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Kardiyak Yeniden Şekillenme ile Kardiyo-Elektrofizyolojik Denge İndeksi Arasındaki İlişki

Association Between Cardilac Remodeling and the Index of Cardiac Electrophysiologic Balance

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Öz

Giriş ve Amaç: Miyokart enfarktüsüne yanıt olarak ortaya çıkan patofizyolojik değişiklikler, kardiyak yeniden şekillenme ile sonuçlanır. Tedavi edilmediği takdirde bu patolojik süreç, ventriküler fonksiyonun bozulmasına ve malign ventriküler aritmilerin gelişmesine neden olur. Son zamanlarda kullanılmaya başlanan EKG tabanlı kardiyo-elektrofizyolojik denge indeksinin çeşitli kardiyak durumlarla ilişkili olduğu gösterilmiştir. Bu çalışmada, miyokart enfarktüsü sonrası gelişen kardiyak yeniden şekillenme ile kardiyo-elektrofizyolojik denge indeksi arasındaki ilişkiyi araştırmayı amaçladık.
Gereç ve Yöntemler: Çalışmaya, Ocak 2020 ile Ocak 2021 arasında hastanemize akut miyokart enfarktüsü ile başvuran ve başarılı perkütan koroner girişim uygulanan 18 yaş ve üzeri hastalar dahil edildi. Kardiyak yeniden şekillenmenin değerlendirilmesi amacıyla; sol ventrikül (SV) kütlesi, sol ventrikül kütle indeksi (SVKİ) ve rölatif duvar kalınlığı (RDK), tedavi başlamadan önce ve işlemden altı ay sonra kardiyo-elektrofizyolojik denge indeksi parametreleri (QT/QRS, QTc/QRS) ile birlikte değerlendirildi.
Bulgular: Çalışmamıza göre, altı aylık takip sonunda QT/QRS ve QTc/QRS değerleri başlangıç değerlerine göre anlamlı derecede düşük bulundu (4.73∓0.60 vs 4.62∓0.55 & 4.93∓0.59 vs 4.78∓0.55, sırasıyla p<0.001). Başlangıç değerlerine kıyasla SV kütle ve SVKİ değerlerinde anlamlı düşüşler tespit edildi (208.85∓40.30 g vs 198.15∓37.18 g & 108.21∓19.84 g/m2 vs 103.49∓19.58 g/m2, sırasıyla p<0.001). Hem SV kütle hem de SVKİ, kardiyo-elektrofizyolojik denge indeksi parametreleri ile anlamlı bir korelasyona sahipti (p<0,001).
Sonuç: Sonuçlarımız, kardiyo-elektrofizyolojik denge indeksi parametrelerinin kardiyak yeniden şekillenmeyi öngörme açısından potansiyel olarak yararlı bir belirteç olabileceğini düşündürmektedir.

Anahtar Kelimeler: Kardiyo-elektrofizyolojik denge indeksi, kardiyak yeniden şekillenme, sol ventrikül kütlesi, sol ventrikül kütle indeksi.

Abstract

Objective: Pathophysiological changes in response to myocardial infarction (MI) result in cardiac remodeling. Left untreated this pathologic process contributes to impairment of ventricular function and development of malignant ventricular arrhythmias. Recently introduced ECG-based marker index of cardio-electrophysiological balance (iCEB) has been shown to be associated with various cardiac conditions. Herein, we aimed to investigate the association between the iCEB and cardiac remodeling in post-MI patients.
Materials and Methods: Patients aged ≥18 years presenting with acute MI who underwent successful percutaneous coronary intervention between January 2020 and January 2021 were recruited. Regarding the assessment of cardiac remodeling, left ventricular (LV) mass, LV mass index (LVMI), and relative wall thickness (RWT) were measured

before the start of treatment and six months after the procedure along with the QT/QRS ratio (iCEB), and QTC/QRS ratio (iCEBc).
Results: According to our study, estimated QT/QRS (iECB) and QTc/QRS (iECBc) ratios were found to be significantly lower at six-month follow-up compared to baseline values (4.73∓0.60 vs 4.62∓0.55 & 4.93∓0.59 vs 4.78∓0.55, p<0.001 respectively). There were significant reductions of estimated LV mass and LVMI at six-month follow-up compared to baseline values (208.85∓40.30 g vs 198.15∓37.18 g & 108.21∓19.84 g/m2 vs 103.49∓19.58 g/m2, p<0.001 respectively). Both LVM and LVMI had a significant correlation with iCEB and iCEBc (p<0.001).
Conclusion: Our results suggest that iCEB may potentially be a useful marker in terms of predicting cardiac remodeling.

