Threatening Arrhythmias (LTA) risk, indicating that higher ICEB values are associated with lower LTA risk.
- The ICEB addition to ESC SCD risk score increases the area under the curve to 0.79, achieving the highest predictive power for SCD risk.
- The Base Model (SCD risk score) alone shows moderate predictive accuracy, whereas adding ICEB significantly improves SCD risk prediction, particularly enhancing risk assessment in gray zone patients.

This study aims to evaluate the prognostic utility of ICEB and ICEBc in predicting Life-Threatening Arrhythmias (LTA) and NSVT in HCM patients, comparing their predictive performance with conventional risk factors. It is hypothesized that ICEB and ICEBc will enhance SCD risk stratification, particularly for gray zone patients, by providing a more comprehensive assessment of electrical stability. This approach aims to improve the identification of high-risk HCM patients, ultimately guiding more precise ICD implantation decisions.

METHODS

Study Design and Patient Selection

This retrospective observational study was conducted at a tertiary cardiovascular center specializing in HCM, between 2017 and 2023. Patients were included if they were diagnosed with HCM according to the 2024 AHA/ACC guidelines, which define HCM as a left ventricular wall thickness of ≥15 mm in the absence of other identifiable causes of hypertrophy.[1] This criterion ensured accurate classification and risk stratification of HCM patients.

Patients were categorized into 3 groups based on the presence and severity of VAs:

- Life-Threatening Arrhythmias Group: Patients who experienced sudden cardiac arrest (SCA) or received appropriate ICD therapy for sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).
- Non-sustained VT (NSVT) Group: Patients with at least 1 episode of NSVT detected on Holter monitoring or ICD interrogation.
- Control Group: The HCM patients without documented VAs throughout the follow-up period.

Exclusion Criteria

Patients were excluded if they had cardiac conditions affecting ventricular repolarization, including bundle branch block, pre-excitation syndromes, or significant coronary artery disease. Those with a history of cardiac surgery or septal reduction therapy, which could alter myocardial architecture and electrophysiological properties, were also excluded. Additionally, patients using antiarrhythmic drugs or medications known to influence ventricular repolarization were excluded to ensure accurate assessment of repolarization parameters. Finally, patients with incomplete medical records or poor-quality electrocardiograms (ECGs), which could compromise the accuracy of repolarization measurements, were excluded to maintain the study's reliability and validity.

Electrocardiographic Assessment

A standard 12-lead ECG was recorded at a paper speed of 25 mm/s and a voltage of 10 mm/mV. The following repolarization parameters were manually measured by 2 independent cardiologists who were blinded to clinical outcomes:

- Index of Cardiac Electrophysiological Balance: Calculated as the QT/QRS ratio, reflecting the balance between ventricular depolarization and repolarization. It was introduced as a biomarker for identifying patients at increased arrhythmic risk.[7,8]

- Corrected ICEB: A heart rate-adjusted variant of ICEB, proposed as a more reliable predictor of arrhythmic risk.[7,8]
- Tp-e/QTc Ratio: Calculated by normalizing the Tp-e interval to the heart rate-corrected QT (QTc) interval, assessing repolarization heterogeneity. It is considered a more stable parameter than the Tp-e interval alone.[10,11]
- Tp-e Interval: Defined as the duration between the peak and end of the T wave, reflecting transmural dispersion of repolarization. It was measured in leads V4, V5, or V6. Prolonged Tp-e interval is associated with increased risk of SCD.[12]
- QRS-T Angle: Representing the discrepancy between ventricular depolarization and repolarization, it was determined using digital ECG analysis. A QRS-T angle ≥90° is associated with an increased risk of VAs.[13,14]

To minimize measurement variability, each parameter was measured 3 times, and the average value was used for analysis.

Study Hypothesis and Outcomes

The primary hypothesis of this study was that repolarization parameters, including the Tp-e interval, Tp-e/QTc ratio, QRS-T angle, ICEB, and ICEBc, are associated with the occurrence of VAs in patients with HCM. The primary outcome was the occurrence of LTA, which included SCA and appropriate ICD therapy for sustained VT or VF. The secondary outcome was the occurrence of NSVT, defined as at least 1 episode of NSVT detected on Holter monitoring or ICD interrogation.

Statistical Analysis

All statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation for normally distributed data or as median (interquartile range, IQR) for non-normally distributed data, while categorical variables were presented as frequencies and percentages. The Kolmogorov–Smirnov test was used to assess the normality of continuous variables. For group comparisons, 1-way ANOVA was applied for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. Post-hoc pairwise comparisons were performed using Tukey's HSD test for parametric variables and Bonferroni-adjusted Dunn's test for nonparametric variables. Categorical variables were compared using the chi-square test or Fisher's exact test.

