Spatial QRS-T angle in peritoneal dialysis patients: association with carotid artery atherosclerosis, coronary artery calcification and troponin T

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Abstract

Background. Abnormal values of the spatial angle between the directions of ventricular depolarization and repolarization (QRS-T) predict potently arrhythmic events and mortality in various patient groups. The study was designed to estimate QRS-T in a group of peritoneal dialysis (PD) patients, and to assess the possible association between QRS-T and coronary artery calcification (CAC), atherosclerosis, and some biochemical measurements.

Methods. The angular differences between the maximum spatial QRS and T vectors were reconstructed from ECGs in 57 selected PD patients and in 54 controls. In patients CAC score was performed by using multi-row computed tomography. Atherosclerotic disease was assessed by measuring carotid arteries' intima-media thickness (IMT) and plaque score (sum of the maximum thicknesses in mm of all plaques on both sides) by using an ultrasound scanner.

Results. QRS-T was higher in patients compared with controls (34.79% B111.97 and 14.95% B17.87 respectively; \( P < 0.001 \)). Median CAC score equalled 104.5 Agatson units (Au) (range, 0–2478). IMT was 0.832% B10.208, and atherosclerotic plaques were detected in 82.5% of patients. The plaque score was 7.97% B14.49. QRS-T was higher in patients with CAC score >400 Au compared with patients with CAC score <400 Au \( (P = 0.011) \). The results of univariate linear regression analysis showed correlation between QRT-T and dialysis duration \( (r = 0.305, P = 0.020) \), LVMI \( (r = 0.311, P = 0.017) \), HDL \( (r = -0.361, P = 0.006) \), cTnT \( (r = 0.442, P < 0.001) \), plaque score \( (r = 0.403, P = 0.001) \) and CAC score \( (r = 0.451, P < 0.001) \).

On multivariate analysis, CAC score, plaque score and troponin T were found to be independent predictors of QRS-T values.

Conclusions. QRS-T is high in PD patients and is mainly associated with coronary artery calcium burden, atherosclerosis and troponin T elevation. The possible clinical importance of the higher QRS-T in PD patients remains to be confirmed in further studies.

Keywords: arrhythmias; atherosclerosis; peritoneal dialysis; QRS-T angle; vascular calcification

Introduction

End-stage renal disease (ESRD) is associated with substantially increased risk for cardiovascular (CV) disease morbidity and mortality. Sudden cardiac death (SCD), in most cases arrhythmic death, accounts for ∼26% of all death in ESRD patients [1]. CV pathology in patients with ESRD is complex and multifactorial in origin. An increasing body of evidence suggests, however, that either accelerated atherosclerosis or vascular calcification plays an important role in the pathogenesis of CV disease, and accounts for the alarmingly high prevalence of coronary artery disease in ESRD patients. Moreover, not only is the prevalence of coronary artery disease very high in ESRD patients, but also is the case fatality rate of cardiac events [2–4]. Therefore, early selection of patients at risk for cardiac events is crucial in the population of ESRD patients.

The noninvasive identification of individuals at risk for CV events and especially SCD presents a significant clinical dilemma. It is generally considered, however, that standard ECG has limited utility to predict the risk for SCD in common cardiac diseases such as coronary artery disease and dilated cardiomyopathy [5]. Recently, there has been renewed interest in the spatial angle between the three-dimensional vectorcardiographic representation of QRS complex and T-wave loops (QRS-T) to quantify ventricular repolarization and depolarization. Depolarization abnormalities reflect ventricular structural abnormalities (damage and/or hypertrophy), whereas repolarization abnormalities represent heterogeneities associated with electrical instability and SCD [6]. The QRS-T is a combined...
measurement of the electrical activity of the heart. Several studies have validated the role of the QRS-T as a sensitive, powerful and independent risk stratifier for cardiac events either in various clinical settings [7–11] or in the general population [6], probably especially suited for the prediction of sudden arrhythmias death [9,12].

To the best of our knowledge there are no data in the literature on differences of the QRS-T between peritoneal dialysis (PD) patients and healthy subjects. Moreover, associations between VCG spatial parameters and carotid artery atherosclerosis or coronary artery calcification (CAC) have never been evaluated either in the dialysis patients or other patient groups.

