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Evaluation of index of cardiac-electrophysiological balance before and after hemodialysis in patients with end-stage renal disease

Serkan Sivri, M.D. *, Mustafa Çelik, M.D.

Department of Cardiology, Ahi Evran University Training and Research Hospital, Kırşehir, Turkey

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ABSTRACT

Background: Ventricular arrhythmias and sudden cardiac deaths are the most common cause of mortality in patients with end-stage renal disease (ESRD). Index of cardiac-electrophysiological balance (iCEB) (QT/QRS) may predict malignant ventricular arrhythmias. In this study, we investigated whether iCEB value is increased in ESRD patients and whether it changes before and after hemodialysis.

Methods: The study included 52 ESRD patients and 53 control subjects matched for age and comorbidities. Biochemical, electrocardiographic and echocardiographic values of all participants were recorded. QRS, QT, Tp-e were measured manually. QTC was calculated using Bazett's formula. Then, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS ratios were calculated. The changes in ECG parameters of the ESRD patients before and after HD were compared using paired *t*-test.

Results: Mean age and male sex ratio was comparable in both groups ($p = 0.448$ and $p = 0.777$, respectively). Comorbidity incidences, and biochemical parameters except eGFR ($p < 0.001$), albumin ($p < 0.001$), HDL cholesterol ($p = 0.03$) and platelet counts ($p < 0.001$) were comparable in both groups. Compared to the control group, QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS ratios were higher in the ESRD group ($p < 0.05$ 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.

Conclusion: In addition to ventricular repolarization dispersion indices in ESRD patients, iCEB elevation and increasing values after HD session indicate the increased risk of TdP-mediated ventricular arrhythmia after HD. Larger studies are needed to confirm our results.

Introduction

Despite the advancements in hemodialysis treatment, the most common cause of mortality with a rate of 24.3% in HD-dependent ESRD patients is still cardiovascular diseases such as arrhythmia and sudden cardiac arrest [1]. Sudden cardiac death (SCD) usually occurs due to ventricular arrhythmia developed secondarily to ventricular conduction and repolarization abnormalities, and this is a very complex and multifactorial process [2] with factors including co-existing coronary artery disease, left ventricular hypertrophy, diabetes, electrolyte, acid-base imbalance, and plasma volume changes [3].

The QT interval (or corrected QT [Corrects the QT interval for heart rate extremes.]) is that the total duration of ventricular depolarization and repolarization which is a highly dynamic process due to electrolyte shifts (especially, potassium, calcium and magnesium) [4], acidosis, various medications, co-existing cardiac disease [5], changes in autonomic tone, and genetics. QT, QTc interval, QT dispersion (QTd) (defined as maximum QT interval minus minimum QT interval), the T peak-to-end (Tpe) interval and the Tpe/QT ratio predict the spatial dispersion of ventricular repolarization, and they are parameters predicting the risk of ventricular arrhythmia with being demonstrated to be increased in ESRD patients compared to the healthy controls [6–8]. However, so far, there has been no generally accepted ECG parameter or an index which can provide a risk classification for SCD [7,9,10].

Index of cardiac-electrophysiological balance (iCEB) (QT/QRS of the electrocardiogram) is a novel and non-invasive marker, which can predict malign ventricular arrhythmias. It is suggested that the iCEB is equivalent to the cardiac wavelength λ (λ = effective refractory period [ERP] × conduction velocity [CV]). Therefore, both increased and decreased iCEB values are associated with ventricular proarrhythmic risk [11]. In this study, we aimed to investigate whether the iCEB values were different compared to the control group and whether they changed with hemodialysis, in patients with ESRD.

* Corresponding author at: Department of Cardiology, Ahi Evran University Training and Research Hospital, Kırşehir Post Code: 40 100, Turkey.
E-mail address: drserkansivri@gmail.com (S. Sivri).

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Methods

Study population

Ninety-six ESRD patients who were receiving routine dialysis treatment in our hospital's hemodialysis unit were evaluated between May and September 2018, and 52 of them were included into the study. Fifty-three control subjects matched for age and comorbidity were included into the study as control group. Patients with pacemaker ($n = 2$), bundle branch block ($n = 13$), atrial fibrillation (n = 13), unmeasurable T waves ($n = 9$), congestive heart failure ($n = 5$), moderate to severe valvular heart disease ($n = 3$), thyroid dysfunction ($n = 2$), acute and chronic infections or inflammatory diseases ($n = 4$), or using antiarrhythmic drugs that lengthen the QT interval ($n = 3$) were excluded from the study.