To evaluate the incremental predictive value of ECG parameters, multiple logistic regression models were constructed, including the Base Model (ESC SCD Risk Score alone) and Base + individual ECG parameters (ICEB, ICEBc, QTc interval, Tp-e interval, Tp-e/QT ratio). Comprehensive multiple regression models including all ECG parameters simultaneously were not performed due to the limited number of endpoints, which could lead to overfitting, and the high collinearity among ECG variables, which increases variance inflation factors. Model performance was assessed using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC), Akaike Information Criterion (AIC), and McFadden's R^2 (R^2McF), with lower AIC and higher R^2McF indicating better model fit. DeLong's test was applied for formal comparison of ROC curves. A P value <.05 was considered statistically significant throughout all analyses.

Ethical Considerations

The study was approved by the local ethics committee with a decision dated April 08, 2025 and numbered 2025/05/1075. Written informed consent was obtained from all participants or their legal guardians, and the study was conducted in accordance with the Declaration of Helsinki. The confidentiality of patient data was maintained, and no identifiable personal information was disclosed in the study report.

RESULTS

This study evaluated the predictive utility of various ECG parameters, focusing on the ICEB and ICEBc, for predicting LTA and NSVT in patients with HCM. ICEB and ICEBc, as novel markers of repolarization heterogeneity, demonstrated superior predictive power compared to traditional parameters, including the SCD Risk Score, QTc interval, Tp-e interval, and Tp-e/QTc ratio, confirming their enhanced utility in risk stratification.

Baseline Characteristics of the Study Population

The study was conducted on 127 patients diagnosed with HCM between 2017 and 2023, divided into 3 groups: LTA group (n = 45), NSVT group (n = 29), and control group (n = 53) (Table 1). There were no significant differences in age, gender, hypertension, diabetes mellitus, smoking status, and ejection fraction among the groups. However, interventricular septum and posterior wall thickness were significantly greater in the LTA group, indicating increased ventricular hypertrophy ($P < .05$). Additionally, the maximum gradient was markedly higher in the LTA group ($P = .039$), suggesting left ventricular outflow tract obstruction. Notably, ICD implantation rates were significantly elevated in the LTA (80%) and NSVT (79.3%) groups compared to the control group (30.2%, $P < .001$), reflecting an increased arrhythmogenic risk (Table 1).

Electrocardiographic Parameters and Arrhythmogenic Risk

The QRS duration was significantly longer in the LTA and NSVT groups compared with the control group ($P < .001$, Table 1), indicating an association between ventricular conduction abnormalities and increased arrhythmogenicity. The Tp-e interval was also significantly prolonged in the LTA (86.8 ± 16.1 ms) and NSVT (85.3 ± 18.9 ms) groups compared with the control group (78.2 ± 11.7 ms, $P = .015$), reflecting greater transmural dispersion of repolarization. Both the Tp-e/QT ratio ($P = .006$) and the Tp-e/QTc ratio ($P = .046$) were significantly higher in the arrhythmic groups, indicating increased repolarization heterogeneity.

Despite these differences, the QRS–T angle did not show statistical significance among the groups ($P = .152$), although a widening trend was observed in the LTA group, suggesting potential repolarization instability that requires further validation. The QT and QTc intervals also did not show significant differences (QT interval: $P = .842$; QTc interval: $P = .295$), indicating limited predictive value for VAs in this population. Although a positive association between QTc interval and LTA risk was suggested (Figure 1), its predictive power