We designed this study with two objectives: (1) to estimate the potential difference in the QRS-T between selected PD patients and healthy subjects and (2) to assess the possible association between QRS-T and coronary artery calcium burden, atherosclerosis and selected biochemical measurements.

**Methods**

**Patients**

Fifty-seven patients (29 females and 28 males), aged 25–57 years (mean 47.7 ± 7.1), who remained on continuous ambulatory peritoneal dialysis (CAPD) from 6 to 78 months (mean 37.7 ± 22.4) were selected from a larger group of patients. Patients were treated with four 2000 ml (2500 ml in five patients) exchanges per day using Baxter Twin Bag (Baxter AG, Ljubljana, Slovenia) and Fresenius A.N.D.Y. Plus or stay safe systems (Fresenius Medical Care, Bad Homburg, Germany). In six patients, one bag was an icodextrin solution. Informed consent was obtained in each case, and the studies were approved by members of the local committees of ethics. The causes of ESRD were glomerulonephritis (n = 19), diabetes (n = 12), interstitial nephritis (n = 10), renal vascular disease (n = 3), hereditary nephropathy (n = 1), analgetic nephropathy (n = 2) and unknown/uncertain (n = 10). All patients were dialyzed for ≥6 months and were clinically stable over the period of at least 3 months prior to the assessment (i.e. displaying no symptoms of acute coronary events, infectious or noninfectious inflammatory disease, including dialysis-related peritonitis). Patients with old myocardial infarctions, ischaemic heart disease (Canadian CV Society class >1), heart failure (New York Heart Association class >II) and ejection fraction <40% or Kt/V value <1.85 were excluded to avoid some known or potential factors that might influence QRS-T values. Patients exhibiting electronic pacing as well as Wolff-Parkinson-White syndrome were also excluded. Out of 57 patients who qualified to the study, 37 (64.9%) were taking angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 35 (61.4%) beta-blockers and 32 (56.1%) calcium blockers.

**Control group**

Fifty-four subjects took part as a control group; the group’s gender distribution (27 females and 27 males) and age range (24–60 years, mean 47.2 ± 8.5) were similar to the group of patients. Controls were selected from patients who came for routine physical checkups, having no abnormalities detected by physical examination, ECG, chest X-ray and laboratory analysis.

**Twelve-lead vectorcardiogram (VCG)**

Surface 12-lead resting ECGs were recorded at the same hours of the day (between 09.00 and 11.00) with a computer-based electrocardiograph (Cardioperfect, version 1.1, CardioControl NV, Rijswijk, The Netherlands). All 12 leads of each ECGs were recorded simultaneously for 300 s. VCG was conducted while subjects were lying in the supine position, breathing normally with abdomen filled with peritoneal fluid.

To derive VCG descriptors, X, Y and Z leads were reconstructed from the 12 leads. The projections of the maximum QRS-T vectors on the frontal (xy), horizontal (xz) and right sagittal (yz) planes were automatically calculated by electrocardiograph. According to previously published trigonometric equations [13], the amplitudes of maximum spatial QRS-T vectors as well as the angular difference between the maximum spatial QRS-T vectors were calculated from the following formulas:

\[
\text{The amplitude of the maximum spatial T vector (T}_{\text{MAX}} = \sqrt{(T_{xy}^2 + T_{xz}^2 + T_{yz}^2)/2}\]

where \(T_{xy}\), \(T_{xz}\) and \(T_{yz}\) are projections of the maximum T vector on the frontal, horizontal and right sagittal planes, respectively.

\[
\text{The amplitude of the maximum spatial QRS (QRS}_{\text{MAX}} = \sqrt{(QRS_{xy}^2 + QRS_{xz}^2 + QRS_{yz}^2)/2}\]

where \(QRS_{xy}\), \(QRS_{xz}\) and \(QRS_{yz}\) are projections of the maximum QRS vector on the frontal, horizontal and right sagittal planes, respectively.

\[
\text{Cos QRS – T angle} = (QRS_x T_x + QRS_y T_y + QRS_z T_z)/(QRS_{\text{MAX}} \times T_{\text{MAX}}).
\]

where \(QRS_x\), \(QRS_y\) and \(QRS_z\) are projections of the maximum QRS vectors on the X, Y and Z planes, respectively, and \(T_x\), \(T_y\) and \(T_z\) are projections of the maximum T vectors on the X, Y and Z planes, respectively.