Keywords: Cardiac remodeling, index of cardio-electrophysiological balance, left ventricular mass, left ventricular mass index,

1.Introduction

Myocardial infarction (MI) has unfavorable effects on the structural and functional properties of the myocardium. Due to the limited regenerative capacity of cardiomyocytes, MI survivors usually present with poor ventricular performance, defined as cardiac remodeling. This condition is commonly associated with heart failure and ventricular arrhythmias [1]. Therefore, several therapeutic interventions including, pharmacological approaches, percutaneous coronary intervention (PCI), and open surgery have been implemented to slow or reverse cardiac remodeling and reduce the risk of ventricular arrhythmias [2-4].

Recently a novel noninvasive marker which reflects the balance between cardiac depolarization and repolarization has been introduced. Index of cardio-electrophysiological balance (iCEB), measured as QT interval divided by QRS duration, serve as an ECG-based derivative of cardiac wavelength and is associated with malignant ventricular arrhythmias [5,6]. However, there is a paucity of data in the literature regarding the association between the iCEB and cardiac remodeling.

In this study, we aimed to investigate the association between the iCEB and cardiac remodeling in post-MI patients.

2. Material and Method

2.1 Study design and population

In this study, patients aged ≥18 years presenting with acute MI who underwent successful PCI between January 2020 and January 2021 were recruited. Diagnosis of acute MI was defined based on criteria by the European Society of Cardiology [7]. Patients with prior history of congestive heart failure, atrial fibrillation (AF), permanent cardiac pacemaker implantation, sick sinus syndrome, any kind of bundle branch blocks, pre-excitation syndromes, or atrioventricular blocks were excluded. Patients who were on medications known to affect cardiac conduction and those nonadherent to their medical treatment following the procedure were also excluded. All subjects were evaluated before the start of treatment and six months after the successful PCI. Patients' demographics, medical history, anthropometric measurements, medications, electrocardiographic and echocardiographic measurements were recorded. Informed consent was obtained from all patients in accordance with ethical guidelines of the 1975 Declaration of Helsinki protocol and approved by the Ethics Committee of Konya State Hospital (approval number: 11-22, date: 11.11.2021).

2.2 Coronary angiograms

PCI procedures were performed through the femoral or radial artery using 6 Fr or 7 Fr sheaths. All patients were treated with dual antiplatelet therapy including aspirin (162–325-mg), and clopidogrel (600 mg) loading dose, or ticagrelor (180 mg) loading dose prior to the procedure. Aspirin was continued indefinitely and clopidogrel or ticagrelor was recommended for 12 months. Other medications, including inhibitor of the angiotensin-converting enzyme (ACE) or angiotensin II type 1 receptor blocker (ARB), beta-blockers, nitrates, and statins were prescribed according to standardized protocols. Adjunctive pharmacotherapies, the type of stent, use of pre-dilatation, and post-dilatation were at the discretion of the interventional cardiologist. Epicardial coronary blood flow was quantified visually using the Thrombolysis in Myocardial infarction (TIMI) flow grade classification [8]. Procedural success was defined as residual stenosis < 20% and TIMI flow grade 3.

2.3 Echocardiographic evaluation

During the echocardiographic examination parasternal long-axis, short-axis, and apical 4-chamber and 2-chamber imageswere obtained and evaluated using M-mode, 2-D, continuous wave Doppler, pulse wave Doppler, and tissue Doppler methods according to American Echocardiography Society criteria [9]. M-mode and standard 2-dimensional (2D*)* echocardiographic evaluation were performed on all patients with TTE using Vivid S5 (GE Healthcare, Horten, Norway) 1-3 MHz transducer. All measurements were performed by a cardiologist who was blind to the patient data and study protocol and verified by a second physician to avoid errors in measurements.

With respect to evaluating cardiac remodeling, we used novel echocardiographic parameters including, left ventricular (LV) mass, LV mass index (LVMI), and relative wall thickness (RWT). In our study, the Devereux equation; LV mass = 0.8 × [1.04 × (interventricular septal thickness + left ventricular end-diastolic diameter + posterior wall thickness)^3 – (left ventricular end-diastolic diameter)^3] + 0.6 (g), was used to calculate left ventricular mass, [10]. LVMI was calculated by dividing an individual's LV mass by body surface area (body weight$^{0.425}$ × height$^{0.725}$ × 0.007184), [11]. RWT was also calculated by using the formula; 2 x

(posterior wall thickness/left ventricular end-diastolic diameter).