Blood sample was obtained before HD from each patient for the measurement of complete blood count, liver and kidney function tests and bleeding profile. Twelve-hour fasting serum lipid profiles were measured by standard enzymatic methods. Just before and immediately after HD, 12-leads standard ECG were recorded using a MAC 2000 (GE Medical Systems Information Technologies, Inc., 8200 W, Tower Avenue, Milwaukee, WI, USA) electrocardiograph at paper speed of 25 mm/s and 50 mm/s and 10 mm/mV, 0.05–40 Hz. Transthoracic echocardiographic (Vivid 7 Dimension, GE Medical Systems, Horten, Norway) evaluation was performed for each patient.

All patients gave informed consent to participate in the study and the Institutional Ethics Committee on Human Research approved the study protocol.

ECG interpretation

All of the ECG papers were scanned and transferred to the digital media, and the digital records were analysed under ×300% magnification in a personal computer. The measurements were obtained in five consecutive complexes of lead V5 [12–14] and the resulting average value was finally accepted. The QT interval was defined as the time between the start of the Q wave and the end of the T wave. We measured the Tp-e interval by using the tangent method, which defines to the time interval between the peak of the T wave and downslope tangent intersecting with the isoelectric line [15]. QRS interval, QT interval and Tp-e interval were measured manually. QTc intervals were obtained using Bazett's formula ($QTc = QT/RR^{-2}$). Then, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS ratios were calculated.

All measurements were taken separately by two different cardiologists who were blind to the clinical and laboratory signs of the patients, and the mean values were transferred to database. The interobserver and intraobserver coefficients of variation were 3.2% and 2.4%, respectively.

Statistics

The statistical analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA) and G-power version 3.1.9.4. Continuous variables are expressed as mean ± standard deviation and 95% Confidence interval. The examination of normality was performed by the Kolmogorov-Smirnov and Shapiro-Wilk tests. Paired *t*-test was used for the comparison of pre- and post-dialysis ECG parameters. Independent *t*-test was used for the comparison of ESRD patients group and control group. *P* value being below 0.05 was considered to be clinically significant.

Results

Baseline clinical, biochemical, echocardiographic, and electrocardiographic characteristics of the ESRD patients (n: 52) and the control group (n: 53) are shown in Table 1.

Table 1
Baseline clinical, laboratory, and electrocardiographic characteristics of the ESRD patients and the control group.

	ESRD patients (n: 52)	Control group (n: 53)	P value
Age (years)	58,7 ± 12,4	56,8 ± 12,6	0,448
Sex (males, %)	25 (48,0%)	24 (45,2%)	0,777
BMI (kg/m^2)	26,4 (23,8–28,9)	28,6 (26,9–30,3)	0,130
DM (n, %)	19 (36,5%)	13 (24,5%)	0,163
HT (n, %)	35 (67,3%)	32 (60,3%)	0,385
HL (n, %)	6 (11,5%)	7 (13,2%)	0,826
Smoking rate (n, %)	5 (9,6%)	11 (20,7%)	0,124
CAD (n, %)	11 (21,1%)	11 (20,7%)	0,920
Glucose (mg/dL)	116,8 ± 57,4	116,6 ± 44,0	0,983
eGFR (mL/min)	5,0 ± 1,47	87,5 ± 16,7	<0,001
Total protein (g/dL)	7,0 ± 0,4	7,1 ± 0,3	0,178
Albumin (g/dL)	4,1 ± 0,3	4,4 ± 0,2	<0,001
Triglyceride (mg/dL)	188,6 ± 129,3	180,7 ± 123,4	0,763
Total cholesterol (mg/dL)	176,4 ± 27,1	181,1 ± 30,5	0,429
LDL cholesterol (mg/dL)	105,0 ± 20,9	109,2 ± 33,4	0,469
HDL cholesterol (mg/dL)	41,9 ± 8,6	46,3 ± 10,7	0,030
WBC (K/uL)	7,60 ± 2,39	8,11 ± 2,16	0,269
Platelet (K/uL)	212,0 ± 60,8	267,3 ± 59,4	<0,001
MPV (fL)	10,4 ± 1,0	10,2 ± 0,8	0,497
hsCRP (mg/L)	0,80 ± 0,99	0,45 ± 0,46	0,053
LVEF, %	58,7 ± 5,8	60,3 ± 6,9	0,411
Electrocardiographic parameters			
Heart rate (beats/min)	76,3 ± 11,0	77,4 ± 11,4	0,626
QT (ms)	378,5 ± 37.52	347,5 ± 27.50	<0,001
QTc (ms)	423,4 ± 28.88	392,1 ± 26.09	<0,001
QRS (ms)	97,0 ± 19.68	98,4 ± 11.21	0,655
Tp-e (ms)	75,6 ± 12.61	64,1 ± 9.74	<0,001
Tp-e/QT	0,202 ± 0.04	0,185 ± 0.03	0,020
Tp-e/QTc	0,179 ± 0.03	0,164 ± 0.02	0,010
iCEB (QT/QRS)	4,02 ± 0.73	3,56 ± 0.43	<0,001
iCEBc (QTc/QRS)	4,42 ± 1.01	4,02 ± 0.73	0,010

BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; eGFR, glomerular filtration rate; HDL, high density lipoprotein; HL, hyperlipidemia; hsCRP, high-sensitive C-reactive protein; HT, hypertension; iCEB; index of cardio-electrophysiological balance, iCEBc; corrected index of cardio-electrophysiological balance; LDL, low density lipoprotein; LVEF, left ventricle ejection fraction; MPV, mean platelet volume; WBC, white blood cell.

The mean age and male sex of the ESRD group (58.7 years) was comparable with that of the control group (56.8 years) ($p = 0.448$ and $p = 0.777$, respectively). The incidence of comorbidities such as DM, HT, HL, CAD, BMI, and smoking rate were comparable between two groups ($p > 0.05$ for each). And also the laboratory parameters such as glucose, total protein, albumin, triglyceride, LDL cholesterol, WBC, MPV, and hsCRP were comparable between two groups ($p > 0.05$ for each). However, eGFR ($p < 0.001$), albumin ($p < 0.001$), HDL cholesterol ($p = 0.03$) and platelet counts ($p < 0.001$) were statistically different. In the electrocardiographic characteristics, QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS were higher in the patient group compared to the control group ($p < 0.05$ for each). QRS interval was comparable in both groups ($p = 0.655$).

According to the result of paired *t*-test which was performed to detect the changes in pre- and post-HD ECG parameters, there was no significant change in QT ($p = 0.873$) and QTc ($p = 0.987$) intervals; but, statistically significant increase was observed in Tp-e, Tp-e/QT, Tp-e/QTc, QT/QRS, and QTc/QRS after HD ($p < 0.05$ for each). QRS interval was decreased significantly after HD ($p = 0.007$) (Table 2).

Discussion

In our study in which we assessed the ventricular repolarization parameters in ESRD patients and evaluated the changes in these parameters after dialysis session, QT, QTc, Tp-e, Tp-e/QT, Tp-e/QTc, iCEB and iCEBc parameters were significantly different in the patient group compared to the control group, and these values, except for QT and QTc, significantly increased after HD session in the patient group.

Table 2
Comparison of electrocardiographic parameters before and after hemodialysis.

Variables	Before HD	After HD	95% confidence interval of the difference (lower; upper)	P value
Heart rate (beats/min)	76,3 ± 11,0	77,3 ± 14,3	(−4.10; 2.10)	0,694
QT (ms)	378,5 ± 37.52	377,3 ± 38.97	(−6.21; 8.63)	0,873
QTc (ms)	423,4 ± 31.83	423,5 ± 28.88	(−7.73; 7.92)	0,987
QRS (ms)	97,0 ± 19.68	87,8 ± 13.91	(4.47; 13.96)	0,007
Tp-e (ms)	75,6 ± 12.68	90,9 ± 12.89	(−19.47; −10.77)	<0,001
Tp-e/QT	0,202 ± 0.04	0,242 ± 0.03	(−0.05; −0.027)	<0,001
Tp-e/QTc	0,179 ± 0.03	0,215 ± 0.02	(−0.04; −0.02)	<0,001
iCEB (QT/QRS)	4,02 ± 0.73	4,38 ± 0.76	(−0.56; −0.16)	0,016
iCEBc (QTc/QRS)	4,42 ± 0.80	4,91 ± 0.73	(−0.64; −0.17)	0,006

