Cerrahpaşa Med J 2023; 47(2): 118-122 REVIEW

The Cardio-Electrophysiological Balance Index in Cardiovascular Diseases

Lütfü Aşkın[1], Okan Tanrıverdi[2]

[1]Department of Cardiology, Gaziantep Islamic Science and Technology University, Gaziantep, Turkey
[2]Department of Cardiology, Adıyaman Training and Research Hospital, Adıyaman, Turkey

Cite this article as: Aşkın L., Tanrıverdi O. The cardio-electrophysiological balance index in cardiovascular diseases. *Cerrahpaşa Med J.* 2023;47(2):118-122.

Abstract

The index of the cardio-electrophysiological balance may be used to assess ventricular arrhythmogenesis. The index of cardio-electrophysiologic al balance has been associated with malignant ventricular arrhythmias. Ventricular arrhythmias caused by drugs have been connected to a new risk measure called the index of cardio-electrophysiological balance the interval from the beginning of the QRS complex to the end of the T wave (QT) interval divided by the deflections in an electrocardiogram (EKG) tracing that represent the ventricular activity of the heart (QRS) duration), which was recently tested in an animal model. The cardiac wavelength index of cardio-electrophysiological balance was considered to equal the effective refractory period multiplied by the conduction velocity. An increase or decrease in the index of cardio-electrophysiological balance could suggest an increased risk of ventricular tachycardia/fibrillation induced by torsades de pointes or non-torsades de pointes. The index of cardio-electrophysio logical balance is one of the most often used methods for measuring the cardiac waveform. Because it is noninvasive and simple to measure, index of cardio-electrophysiological balance may be used to predict ventricular arrhythmia risk.

Keywords: Cardiac wavelength, effective refractory period, electrocardiography, electrophysiological balance index, ventricular repolarization

Introduction

There is no comprehensive easy-to-measure risk marker for drug-induced ventricular arrhythmias (VAs) to assess sudden cardiac death (SCD). The QT interval, a measure of action potential length on an electrocardiogram (ECG), can be used to estimate VA risk. The prolonged corrected (QTc) interval alone is insufficient for identifying malignant ventricular arrhythmias.Because QTc alone cannot predict the risk of developing non-torsadogenic ventricular tachycardia/fibrillation (VT/VF), other biomarkers are now being used.[1,2]

Robyns et al[2] showed that the effective refractory period (ERP) and the QT interval happen at the same time when looking at invasive electrophysiology. Both the index of cardio-electrophysiologic al balance (iCEB) and the cardiac wavelength (ERP, conduction velocity) measure how quickly action potentials repolarize and depolarize. An important part of VAs is the invasive electrophysiology method of measuring the cardiac wavelength. The iCEB may be a simple way to find out who is more likely to get an irregular heartbeat. The iCEB can be used to predict when drug-induced VAs will start. Studies on animals have shown a link between the QT interval and the ERP, as well as between changes in the length of the QRS and the speed of conduction.[3]

The iCEB is calculated by dividing the QT interval by the duration of the QRS (QT/QRS). The cQT/QRS ratio is used to analyze the corrected index of cardio-electrophysiological balance (iCEBc).[4] The iCEB is used to assess the possibility of non-invasive VT. Repolarization distribution and abnormal conduction velocity are important indicators of arrhythmia occurrence. Malignant VAs are associated with cardiac wavelength (ERP). Li et al[5] previously published a related article on this topic.

So far as we know, this is the first time we have looked at the iCEB and iCEBc parameters in cardiovascular disease. Checking for changes in the cardiac action potential balance (iCEB and iCEBc), which assesses the ratio of depolarization to repolarization in the heart, may be as simple and noninvasive as determining the risk of proarrhythmia. This review was written to emphasize the link between these electrophysiological changes and VAs.

The Relationship Between Index of Cardio-Electrophysiological Balance and Ventricular Arrhythmias

The iCEB is a measure of the balance between the sympathetic and parasympathetic nervous systems in the heart. It reflects the autonomic modulation of the heart rate and can be used to assess the risk of developing VAs. The VAs are abnormal heart rhythms that originate in the ventricles (the lower chambers of the heart). These arrhythmias can range from mild, harmless palpitations to life-threatening conditions such as VF.