Table 1. Baseline Demographic and Clinical Characteristics of Study Groups

Variables	LTA (n = 45)	NSVT (n = 29)	No Arrhythmia (n = 53)	*P*
Gender, male (%)	28 (62.2)	20 (69.0)	31 (58.5)	.646
Age (mean ± SD)	46 ± 12.9	50.6 ± 11.9	48 ± 12.9	.320
Hypertension (%)	13 (28.9)	10 (34.5)	16 (30.2)	.873
Diabetes mellitus (%)	2 (4.4)	1 (3.4)	6 (11.3)	.366
Smoking (%)	4 (8.9)	5 (17.2)	5 (9.4)	.475
Surgery (marrow) (%)	2 (4.4)	1 (3.4)	0 (0)	.329
Family history of SCD (%)	10 (22.2)	5 (17.2)	14 (26.4)	.634
Syncope (%)	15 (33.3)	12 (41.4)	14 (26.4)	.376
Ejection fraction (EF, %)	63 ± 4.73	63.1 ± 3.89	62.8 ± 5.79	.965
Interventricular septum (IVS, mm)	26 ± 6.21	24.2 ± 4.20	22 ± 5.80	.009[c]
Posterior wall thickness (PW, mm)	15.3 ± 5.29	14.9 ± 3.31	13.2 ± 2.81	.028[c]
Left ventricular end-diastolic diameter (LVEDD, mm)	42.6 ± 4.56	43.2 ± 3.76	43.6 ± 3.71	.462
Left ventricular end-systolic diameter (LVESD, mm)	26.2 ± 5.75	25.8 ± 4.28	27.0 ± 2.53	.422
Left atrium (LA, mm)	40.0 ± 6.40	40.8 ± 6.65	40.9 ± 5.86	.756
Maximum gradient (max grad, mm Hg)	68.5 (45-90.5)	55 (22-72)	37 (16-80)	.039[b]
Mitral valve regurgitation (MVR, %)	1 (2.2)	0 (0)	0 (0)	.583
ICD implanted (%)	36 (80)	23 (79.3)	16 (30.2)	<.001[b, c]
Follow-up duration (months)	(64-96)	72 (64-84)	70 (56-80)	–
DCCV vs. ATP (%)	10 (30.3)	11 (73.3)	N/A	<.001
Number of shocks	0 (0-8)	0 (0-17)	N/A	.293
ASA (%)	12 (26.7)	5 (17.2)	5 (9.4)	.080
Beta-blocker use (%)	30 (66.7)	22 (75.9)	52 (98.1)	<.001[b, c]
Calcium channel blocker (%)	3 (6.7)	0 (0)	4 (7.5)	.422
ACEI/ARB use (%)	6 (13.3)	3 (10.3)	17 (32.1)	.022[b, c]
Heart rate (bpm)	69.9 ± 15.6	70.9 ± 16.0	68.8 ± 10.1	.790
QRS duration (ms)	119 ± 37.8	116 ± 29.7	94.3 ± 12.4	<.001[b, c]
QT interval (ms)	421 ± 48.6	416 ± 44.5	421 ± 35.1	.842
QTc interval (ms)	454 ± 43.3	450 ± 46.6	442 ± 25	.295
Tp-e interval (ms)	86.8 ± 16.1	85.3 ± 18.9	78.2 ± 11.7	.015[c]
Tp-e/QT ratio	0.207 ± 0.035	0.205 ± 0.038	0.187 ± 0.028	.006[b, c]
Tp-e/QTc ratio	0.192 ± 0.035	0.190 ± 0.041	0.177 ± 0.023	.046[c]
QT dispersion (ms)	10.2 (5.7-27.6)	17.6 (12-28.4)	9.1 (5.3-12.1)	<.001[b, c]
QRS-T angle (degrees)	122 ± 33.2	121 ± 43.2	107 ± 46.6	.152
ICEB	3.70 ± 0.71	3.76 ± 0.77	4.52 ± 0.56	<.001[b, c]
ICEBc	4.01 ± 0.8	4.07 ± 0.78	4.77 ± 0.65	<.001[b, c]
SCD risk score	8.04 (5.2-10.4)	9.6 (5.6-12.6)	2.4 (1.6-3.49)	<.001[b, c]
Mortality (%)	0 (0)	1 (3.4)	1 (1.9)	.702

Values are presented as n (%), mean ± SD, or median (IQR). $P < .05$ indicates statistical significance.
[a]LTA vs. NSVT.
[b]NSVT vs. control group.
[c]LTA vs. control group.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker, ASA, alcohol septal ablation; ATP, anti-tachycardia pacing; DCCV, direct current cardioversion; EF, ejection fraction; ICD, implantable cardioverter defibrillator; ICEB, Index of Cardiac Electrophysiological Balance; ICEBc, Corrected Index of Cardiac Electrophysiological Balance; IVS, interventricular septum; LA, left atrium; LTA, Life-Threatening Arrhythmias; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; Max Grad, maximum gradient; MVR, mitral valve regurgitation; NSVT, non-sustained ventricular tachycardia; PW, posterior wall thickness; QRS, QRS complex on ECG; QT, QT interval on ECG; QTc, corrected QT interval; SCD, sudden cardiac death; Tp-e, T-peak to T-end interval; Tpe/QT, ratio of Tpe interval to QT interval.

remains limited in this cohort. Heart rate likewise did not differ significantly between groups ($P = .790$).

Conversely, ICEB and ICEBc values were significantly lower in both the LTA (3.70 ± 0.71) and NSVT (3.76 ± 0.77) groups compared with the control group (4.52 ± 0.56, $P < .001$, Table 1). These findings indicate that reduced ICEB and ICEBc values are strongly associated with increased VA risk, reflecting enhanced repolarization heterogeneity and electrical instability (Figure 1).

Prediction of Life-Threatening Arrhythmias

The ROC analysis demonstrated the superior discriminatory power of ICEB and ICEBc compared to traditional ECG parameters (Table 2). The Base Model, which included only