2.4 ECG interpretation

The standardization and interpretation of the ECG parameters were performed according to the guidelines of the American Heart Association and the Heart Rhythm Society [12]. The 12-lead ECGs were recorded at a gain of 10mm/mV and a paper speed of 25mm/s (Nihon Kohden, Tokyo, Japan) at rest in the supine position. All of the ECG recordings were sent to a digital platform to decrease the margin of error during evaluation and then a software (Adobe Photoshop) was used for magnification. An appropriate ECG was defined as at least 10 analyzable leads for the required measurements. Otherwise, the ECG was considered to be inadequate. Standard ECG parameters including heart rate (b.p.m.), P wave, QRS interval (ms), QT interval (ms), corrected QT (QT_C) interval (ms), QT/QRS ratio (iCEB), and QT_C/QRS ratio (iCEBc) were analyzed. ECG measurements were performed by a cardiologist who was blind to the patient data and verified by a second physician to avoid errors in measurements. An average value of three readings was calculated for each lead. QT interval was measured from the onset of the QRS complex to the point at which the tangent of the maximal downslope of the descending limb of the T wave crossed the isoelectric baseline and was corrected for heart rate with the Bazett formula: $cQT = QT\sqrt{(R–R\ interval)}$. QTc difference (V1-V6) was measured by subtracting the QTc in lead V6 from that in lead V1 and these intervals should be validated as the mean value from at least 3 to 5 cardiac cycles [13]. Finally, the iCEB and iCEBc were calculated from these measurements. Intraobserver and interobserver coefficients of variation (SD of differences between two observations divided by the mean value and expressed as percent) were found to be 1.0% and 1.6% respectively.

2.5. Statistical analysis

Data were analyzed with the SPSS software version 21.0 for Windows (IBM SPSS Statistics for Windows Version 21.0. Armonk, NY: IBM Corp, USA). In this study, data are expressed as mean±SD for continuous variables and as counts and percentages for categorical variables. The Kolmogorov-Smirnov's and Shapiro–Wilk test was used to evaluate the distribution of continuous variables. The $\chi 2$ test and Fisher's exact test were used to analyze categorical variables. Student's t-test was used for continuous variables with normal distribution and the values were presented as mean ± SD. Comparison of intergroup continuous variables without normal distribution was analyzed using Mann-Whitney U-test. Relationships between continuous variables were calculated by using Spearman's rank correlation coefficient. In all analyses, $p<0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Results

Of the 813 patients initially screened, 136 patients (66.9% men; mean age: 63.24±7.96 years) were enrolled. The patient characteristics are presented in Table 1.

Table 1. Comparison of baseline and sixth-month follow-up clinical and laboratory findings of patients

Variables						
Age				63.24±7.96		
Sex, n (%)	Female			45	(33.09)	
	Male			91	(66.91)	
Smoking history, n (%)				85	(62.50)	
DM, n (%)				54	(39.70)	
HT, n (%)				81	(59.55)	
Prior CAD, n (%)				69	(50.74)	
COPD, n (%)				36	(26.45)	
	Baseline		**6th month follow up**			***p*-value**
BMI, k/m^2	28.26±3.93		28.28±3.88			0.834
Total Cholesterol (mg/dL)	221.06±42.92		207.49±15.26			0.066
HDL (mg/dL)	33.63±12.92		38.26±10.32			0.052
LDL (mg/dL)	160.55±42.48		131.54±42.42			**0.006**
Triygliceride (mg/dL)	211.87±91.17		183.61±95.35			0.078
Glucose (mg/dL)	157.17±56.44		133.07±64.25			**0.015**
HbA1c (%)	7.18±1.68		6.88±1.08			**0.009**
Uric acid (mg/dL)	5.87±1.22		5.01±1.68			**0.002**
Creatinine (mg/dL)	0.91±0.23		1.05±0.36			**0.001**
eGFR (CKD-EPI)	99.73±23.46		82.57±27.71			**0.001**
WBC (10^3 /mm^3)	9.23±1.69		8.19±2.64			0.052
Hemoglobin (g/dL)	13.58±1.60		13.66±1.74			0.701
Platelet (10^3 /mm^3)	242.97±68.21		257.34±66.47			0.079
Neutrophil (10^3 /mm^3)	6.18±1,33		5.54±1,39			**0.001**
Lymphocyte (10^3 /mm^3)	2.26±0.65		2.25±1.74			0.966

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, BMI: body mass index, HDL: high-density lipoprotein, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, WBC: white blood cell

Follow-up outcomes of electrocardiographic measurements are presented in Table 2. According to our study, there were significant improvements in calculated QRS, QT, and QTc intervals ($p<0.05$). In addition, estimated QT/QRS (iECB) and QTc/QRS (iECBc) ratios were found to be significantly lower at six-month follow-up compared to baseline values (4.73 ∓ 0.60 vs 4.62 ∓ 0.55 & 4.93 ∓ 0.59 vs 4.78 ∓ 0.55, $p<0.001$ respectively). Baseline and follow-up echocardiographic measurements are presented in Table 3.