Studies have shown that an imbalance in the autonomic nervous system can increase the risk of developing VAs. A high iCEB, indicating a sympathetic predominance, has been associated with an increased risk of VAs in patients with various cardiac conditions, including heart failure and myocardial infarction. On the other hand, a low iCEB, indicating a parasympathetic predominance, has been associated with a decreased risk of VAs in some studies. However, the relationship between iCEB and VAs is complex and may vary depending on the underlying cardiac condition and other factors.

Overall, the iCEB can provide valuable information about the autonomic regulation of the heart and may be useful in predicting the risk of VAs in certain patient populations. However, further research is needed to fully understand the relationship between

Received: December 21, 2022 **Accepted:** March 25, 2023
Publication Date: August 22, 2023
Corresponding author: Lütfü Aşkın, Department of Cardiology, Gaziantep Islamic Science and Technology University, Gaziantep, Turkey
e-mail: lutfuaskin23@gmail.com
DOI: 10.5152/cjm.2023.22127

iCEB and VAs and to determine the optimal use of this measure in clinical practice.

Ventricular Tachycardia and Ventricular Fibrillation with No Structural Heart Disease

The VT and VF are rapid and potentially life-threatening heart rhythms that originate in the ventricles, the lower chambers of the heart. In some cases, these arrhythmias can occur in people with no underlying structural heart disease, a condition known as idiopathic VA. The iCEB is a measure used to assess the balance between sympathetic and parasympathetic nervous system activity in the heart. It is calculated using the heart rate variability (HRV) and heart rate turbulence parameters obtained from an ECG.

In patients with idiopathic VT or VF, studies have shown that a low iCEB may be associated with a higher risk of recurrent arrhythmias. This suggests that an imbalance between sympathetic and parasympathetic nervous system activity may play a role in the development and maintenance of these arrhythmias. However, it is important to note that the relationship between iCEB and idiopathic VT/VF is still an area of active research, and further studies are needed to fully understand the mechanisms involved. Additionally, other factors such as genetic predisposition and environmental triggers may also contribute to the development of these arrhythmias in patients with no structural heart disease.

Malignant Ventricular Arrhythmias

Torsades de Pointes

Changes in iCEB levels may indicate an increased risk of malignant VAs such as torsades de pointes (TdP). The TdP was detected in rabbit ventricular wedge samples following dofetilide, an IKr blocker that improved QT, Tp-e intervals, and iCEB. Encainide, a sodium channel current (INA) blocker, had no effect on QT or Tp-e intervals, although it did reduce iCEB levels and caused VT that was not TdP-like. It can be argued that iCEB predicts drug-induced non-TdP-like VA better than Tp-e and QT intervals. Sotalol flecainide, which modifies iCEB, should be avoided in paroxysmal supraventricular arrhythmias.[6]

The QRS duration is frequently inversely proportional to cardiac conduction velocity in the absence of a clearly defined bundle branch block.[6] Because amiodarone is a multi-ion channel blocker, the QT/QRS ratio may not change. The Antiarrhythmic drugs (AADs) that prolong the QT interval increase the iCEB and iCEBc times, whereas AADs that prolong the QRS duration decrease the iCEB and iCEBc times. As a result, iCEBc lengthening or shortening increases the risk of malignant arrhythmia (Figure 1).[7]

Due to measurement difficulties at the cardiac wavelength, finding a risk classifier in vitro is difficult. The relationship between QTc and ERP is weak.[8,9] For the last 2 decades, the pharmaceutical industry has focused on drug-induced arrhythmia.[10] To determine the cardiac risk of new drugs, extensive QT clinical studies are required. However, in drug-induced VAs, adherence to QT alone has raised some concerns. Although VP is still common, it can cause repolarization heterogeneity and increase the risk of TdP.[11,12] Clinicians should be aware of the link between drug and pacing-induced QT interval prolongation, repolarization changes, and the risk of VAs.[13]

iCEBc, a new, noninvasive marker, may predict PVCs in structurally normal hearts. The iCEBc indicates electrophysiological balance and arrhythmia risk beyond other ECG measures.[14] Afsin et al[15] discovered that amiodarone patients had larger cTp-e intervals, Tp-e/QTc ratios, and iCEBc characteristics, whereas propafenone patients had the lowest. The iCEB and iCEBc, which indicate the balance between cardiac action potential depolarization and repolarization, maybe a noninvasive, simple, and innovative biomarker for increased proarrhythmia risk in AF patients on antiarrhythmic drugs. These electrical abnormalities may be linked to VAs in AF patients on antiarrhythmic drugs. Further research is required.