QT intervals values were adjusted for heart rate according to Fridericia’s formula (\(QT_{CF} = QT/RR^{3/2}\)).

**Evaluation of carotid atherosclerosis**

Examination of the carotid arteries was performed in a B-mode presentation using the ultrasound system GE LOGIQ 500 with a 6–12 MHz linear transducer. Intima-media thickness (IMT) measurements were performed bilaterally in plaque-free arterial segments on the far wall of the common carotid arteries and internal carotid arteries, in the diastolic phase of the heart cycle. In the case of the common carotid arteries, measurements were performed 2–4 cm proximally to the bifurcation. In the case of internal carotid arteries, measurements were performed 1–3 cm from the
carotid bifurcation. Three measurements from both sides were averaged to give the mean.

Carotid artery plaques were examined in longitudinal and transverse projections. The number and thickness of plaques were measured from both carotid systems. The plaque score was computed by summing maximum thickness in millimetres of plaques in each segment on both sides [14]. All ultrasound studies were performed by the same expert investigator (A.D.Z), who was blinded to patients’ clinical and laboratory data. The intraobserver coefficient of variation was 7.3%.

Evaluation of CAC

Multidetector computed tomographic examinations were carried out with a 64-slice scanner (LightSpeed VCT, GE Health Systems, Milwaukee, WI, USA). The native scans were performed using prospective ECG gating at 70% of the cardiac cycle, 120 kV, 200–250 mA, 1.2-mm slice collimation and 0.5 s gantry rotation. Tomographic imaging proceeded from the level of the carina to the diaphragm. The entire heart was covered in a single breath hold. All images from multi-slice CT were transferred to a dedicated workstation (Advantage Windows 4.2 with GE SmartScore software - General Electric Health Systems, Milwaukee, WI, USA). The calcification score was evaluated according to the algorithm suggested by Agatson et al. [15]. All pixels with density >130 Hounsfield units were automatically highlighted in colour on the images. The individual calcification scores were calculated for the right coronary artery, left main, left anterior descending and left circumflex branch of the left coronary artery. Scores were summed to calculate the total coronary calcification score. The final score was expressed in modified Agatson units (Au) [15], and patients were classified according to the classification system proposed by Rumberger et al. [16] as presenting no or minimal (<10 Au), moderate (11–100 Au), significant (101–400 Au) or severe calcification (>400 Au).

Biochemical measurements

The following parameters were measured by automated analysers: serum sodium, potassium, magnesium, calcium, phosphate, creatinine, urea, intact parathormonu (i-PTH), haematoctrit, haemoglobin (Hb), albumin, C-reactive protein (CRP), total cholesterol, high-density lipoprotein (HDL cholesterol) cholesterol and triglycerides. Low-density lipoprotein (LDL cholesterol) cholesterol was calculated using the Friedewald equation: 

$$LDL = \frac{(Total\ cholesterol\ (mg/dl) - HDL\ cholesterol\ (mg/dl))}{(triglycerides\ (mg/dl))}$$

Cardiac troponin T (cTnT) in plasma was measured by the electrochemiluminescence immunoassay (Elecsys 2010 analyser, Roche Diagnostics) with a detection limit of 0.01 µg/l. Blood was obtained after at least 10 h fasting.

Mean blood pressure

Mean blood pressure (MBP) was calculated from the following standard equation: 

$$MBP = \frac{1}{3}\ of\ the\ systolic\ blood\ pressure + \frac{2}{3}\ of\ the\ diastolic\ blood\ pressure.$$
Sodium (mmol/l) 137.9

Total-cholesterol and atherosclerotic plaques were detected in 47 patients. IMT of the common carotid artery was 0.832 ± 0.166 and 45.86 ± 21.76.