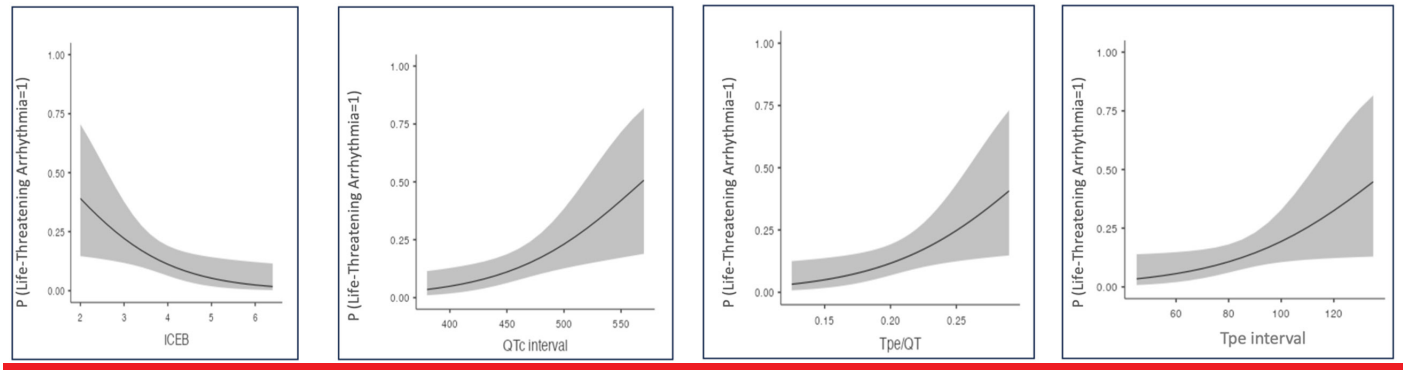

Figure 1. Partial effect plots for predicting Life-Threatening Arrhythmias (LTA) using ICEB, QTc interval, Tp-e/QT ratio, and Tp-e interval. These plots illustrate the relationship between ICEB, QTc Interval, Tp-e/QT Ratio, and Tp-e interval with the probability of Life-Threatening Arrhythmias (LTA); ICEB shows an inverse correlation with LTA risk, indicating that higher ICEB values are associated with lower LTA risk. This suggests that ICEB may reflect electrical stability. QTc Interval, Tp-e/QT Ratio, and Tp-e interval display positive associations with LTA risk, showing that higher values of these parameters are linked to an increased risk of LTA.

the ESC SCD Risk Score, showed moderate discriminatory capability (AUC = 0.74). In contrast, adding ICEB to the model significantly improved its predictive power, yielding the highest AUC of 0.79, confirming ICEB's effectiveness in predicting LTA risk (Figure 2). For LTA, an ICEB cut-off of 3.84 was identified (AUC = 0.707, sensitivity 76.8%, specificity 60%), while the corresponding cut-off for ICEBc was 4.08 (AUC = 0.668, sensitivity 76.8%, specificity 62.2%) (Supplementary Table 1).

Table 2. Incremental Predictive Value of ECG Parameters Added to the ESC SCD Risk Score for Life-Threatening Arrhythmias (LTA)

Model	AIC	BIC	R^2McF	AUC	Significant Predictors	Adjusted Odds Ratio (95% CI, *P*)
Base model	100	106	0.071	0.74	SCD risk score	OR = 1.15 (95% CI: 1.04-1.28, *P* = .006)
Base + QTc interval	95.4	104	0.138	0.75	QTc interval	OR = 1.02 (95% CI: 1.00-1.03, *P* = .047)
Base + Tp-e interval	98.0	107	0.113	0.74	Tp-e interval	OR = 1.04 (95% CI: 1.00-1.07, *P* = .039)
Base + Tp-e/QTc ratio	96.8	105	0.124	0.76	Tp-e/QTc ratio	OR = 9.27 (95% CI: 6.12-14.03, *P* < .001)
Base + ICEB	97.0	106	0.122	0.79	ICEB	OR = 0.44 (95% CI: 0.22-0.89, *P* = .021)
Base + ICEBc	96.2	105	0.128	0.77	ICEBc	OR = 0.47 (95% CI: 0.26-0.83, *P* = .011)

Values are presented as adjusted odds ratios (OR) with 95% CI and *P* values. A *P* value <.05 was considered statistically significant.

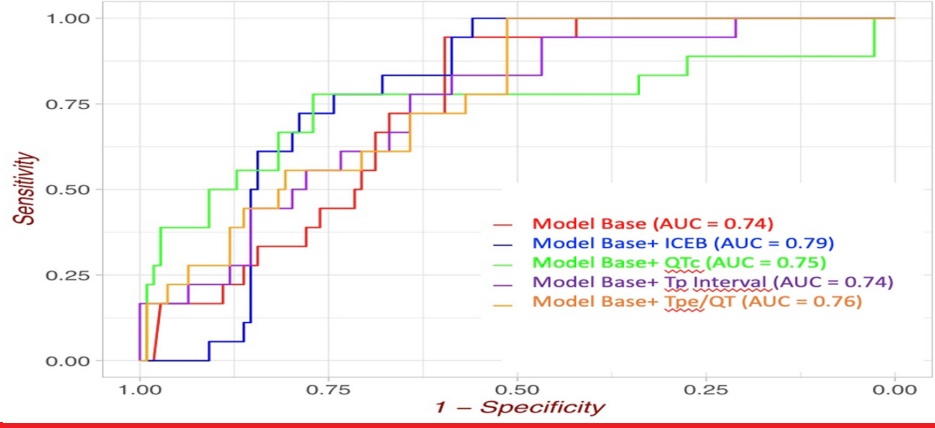

Figure 2. ROC curve for predicting Life-Threatening Arrhythmias using different models. The ROC curve compares the diagnostic performance of different repolarization parameters for predicting SCD risk in HCM patients: Base Model (AUC = 0.74): Includes only the ESC SCD Risk Score and shows moderate discriminatory power for predicting SCD risk. ICEB addition increases the AUC to 0.79, achieving the highest predictive power for SCD risk. Tp-e/QT ratio (AUC = 0.76) and QTc (AUC = 0.75) provide additional predictive value but are less effective than ICEB. Tp-e interval (AUC = 0.74) does not enhance the performance of the Base Model. The Base Model (SCD Risk score) alone shows moderate predictive accuracy, whereas adding ICEB significantly improves SCD risk prediction, particularly enhancing risk assessment in gray zone patients.