Pre- and post-dialysis SCD risk is increased in ESRD patients. While pre-HD increased SCD risk is usually associated with non-VF, bradyarrhythmia especially due to hyperkalemia, post-HD risk is associated with fatal ventricular arrhythmia due to prolonged QT [16]. Studies have shown that ESRD patients have prolonged QTc interval and this is associated with ventricular arrhythmia, SCD and total mortality [17,18]. There are contradicting results in the QTc interval change after hemodialysis sessions performed in this patient group. While many of the studies have emphasized that QTc interval is increased during or right after HD session [2,19,20], some studies have observed that hemodialysis has a neutral [8,21], or even negative effect on this interval [22]. Current evidence holds the shift of electrolytes such as potassium and calcium during hemodialysis responsible for the QT interval prolongation. The emphasis is especially made on the difference between pre-HD corrected total serum calcium level and dialysate calcium level also known as high calcium gradient [16]. The reason for different results was considered to be caused by comorbid diseases, cardiac diseases -especially left ventricular hypertrophy-, and variability in electrolyte concentrations.

Electrocardiographic T-wave shows ventricular repolarization. The Tp-e interval, which is the interval between the peak and the end of a single T wave, and also ratios like Tp-e/QT and Tp-e/QTc, more sensitively than Tp-e, are novel parameters predicting the ventricular repolarization dispersion [23,24]. Tp-e and Tp-e/QT ratio have been demonstrated to be increased in cardiac diseases such as long QT syndrome, short QT syndrome, Brugada syndrome and acute myocardial infarction with increased malignant ventricular arrhythmia risk, and also non-cardiac diseases such as obstructive sleep apnea, psoriasis and autoimmune hepatitis [24–27]. Tp-e and Tp-e/QT ratio have been investigated in two studies performed in ESRD patients. In the first study, QT dispersion and Tp-e [28], and in the study by Kalantzi et al. in 66 patients [8], Tp-e and Tp-e/QT have been observed to statistically significantly increase compared to the baseline values. Consistent with these results, Tp-e and Tp-e/QT values statistically significantly increased after HD session in our study.

Index of cardiac-electrophysiological balance (ratio of QT/QRS or JT/QRS of the ECG) is a non-invasive parameter showing the risk of ventricular proarrhythmia. As QT or JT interval is comparable with ERP, and QRS interval change with CV, iCEB can provide information about both the depolarization and repolarization phases of the cardiac action potential. Thanks to this aspect, it can better predict the cardiac proarrhythmic risk than T-wave transmural dispersion and QT interval instability showing only repolarization [29]. High iCEB values are associated with TdP, and low values with non-TdP mediated VT/VF [29]. There are not many studies in the literature on iCEB. In their study, Nafakhi et al. have found that high iCEB values in the group who underwent imaging using computerized tomographic angiography due to suspected CAD are associated with increased pericardial fat volume [30]. In their study in acute myocarditis patients, Yumurtacı et al. have shown that Tp-e, Tp-e/QT, Tp-e/QTc and iCEB values are significantly higher in the group with arrhythmia compared to the group without arrhythmia [31]. A recent study has shown that compared to the healthy controls, iCEB and iCEBc values are also increased in rheumatoid arthritis patients known to have a higher risk of SCD compared to the healthy individuals [32]. In our study, we observed that iCEB and iCEBc values are higher and more increased after HD session in ESRD patients compared to the healthy controls.

Limitations

Our study has a few limitations. First one is the low number of patient and being a single-center study. Secondly, the patients were not followed up in terms of clinical events such as malignant ventricular arrhythmia and SCD development, and their ECG changes. Thirdly, robust heartbeat detection using multimodal recordings and ECG quality assessment with signal amplitudes dispersion was not used in our study. Fourthly, online tools that can do analysis of the digital signal of the ECG were not used. Lastly, the presence of an association between the pre- and post-HD electrolyte, arterial pH, bicarbonate (HCO_3^-), and fluid changes, and Tp-e, Tp-e/QT, Tp-e/QTc and iCEB parameters was not evaluated.

Conclusion

To the best of our knowledge, there is no study investigating iCEB parameter in ESRD patients in the literature. In our study, we observed higher Tp-e, Tp-e/QT, Tp-e/QTc, and iCEB parameters and more increased values after HD in the patient group compared to the control group suggesting that TdP-associated malignant ventricular arrhythmia risk increases after HD. Larger studies on this subject are needed to confirm our results.

Conflict of interest

The authors declare that there is no conflict of interests.

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