Ca × P score (mg/dl²) 48.51 ± 10.62

Total-cholesterol (mg/dl) 217 ± 41

LDL-cholesterol (mg/dl) 129 ± 21.7

HDL-cholesterol (mg/dl) 42.5 ± 9.4

Triglycerides (mg/dl) 226 ± 82

Albunin (g/dl) 3.69 ± 0.54

CRP (mg/dl) 7.41 range (0.82–19.8)

PTH (pg/ml) 332 range (9–1351)

Troponin T (µg/l) 0.069 range (0.00–0.39)

Kt/V (n) 2.09 ± 0.13

CRP = C-reactive protein; PTH = parathormone; NA = not applicable; ND = not done; NS = not significant.

*Except for PTH and CRP levels—presented as median and range.

Table 2. The ECG, VCG and echocardiographic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients (mean ± SD)</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>81.1 ± 4.89</td>
<td>71.8 ± 3.64</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>427.6 ± 28.5</td>
<td>376.8 ± 18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVMi (g/m²)</td>
<td>143.4 ± 37.1</td>
<td>113.1 ± 16.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spatial QRS-T angle (°)</td>
<td>34.79 ± 11.97</td>
<td>14.95 ± 7.87</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QRS-T angle/LVMi</td>
<td>0.245 ± 0.105</td>
<td>0.131 ± 0.081</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR = heart rate; QTcF = QT interval corrected for heart rate using the Fridericia formula; LVMi = left ventricular mass index.

The number of plaques ranged between 0 and 11 (mean 3.76 ± 2.93). The mean plaque score was 7.97 ± 4.49 mm.

The results of univariate linear regression analysis (Pearson test) showed significant correlations between spatial QRS-T and dialysis duration (r = 0.305, P = 0.020), LVMi (r = 0.311, P = 0.017), spatial QRS-T and dialysis duration (r = 0.295, P = 0.06), PL (r = 0.403, P = 0.001), cTnT (r = 0.442, P < 0.001) and CAC score (r = 0.451, P < 0.001). Adjusting for LVMi did not eliminate the relationship between QRS-T and PL (r = 0.353, P = 0.009), cTnT (r = 0.360, P = 0.006), plaque score (r = 0.427, P < 0.001) and CAC score (r = 0.457, P < 0.001).

The results of multiple regression analysis showing independent variables influencing the QRS-T are presented in Table 4. The independent predictors of QRS-T values were (1) CAC score (2) plaque score and (3) cTnT level.

Discussion

Our study generated two major findings: (1) QRS-T was increased (more than twofold) in CAPD patients compared with healthy subjects; (2) CAC scores, plaque score values, and cTnT levels were found to be independent predictors of the QRS-T.

Several recent studies have demonstrated that increased QRS-T, which reflects increased repolarization heterogeneity, is a strong and independent predictor of either cardiac events or cardiac and arrhythmic death. The role of QRS-T as a risk stratifier has been established both in general population and in some clinical settings such as, among others, coronary heart disease, myocardial infarction, LVH, hypertension or in patients with diabetes [6–11,18–20].
The prevalence of coronary artery disease in dialysis patients is high, and acute myocardial infarction contributes to a great extent to the steep mortality in ESRD population [1,2]. According to our knowledge, ours is the first study that shows that QRS-T increased in PD patients, and the difference remained significant also after adjustment for LVMI. It is difficult, however, to compare directly our results to the available data from other populations. This is largely due to different methodological standards of the QRS-T measurements, which included calculations based on QRS and T-wave areas [7], integration of angles between parts of the QRS-T [18] and trigonometric calculations between vectors of maximum spatial amplitude [6,20]. It is important to note that the relationship between these expressions is weak [12]. In our study, QRS-T was higher (34.79 ± 11.97) than that in subjects with type 2 diabetes (25.6 ± 11.8) in whom the same standards of the QRS-T measurements were used [20]. Further studies are required to confirm our preliminary results in a larger group of ESRD patients and determine the possible clinical importance of abnormal QRS-T in dialysis patients, especially the relationship between QRS-T and CV as well as arrhythmic death.