Traditional ECG parameters provided only minimal improvements in AUC values:

- Base + QTc Model: AUC = 0.75
- Base + Tp-e/QTc Ratio Model: AUC = 0.76
- Base + Tp-e interval Model: AUC = 0.74 (no improvement)

These findings illustrate the limited predictive value of conventional ECG markers in risk stratification, while ICEB emerged as the most effective predictor for LTA, highlighting ICEB's potential to enhance risk stratification and optimize preventive strategies in HCM patients.

Prediction of Non-Sustained Ventricular Tachycardia

ICEB and ICEBc emerged as the most powerful predictors of NSVT among all evaluated electrocardiographic parameters.

Figure 3 illustrates an inverse relationship between ICEB/ICEBc values and NSVT risk, indicating that higher ICEB or ICEBc values are associated with lower arrhythmic risk, emphasizing their role as markers of electrical stability. This inverse relationship remained consistent across all levels of the ESC SCD Risk Score, underscoring their robust predictive capacity.

As summarized in Table 3, adding ICEB or ICEBc to the Base Model (ESC SCD Risk Score alone) improved model performance, yielding the highest discriminative ability:

- Base + ICEB Model: AUC = 0.804
- Base + ICEBc Model: AUC = 0.801

For NSVT prediction, an ICEB cut-off of 4.09 (AUC = 0.696, sensitivity 65.4%, specificity 67.4%) and an ICEBc cut-off of