Table 2. Comparison of baseline and sixth-month follow-up electrocardiographic findings of patients

	Baseline	6th month follow-up	*p*-value
Heart rate, ms	69.22±8.68	68.12±4.98	0.051
P wave, ms	79.12±5.54	77.52±4.24	0.058
QRS, ms	98.06±13.03	96.13±12.27	**0.006**
QT, ms	459±49.17	440±53.91	**0.001**
QTc, ms	478.91±50.40	456.38±53.99	**0.004**
Tpe, ms	90.56±9.05	87.21±10.01	**0.001**
Tpe/QT	0.197±0.01	0.199±0.02	**0.228**
Tpe/QTc	0.189±0.01	0.191±0.02	**0.008**
iCEB	4.73±0.600	4.62±0.552	**<0.001**
iCEBc	4.93±0.593	4.78±0.558	**<0.001**

iCEB: index of cardiac electrophysiological balance, iCEBc: corrected index of cardiac electrophysiological balance, ms: millisecond

Table 3. Comparison of baseline and sixth-month follow up echocardiographic findings of patients

	Baseline	6th month follow-up	*p*-value
LVEF, %	47.74±11.17	53.9±8.55	**0.001**
LVEDD, mm	51.05±4.22	50.61±4.44	0.058
LVESD, mm	30.03±5.88	33.07±6.17	**0.026**
LA, mm	38.69±4.26	36.75±4.39	**0.001**
RA, mm	33.24±3.22	32.19±2.76	**0.004**
IVS, mm	90.56±9.05	85.21±10.01	**0.001**
PW, mm	100.3±1.36	98.68±1.14	0.058
LV mass, g	208.85±40.30	198.15±37.18	**<0.001**
LVMI, g/m^2	108.21±19.84	103.49±19.58	**<0.001**
RWT	0.428±0.069	0.421±0.042	**0.008**

LVEF: left ventricular ejection fraction, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: left atrium, RA: right atrium, IVS: interventricular septum, PW: posterior wall, LVMI: left ventricular mass index, RWT: relative wall thickness

According to our study, there were significant improvements in terms of changes in left ventricular ejection fraction (LVEF), left ventricular end-systolic (LVESD), left atrial (LA), right atrial (RA) diameter, and interventricular septum (IVS) thickness (p<0.05). Regarding echocardiographic indices of cardiac remodeling, there were significant reductions of estimated LV mass and LVMI at six-month follow-up compared to baseline values (208.85∓40.30 g vs 198.15∓37.18 g & 108.21∓19.84 g/m^2 vs 103.49∓19.58 g/m^2, p<0.001 respectively). This trend was also observed in RWT (0.428±0.069 vs 0.421±0.042, p=0.008).

Spearman's rank correlation coefficient analysis for LVM and LVMI showed that both LVM and LVMI had a significant inverse correlation with LVEF, iCEB, and iCEBc (p<0.001 for both comparisons); and a positive correlation with serum creatinine and eGFR (p<0.05 for both comparisons) (Table 4).

Table 4. Correlation of laboratory, electrocardiographic, and echocardiographic parameters with LV mass and LVMI in the entire study population

	LV Mass, g	LVMI, g/m^2
Creatinine (mg/dL)	0.232*	0.236*
eGFR (CKD-EPI)	0.279*	0.283*
QT, ms	–0.295*	0.124
QTc, ms	–0.269*	0.095
Tpe, ms	0.034	0.028
iCEB	–0.412**	–0.503**
iCEBc	–0.523**	–0.582**
LVEF, %	–0.443**	–0.511**
RA, mm	–0.029	0.188
LA, mm	–0.389*	–0.409**

*p<0.05, **p<0.001; Spearman's rank correlation

3.2. Discussion

In the present study, we investigated the association between the iCEB and cardiac remodeling in post-MI patients by using echocardiographic indices of cardiac remodeling. Our results indicate that improvement in iCEB is strongly associated with reverse cardiac remodeling.