Structural Ventricular Tachycardia/Ventricular Fibrillation

The iCEB is a measure of the balance between electrical and structural properties of the heart that influence arrhythmia

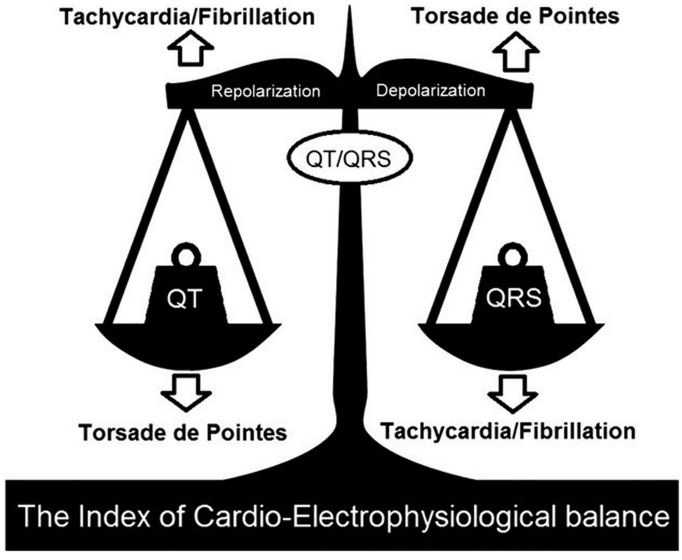

Figure 1. iCEB diagram. The deflections in an electrocardiogram (EKG) tracing that represent the ventricular activity of the heart (QRS) and the interval from the beginning of the QRS complex to the end of the T wave (QT) Changes in the index of (iCEB): significant increases/decreases in the QT interval or QRS duration may be proarrhythmic for TdP-mediated and non-TdP-mediated VT/VF (imbalance of cardiac electrophysiology). iCEB: index of the cardio-electrophysiological balance; VF, ventricular fibrillation; VT, ventricular tachycardia; TdP, torsades de pointes. Other publication containing the figure in the manuscript include *Ann Noninvasive Electrocardiol* 2016, 21(3):294-304.

susceptibility. It is based on the concept that arrhythmias are more likely to occur when there is an imbalance between electrical properties (such as repolarization) and structural properties (such as fibrosis or scarring) of the heart. Structural VT/VF refers to abnormal rapid heart rhythms that originate in the ventricles (lower chambers of the heart) and are associated with structural abnormalities such as scar tissue or cardiomyopathy.

The iCEB can be used to help identify patients who are at risk for VT/VF and guide treatment strategies. A high iCEB suggests that the electrical properties of the heart are relatively preserved compared to structural properties and may indicate a greater risk for arrhythmias. Conversely, a low iCEB suggests a relative preservation of structural properties and a lower risk for arrhythmias. The management of patients with structural VT/VF depends on the severity and underlying cause of the condition. Treatment may include medications to control heart rate and rhythm, implantable devices such as defibrillators, or catheter ablation to target the abnormal electrical pathways in the heart.

Long QT Syndrome

In genotype-independent long the interval from the beginning of the QRS complex to the end of the T wave (QT) syndrome (LQTS) patients, iCEB is significantly higher than other putative risk factors such as Te-Tp.[16] The development of malignant arrhythmias in LQTS and Brugada syndrome (BrS) is likely due to genetically derived iCEB changes.[17]

Delays in the slow or fast components of LQT1, the KCNQ1 gene, and IKs are the most common causes of congenital LQTS, as is the acquisition of function of the cardiac sodium channel represented by the SCN5A gene (LQT3; SCN5A gene; Ina). An increase in iCEB could be the mechanism underlying the prolongation of action potential duration. The ability of flecainide to inhibit sodium channels is well known.[18] The SCN5A mutations result in sodium channel dysfunction, decreased sodium current, and thus decreased action potential.[19] The decrease in iCEB is most likely due to this effect on the action potential.[2]

Brugada Syndrome

Due to malignant VAs, BrS causes SCD. Type 1 BRS is more dangerous than type 2 BRS. BRS VAs occur as a result of abnormal conduction and repolarization. Higher transmural repolarization gradients detectable by QT dispersion are caused by regional differences in transient outward potassium channel activity.[20,21] Conduction and repolarization dispersion are increased in patients with type 1 BrS. This could explain why type 1 BRS has a higher VA.[22]