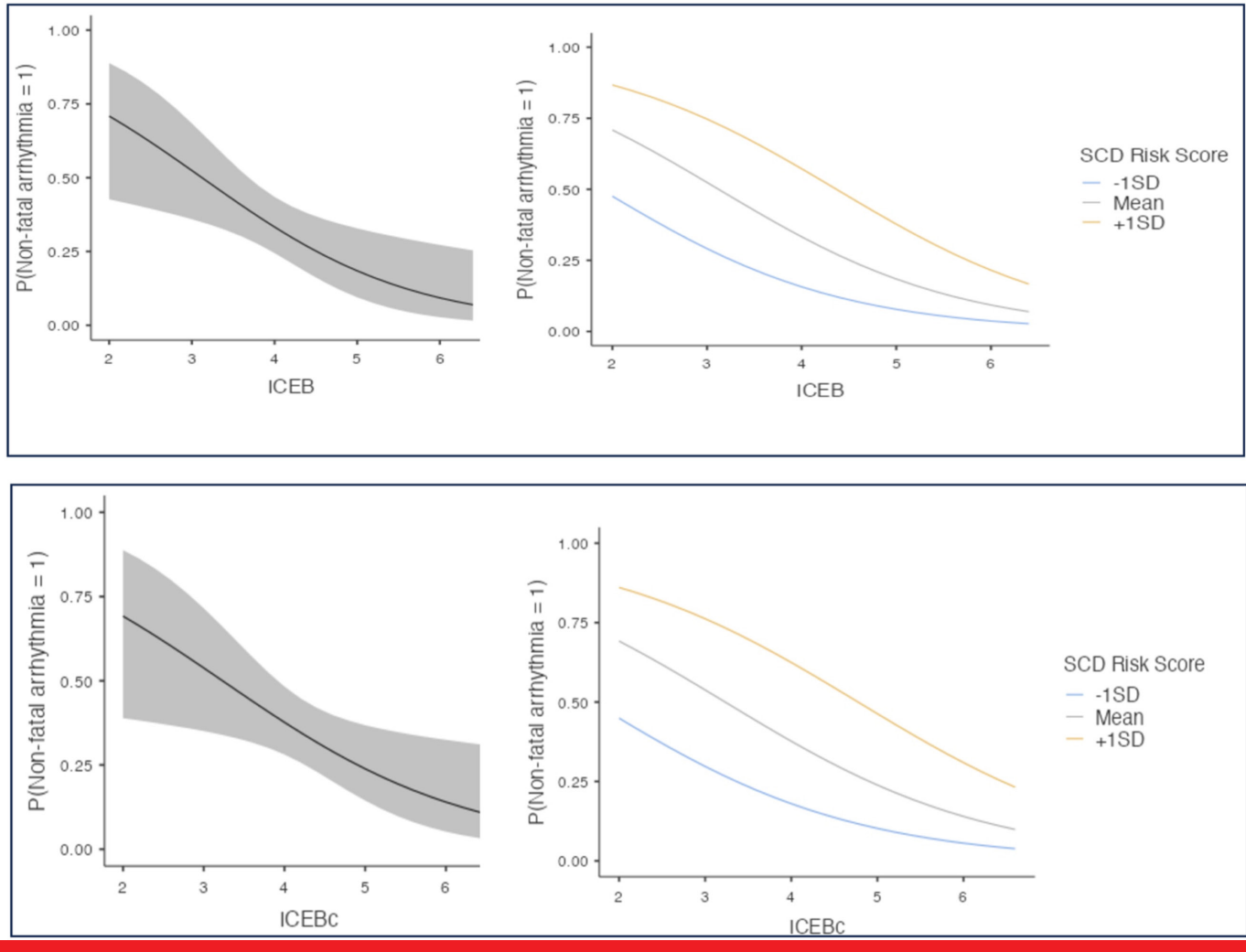

Figure 3. Prediction of NSVT using ICEB and ICEBc: interaction with ESC SCD Risk Score. This figure illustrates the relationship between ICEB and ICEBc with the probability of non-fatal arrhythmias, along with their interaction with the SCD Risk Score; Top Left (ICEB): Shows an inverse correlation with non-fatal arrhythmia risk, indicating that higher ICEB values are associated with lower arrhythmia risk. This suggests that ICEB may be a marker of electrical stability. Bottom Left (ICEBc): Similarly, higher ICEBc values correspond to reduced arrhythmia risk, consistent across both uncorrected and corrected versions. Top Right (ICEB with SCD Risk Score) and bottom right (ICEBc with SCD Risk Score): These plots display the interaction between ICEB/ICEBc and SCD Risk Score, with lines representing different levels of SCD Risk Score: −1SD (Blue): Represents patients with a lower-than-average SCD risk score, showing the lowest probability of arrhythmias. Mean (Gray): Shows a moderate risk profile, with a decreasing trend as ICEB/ICEBc increases. +1SD (Yellow): Represents high-risk patients with the highest probability of arrhythmias. However, increasing ICEB/ICEBc values are associated with a reduced risk, suggesting a potential protective effect even in high-risk groups.

Table 3. Incremental Predictive Value of ECG Parameters Added to the ESC SCD Risk Score for Non-Sustained Ventricular Tachycardia (NSVT)

Model	AIC	R^2McF	AUC	Significant Predictors	Adjusted Odds Ratio (95 % CI, *P*)
Base model	142	0.168	–	SCD Risk Score	OR = 1.267 (95% CI: 1.148-1.399, *P* < .001)
Base + QTc interval	144	0.168	–	SCD Risk Score	OR = 1.269 (95% CI: 1.148-1.400, *P* < .001)
Base + Tp-e interval	144	0.168	–	SCD Risk Score	OR = 1.269 (95% CI: 1.142-1.410, *P* < .001)
Base + Tp-e/QTc ratio	144	0.169	–	SCD Risk Score	OR = 1.258 (95% CI: 1.135-1.396, *P* < .001)
Base + ICEB	137	0.214	0.804	SCD Risk Score, ICEB	OR = 1.243 (95% CI: 1.124-1.374, *P* < .001) OR = 0.453 (95% CI: 0.253-0.810, *P* = .008)
Base + ICEBc	138	0.204	0.801	SCD Risk Score, ICEBc	OR = 1.250 (95% CI: 1.132-1.381, *P* < .001) OR = 0.519 (95% CI: 0.301-0.896, *P* = .011)

Values are presented as adjusted odds ratios (OR) with 95% CI and *P* values. A *P* <.05 was considered statistically significant. Both SCD Risk Score and ICEB/ICEBc were included in the same multiple logistic regression model; therefore, 2 odds ratios are reported for each model.

4.21 (AUC = 0.667, sensitivity 69.1%, specificity 60.1%) were identified (Supplementary Table 1).

These findings demonstrate that ICEB and ICEBc provide incremental predictive value beyond the ESC SCD Risk Score, supporting their potential integration into clinical risk-stratification frameworks for HCM.

Comparative Performance of Index of Cardiac Electrophysiological Balance and Its Corrected Variant in Predicting Non-Sustained Ventricular Tachycardia

The predictive utility of electrocardiographic parameters was assessed by comparing models incorporating ICEB, ICEBc, QTc interval, Tp-e interval, and Tp-e/QTc ratio with the Base Model, which included only the ESC SCD Risk Score. Figure 4 illustrates that ICEB and ICEBc provide higher sensitivity and specificity in predicting NSVT risk compared to conventional ECG parameters, with ROC curves positioned closer to the top-left corner, indicating superior discriminatory power. In contrast, traditional markers, including QTc interval, Tp-e interval, and Tp-e/QTc ratio, exhibited lower predictive ability, highlighting their limited utility for risk stratification in this cohort. Although DeLong's test revealed no statistically significant differences in discriminatory performance between the Base Model and any of the evaluated models for both LTA and NSVT endpoints, numerical trends toward improved model fit, along with lower AIC and BIC values when ICEB or ICEBc were added, suggest potential incremental predictive value. These findings indicate that, even in the absence of formal statistical significance, ICEB and ICEBc may provide clinically relevant information for risk stratification, particularly in gray zone patients.