It has been well established that pathophysiological changes in response to myocardial injury result in cardiac remodeling as well as development of adverse cardiac events [14]. Among the various known factors, MI is the most common etiologic factor associated with cardiac remodeling. Myocardial injury secondary to MI results in structural and functional changes in the infarcted area [15,16]. In response to myocardial injury following MI, cellular and molecular alterations occurring in the infarcted area begin rapidly and continue to proceed depending on the severity of the disease and associated factors. Left untreated this pathologic process contributes to impairment of ventricular function and development of malignant ventricular arrhythmias. Besides, ventricular dysfunction complicating MI significantly increases the risk of death [17-20]. Therefore, a better understanding of the predictors of cardiac remodeling in post-MI patients and administrating treatment modalities that are proven to improve this pathological condition is mandatory.

In this study, we used a novel ECG-based marker, index of cardio-electrophysiological balance (iCEB), not only for observing the impact of MI on ventricular functions but for evaluating the effects of applied therapeutic approaches on cardiac remodeling following MI. With respect to assessing ventricular functions and cardiac remodeling, we preferred echocardiographic indices of

cardiac remodeling including LV mass, LVMI, and RWT. Among the well-known parameters for determining cardiac remodeling, these echocardiographic indices give the most precise results and have been extensively validated in clinical practice. In addition, these geometrical indices are strongly associated with adverse cardiac events in various clinical conditions [21,22]. However, alterations in cardiac wavelength resulting from myocardial injury and its relation to geometrical indices of cardiac remodeling have yet to be determined.

According to our study, there was an absolute reduction in echocardiographic indices of cardiac remodeling in post-MI patients who underwent successful PCI accompanied by optimal medical treatment, and this reduction was strongly associated with improvements in calculated iCEB and iCEBc values. Despite the calculated several parameters, both iCEB and iCEBc showed the most significant correlation between the LVM and LVMI (p<0.001 for both comparisons). The iCEB is an ECG-based parameter that is equal to the cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity). Recent studies have shown that this parameter provides a more reliable prediction of cardiac proarrhythmic risk compared to other ECG parameters including Tp-e, Tp-e/QT, Tp-e/QTc. High iCEB values are associated with TdP, whereas low values are associated with non-TdP mediated VT/VF. According to those studies, there was a strong association between increased values of iCEB and the development of malignant ventricular arrhythmias following the administration of dofetilide, an IKr blocker. In addition, iCEB and iCEBc were significantly increased in genotype-positive congenital long QT syndrome (LQTS) patients [5,6]. Apart from those studies, estimated iCEB and iECBc ratios were found to be higher in patients with acute myocarditis compared to healthy control subjects which speculated as the underlying mechanism of increased frequency of ventricular arrhythmias in this patient population [23]. This relation was also observed in high risk patients with pulmonary embolism. According to a study conducted by Alsancak et al. hemodynamically unstable patients with pulmonary embolism who underwent thrombolytic therapy showed higher values of Tp-e/QT and Tp-e/QTc ratio compared with healthy control participants. They also observed a significant reduction in calculated iCEB and iCEBc values following thrombolytic therapy in this patient population. Considering the strong association between the impaired right ventricular functions and pro-arrhythmogenic status in patients with pulmonary embolism, they speculated that improvements in iCEB and iCEBc may predict reverse right ventricular remodeling in high risk patients following thrombolytic therapy [24].

Results of our study are compatible with the outcomes of previous studies that showed the strong association between the iCEB and increased risk of ventricular arrhythmias. Considering the strong link between cardiac remodeling and the development of ventricular arrhythmias, our study also confirmed that reverse cardiac remodeling is associated with decreased risk of ventricular arrhythmias.

Limitations

The major limitation of this study is participants were observed over a relatively short period. Randomized trials with long-term follow-up can provide more detailed information about the association between the iCEB and cardiac remodeling. It is also a relatively small, single-center study. In addition, we did not subgroup patients into STEMI and UNSTEMI and did not interpret the available parameters according to these subgroups. Finally, the determination of LV mass, LVMI, and RWT were limited by the availability and interpretability of conventional echocardiographic measurements. Assessment of those parameters by cardiac magnetic resonance imaging (MRI) or computerized tomography (CT) will provide more accurate results.

4. Conclusion

The present study highlights that successful revascularization accompanied by optimal medical treatment has favorable effects on LV geometry and iCEB. Our results suggest that iCEB may potentially be a useful marker in terms of predicting cardiac remodeling.

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