In LQTS, the QT interval lengthens due to the loss of the slow (IKs) or fast (IKr) IK function. In the treatment of class IC medications, blocking fast Na+ channels may reduce the iCEB. Reduced sodium current is the primary cause of an iCEB decrease in BrS, which results in cardiac sodium channel dysfunction. As a result, the upstroke velocity of phase 0 decreases. This leads to a prolonged QRS, as shown by the surface ECG. While LQTS has higher iCEB and iCEBc levels, BrS has lower iCEB and iCEBc levels. Class III drugs can suppress IKr, increasing the action potential's stage 3 and ERP.[23]

Myocardial Infarction

Research has shown that an imbalance in the activity of these 2 nervous systems can increase the risk of cardiovascular disease, including heart attacks. The iCEB is calculated based on HRV, which is a measure of the variation in time between successive heartbeats. A high iCEB indicates a greater balance between the sympathetic and parasympathetic nervous systems, which may be protective against heart attacks and other cardiovascular diseases. However, more research is needed to fully understand the relationship between the iCEB and cardiovascular health.[24]

Stroke

A stroke is a medical condition that occurs when blood flow to the brain is disrupted, either due to a blockage in a blood vessel or bleeding in the brain. This disruption of blood flow can lead to damage or death of brain cells, which can result in a range of symptoms, including weakness or paralysis on one side of the body, speech difficulties, vision problems, and cognitive impairment. There are several factors that can contribute to an imbalance in iCEB and increase the risk of stroke. These include high blood pressure, diabetes, high cholesterol, atrial fibrillation (an irregular heartbeat), and other heart conditions. To reduce the risk of stroke, it is important to maintain a healthy lifestyle, including regular exercise, a balanced diet, and avoidance of smoking and excessive alcohol consumption. Additionally, individuals with risk factors for stroke should work closely with their healthcare providers to manage their conditions and reduce their risk.[25]

Sudden Cardiac Death

Sudden cardiac death is an unexpected death due to cardiac causes that occur within a short time period, typically within one hour of the onset of symptoms. Sudden cardiac death is often caused by an abnormal heart rhythm called ventricular fibrillation, which prevents the heart from pumping blood effectively. The iCEB is thought to be a useful tool for predicting the risk of SCD in patients with heart disease. A low iCEB indicates that the electrical and mechanical properties of the heart are out of balance, which may increase the risk of SCD. On the other hand, a high iCEB suggests that the heart is functioning well and may be less likely to experience sudden cardiac events. While the iCEB is a promising tool for assessing the risk of SCD, more research is needed to determine its accuracy and usefulness in clinical practice. Additionally, it is important to note that the iCEB is just one of many factors that can contribute to the risk of SCD, and other factors such as age, sex, and underlying medical conditions should also be considered when evaluating an individual's risk.[26]

Cornerstone studies on iCEB were shown in Table 1.

Limitations

One could say that the idea that LQTS and BrS increase the risk of arrhythmias is not entirely true because of poor penetration and a positive genotype that shows itself in different ways. Sometimes it is riskier to have a dangerous mutation that does not cause any symptoms.[27] The iCEB is not independent of heart rate, and even healthy adults have QRS shortening at high heart rates.[28] Class I antiarrhythmic drugs are well known for their rate-dependent effects.[29] The rate-dependent expansion of the QRS duration demonstrates this. Bazett's approach to heart rate correction is less reliable in patients with LQTS and BrS because QT rate calculation is individual and is significantly affected in these patient groups.[30-32]

Conclusion

Increased iCEB is linked to sotalol-associated TdP and congenital LQTS. The BrS and Flecainide use is associated with decreased iCEB, but they also raise the possibility of non-TdP-mediated VT/VF. The iCEB may therefore serve as a marker for VA prediction. For our findings to be verified, further thorough investigations must be conducted.

Table 1. Cornerstone Studies on iCEB.