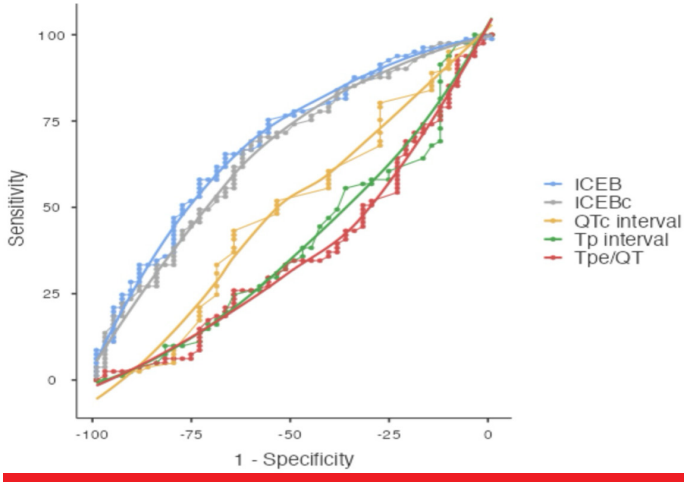

Figure 4. ROC curve: comparison of repolarization parameters in predicting NSVT. This ROC curve illustrates the performance of various repolarization parameters in predicting the risk of non-sustained ventricular tachycardia (NSVT) in patients with hypertrophic cardiomyopathy (HCM). The parameters compared are ICEB, ICEBc, QTc interval, Tp-e interval, and Tp-e/QT. The proximity of the curve to the top left corner indicates a higher combination of sensitivity and specificity. The results show that ICEB and ICEBc demonstrate the best performance in predicting NSVT, whereas Tp-e/QT and Tp-e interval exhibit lower predictive power.

Implications for Clinical Practice

These findings highlight the clinical utility of ICEB and ICEBc as robust markers of repolarization heterogeneity and effective risk stratification tools for predicting LTA and NSVT. Integrating ICEB and ICEBc into clinical practice could enable more accurate risk stratification and optimization of preventive strategies, particularly for HCM patients in the intermediate-risk (gray zone) category.

DISCUSSION

The findings indicate that the ICEB and its modified version may serve as effective predictors of LTA and NSVT in patients with HCM. Although further validation is required for definitive conclusions, these indices appear to provide a broader assessment of electrical stability by evaluating the dynamic interaction between ventricular depolarization and repolarization.[15]

The capacity of these indices to capture subtle electrical instabilities, such as repolarization heterogeneity and heart rate variability, may contribute to their prognostic value.[15] Specifically, in patients with an intermediate risk of SCD—those who cannot be clearly stratified by conventional models—these measures may allow for a more refined risk evaluation.[6] However, it is important to note that the observed association does not establish causality, and further prospective studies are needed to determine the impact of these parameters on clinical decision-making.

Traditional ECG parameters, including the Tp-e interval, Tp-e/QTc ratio, and QRS-T angle, are commonly used to evaluate repolarization heterogeneity and assess VA risk.[9,10] However, these conventional markers primarily reflect spatial repolarization dispersion and cannot adequately represent the complex interaction between depolarization and repolarization, which may limit their predictive performance.[12,13] Indeed, the current study, in line with prior evidence, demonstrated that conventional electrocardiographic indices have only limited predictive value.[14] Particularly in patients with borderline risk profiles, these parameters lead to ambiguous assessments, thereby complicating the clinical decision-making process. The ICEB and ICEBc, however, evaluate the dynamic interaction between ventricular depolarization and repolarization through a holistic approach, providing a more accurate representation of myocardial electrical stability. Given that heterogeneous myocardial fibrosis in HCM causes electrical instability and increases the risk of reentrant VAs, the ability of ICEB and ICEBc to sensitively measure this dynamic balance suggests that they may serve as more reliable electrophysiological stability indicators compared to traditional ECG parameters, particularly in gray zone patients.[16,17]

In HCM, late gadolinium enhancement (LGE) on cardiac magnetic resonance—a marker of myocardial fibrosis—may be associated with surface electrocardiographic abnormalities. It has been reported that patients with enhancement may exhibit substantially wider QRS-T angles, and a frontal QRS-T angle ≥90° may predict the presence of fibrosis.[18] These observations may support the concept that repolarization and conduction heterogeneity could reflect the underlying fibrotic substrate. Given that the ICEB is derived from the QT interval and QRS duration, it may have the potential to capture related electrophysiological imbalance; however, to the best of knowledge, a direct association between the index and LGE specifically in HCM has not yet been demonstrated and warrants further investigation.[19]

The study findings suggest that ICEB and ICEBc may have potential for improving risk stratification and guiding preventive strategies in HCM patients, particularly those in the gray zone. The gray zone represents a subgroup of patients with intermediate SCD risk, where risk stratification may remain ambiguous, potentially influencing clinical decision-making.[6] When current risk models fail to adequately classify gray zone patients as either high risk or low risk, unnecessary ICD implantations or risk underestimation may occur. The ability of ICEB and ICEBc to detect changes in electrophysiological stability suggests that risk assessment could be improved for gray zone patients, potentially enhancing clinical decision-making and allowing for more targeted preventive strategies.[15] However, for these parameters to be implemented in clinical practice, validation in larger populations using prospective study designs appears necessary.[4] Additionally, the establishment of standardized cutoff values and assessment of long-term prognostic value remain important.

By incorporating electrophysiological balance into assessment, ICEB and ICEBc may provide incremental value to current guideline-based risk models that mainly focus on structural and clinical features.[1,3] Through direct evaluation of electrophysiological stability, these indices may have the potential to address limitations of conventional models that account for repolarization heterogeneity and electrical instability to a limited extent.[15] For patients in the gray zone, integration of ICEB and ICEBc into current risk models may enhance predictive accuracy and contribute to more systematic approaches in ICD implantation decisions.[4,5] This approach may allow for individualized risk assessments and could support clinical decision-making processes in a manner that may reduce both undertreatment and over-treatment scenarios. Nevertheless, the clinical utility of ICEB and ICEBc in gray zone patients requires comprehensive validation through multicenter, prospective studies. Investigation of their integration with genetic testing and advanced imaging modalities may also contribute to the development of more comprehensive risk assessment frameworks.

Limitations and Future Directions

This study has several limitations. The retrospective, single-center design and relatively small sample size may limit the generalizability of the findings. Moreover, the study predominantly included patients from a Turkish population, which may restrict the applicability of the results to other ethnic groups. Selection bias and confounding factors should also be considered. Especially high rate of ICD implantation in the LTA and NSVT groups may introduce a selection bias and influence the observed associations between ICEB/ICEBc and arrhythmic events.

The absence of genetic testing limits the understanding of genotype-phenotype correlations, which could influence repolarization heterogeneity and arrhythmic risk.[20] Recent multicenter studies from diverse populations, such as the Turkish cohort analysis by Oktay et al,[21] have demonstrated the importance of comprehensive genetic screening in identifying both sarcomeric and non-sarcomeric mutations that may influence electrophysiological properties and arrhythmic risk stratification in HCM patients. Additionally, the lack of comparison with advanced imaging techniques, such as cardiac magnetic resonance imaging and LGE, restricts the comprehensive evaluation of myocardial fibrosis and its relationship with electrophysiological instability.[22] Another limitation of the study is the lack of intraobserver and interobserver reproducibility analyses for ICEB and ICEBc measurements, which might have further strengthened the reliability of the results.

Future studies should aim to validate ICEB and ICEBc in larger, more diverse populations using prospective, multicenter designs. Additionally, integrating genetic testing and advanced imaging modalities may provide a more comprehensive risk assessment. Investigating the utility of ICEB and ICEBc in other cardiovascular populations characterized by electrophysiological instability could further expand their clinical applicability.

CONCLUSION

The ICEB and ICEBc are powerful predictors of LTA and NSVT in HCM patients. Their integration into current SCD risk stratification models could enhance predictive accuracy, particularly for patients in the "gray zone." This approach would lead to more accurate identification of high-risk patients, optimizing preventive strategies and improving clinical decision-making. This study demonstrates the superior predictive power of ICEB and ICEBc compared to traditional ECG parameters, offering a novel approach to risk stratification in HCM. Future studies should validate these findings in larger, multicenter cohorts and explore the integration of ICEB and ICEBc with advanced imaging techniques and genetic testing to develop more comprehensive and robust risk prediction models for HCM.

Ethics Committee Approval: The study was approved by the Institutional Review Board of Kartal Koşuyolu Training and Research Hospital with the decision dated April 08, 2025 and numbered 2025/05/1075.

Informed Consent: Written informed consent was obtained from all participants.

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Supplementary Table 1. ROC-derived cut-off values, area under the curve (AUC), sensitivity, and specificity of ICEB, ICEBc, and repolarization parameters (QTc, TP interval, Tpe/QT) for predicting life-threatening arrhythmia (LTA) and non-sustained ventricular tachycardia (NSVT)

Variables	Cut-off (LTA)	AUC (LTA)	Sens (%)	Spec (%)	Cut-off (NSVT)	AUC (NSVT)	Sens (%)	Spec (%)
ICEB	3.84	0.707	76.8	60	4.09	0.696	65.4	67.4
ICEBc	4.08	0.668	76.8	62.2	4.21	0.667	69.1	60.1
QTc	480	0.564	35.5	87.8	453	0.494	43.2	65.2
TP interval	73.2	0.612	93.3	34.1	82.8	0.599	52.1	64.2
Tpe/QT	0.194	0.626	60	64.6	0.193	0.621	60.9	62.9