Reference no.	Authors	Subjects	Numbers	Main Theme	Results
Ref [4]	Ardahanlı et al	COVID-19 patients	63	The ICEB can monitor arrhythmias in COVID-19 patients receiving short-term therapy.	The ICEB rose following short-term hydroxychloroquine and azithromycin therapy, while QT and cQT intervals did not change.
Ref [5]	Li et al	The horses	34	It may be a novel cardiac electrophysiological animal model for studying sudden cardiac mortality in sports.	Horses can maintain electrophysiological stability despite elevated HRs. Horses may raise HRs to satisfy metabolic needs during exercise and racing.
Ref [6]	Kaufman et al	Heart failure with reduced ejection fraction (HFrEF) patients	24	Other therapeutic methods for intermediate-risk persons were debated.	Twenty-four LQTS experts were surveyed. Four complex clinical situations were provided to specialists from various colleges to explain their treatment recommendations. All 24 authors voted on case-specific considerations. Twenty-three writers voted, 1 abstained. Discussed voting outcomes. Diagnostic examination and beta-blocker usage were agreed upon.
Ref [7]	Sivri et al	End-stage renal disease (ESRD) patients	52	ESRD patients with elevated iCEB following Hemodialysis (HD) are at risk of TdP-mediated ventricular arrhythmia.	Compared to the control group, The interval from the beginning of the QRS complex to the end of the T wave (QT), corrected QT (QTc), The peak and the end of the T wave (Tp-e), Tp-e/QT, Tp-e/QTc, QT/ The deflections in an electrocardiogram (EKG) tracing that represent the ventricular activity of the heart (QRS), and QTc/QRS ratios were higher in the ESRD group ($P < .05$ for each). While QT and QTc intervals did not change after HD in ESRD patients, Tp-e, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS parameters increased significantly.
Ref [9]	Uzelac et al	- (Review)	- (Review)	In six species, we showed that semasbestic excitation wavelengths do not change the signal for one dye and can capture signals from another dye without cross-talk.	
Ref [11]	Ning et al	Rabbits	30	Contractility modulation reduces CHF-related myocardial structural and electrical remodeling.	The CHF group had a significantly prolonged corrected QT interval and ventricular ERP, and increased inducibility of ventricular tachycardia. Prominent myocardial fibrosis and increased hydroxyproline content were observed in the CHF group, but these were suppressed in the CCM group.
Ref [13]	Schurr et al	- (Review)	- (Review)	We discuss arrhythmogenic QT prolongation, repolarization anomalies, heart rate correction, and pharmaceutical therapy to screen for drug-induced long QT syndrome in ventricular pacing (VP) patients.	
Ref [15]	Chandler et al	Pediatric patients	190	Since there were no deaths or dangerous arrhythmias in this group, the number of bad things that happened to kids who started taking sotalol for atrial tachycardia, supraventricular tachycardia, or VT is low (3%).	The number of adverse events in pediatric patients taking sotalol for the first time to treat atrial tachycardia, supraventricular tachycardia, or VT is low (3%), and no deaths or dangerous rhythms have been reported in this series.
Ref [20]	Tse et al	BrS patients	29	Type 1 BrS patients have more ventricular arrhythmias due to increased conduction and repolarization dispersion.	Spontaneous type 1 BrS patients had similar iCEB and corrected iCEB to non-type 1. Higher QRS dispersion was seen in type 1 subjects
Ref [24]	Askin et al	CSF patients	100	Coronary slow flow (CSF) patients had elevated iCEB and iCEBc. CSF may cause malignant arrhythmias.	Tp-e/QTc ratio and intervals (QT and QTc intervals) were higher in the CSF group compared to controls. Compared to controls, iCEB and iCEBc were considerably higher.
Ref [25]	Castiglione et al	- (Review)	- (Review)	LQTS treatment is multimodal. Avoiding risk factors, QT-prolonging medications, and non-selective beta blockers is the treatment. Implantable Cardioverter Defibrillator (ICD) or pacemaker installation should be considered based on risk and lifestyle.	

BrS, Brugada syndrome; CCM, cardiac contractility modulation; CHF, chronic heart failure; CSF, coronary slow flow; ERP, effective refractory period; HRs, heart rates; iCEB, cardio-electrophysiological balance index; LQTS, long QT syndrome; VT, ventricular tachycardia.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception – L.A.; Design – L.A.; Supervision – O.T.; Resources -L.A.; Materials – O.T.; Data Collection and/or Processing – L.A.; Analysis and/or Interpretation – L.A.; Literature Review – O.T.; Writing – L.A.; Critical Review – O.T.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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