We have demonstrated that carotid atherosclerosis was an independent predictor of the QRS-T. In ESRD patients the main cause of CV events contributing to a high rate of mortality in an ESRD population is atherosclerotic coronary disease [4]. Autopsy and clinical studies have shown that atherosclerotic changes located in the carotid artery mirror either general atherosclerosis or coronary artery lesions [21]. Carotid atherosclerosis is considered a strong and independent predictor of either coronary and cerebrovascular events or CV mortality in the general population [22] as well as in dialysis patients [23–25]. However, according to our knowledge, the association of carotid atherosclerosis and QRS-T has not been reported previously in the literature. Interestingly, our study has demonstrated that the extent of plaque burden, described as the plaque score, was a better predictor of QRS-T than IMT. An increasing body of evidence suggests that atherosclerosis in ESRD patients differs from that found in the general population in terms of advancement and localization of vascular lesions [26]. Most authors have found [14,27] that increased plaque burden, rather than increased IMT, seems to be the most typical finding in dialysis patients. Another explanation is that a plaque score describes more advanced atherosclerosis than IMT. The plaque score has not been widely used as a predictor of CV events in dialysis patients; therefore, it is difficult to compare our results with results obtained by other authors. However, our results confirm some previous analysis performed in the general population [28], suggesting that the presence of plaque, rather than the IMT, appears to be the major criterion of high risk of CV disease. More detailed studies are required to confirm our results and to determine the possible clinical importance of the relation between carotid atherosclerosis and depolarization abnormalities represented by QRS-T.

Our study has revealed that the second independent predictor of the QRS-T was calcification, expressed as a CAC score. According to our knowledge, the association between CAC and QRS-T has not been reported previously in the literature. In patients with ESRD, vascular disease is often accompanied by arterial calcification. It is important to note, however, that substantial differences exist in the characteristics of vascular calcification between the general population and ESRD patients. Dialysis patients are more prone to accumulate calcium–phosphate deposits not only within atherosclerotic plaques but also within the vascular wall, predominantly within the medial wall of arteries (Mönckeberg type calcification) [29,30]. Widespread consensus exists that in dialysis patients, arterial calcifications is a strong prognostic marker of all-cause and CV mortality, independent of classical atherogenic factors. Arterial calcification is associated with adverse clinical outcomes, including myocardial infarction, congestive heart failure, endocarditis, valvular heart disease and death [25,29–31].

In our study we did not distinguish between atherosclerotic plaques calcification and arterial media calcification. It would be a particularly interesting issue, because arterial media calcification is responsible for stiffening of the arteries with increased left-ventricular afterload and abnormal coronary perfusion as the principal clinical consequences. The potential clinical importance of the association between QRS-T and calcification is to be established in further studies.

In our study, cTnT was the third independent factor that affected the QRS-T. According to our knowledge, this association also has not been reported previously in the literature. The cTnT is a specific marker of myocardial injury and, therefore, a strong predictor of adverse outcomes in myocardial infarction and unstable angina. However, elevated cTnT levels have been observed in 30–75% of dialysis patients in the absence of an acute myocardial injury. Elevated cTnT has been shown to be a strong predictor of mortality and CV disease events in clinically stable asymptomatic dialysis patients and this phenomenon is independent of previous CV complications [32–35]. The cTnT elevation in dialysis patients may result from reduced renal clearance, minor myocardial damage without clinically significant coronary artery disease, direct injury to myocardial cells (toxins, hypoxia, stretching), reversible myocardial ischaemic release in the absence of myocardial necrosis and, importantly, from LVH [32–34,36]. LVH is an independent risk factor for CV mortality; therefore, strong link between LVMI and either cTnT levels or QRS-T values could be the potential explanation to why cTnT level correlated with QRS-T. However, in our study QRS-T correlated with cTnT even after the adjustment for LVMI. Moreover, cTnT remained an independent predictor of QRS-T in multiple regression analysis. Further studies are required to determine the possible clinical importance of the relation between cTnT and QRS-T.

Further studies are required to determine the possible clinical importance of the relation between QRS-T and clinical outcomes in dialysis patients. The limitations of our study include the relatively small patient numbers and the impossibility of controlling all possible factors that might influence QRS-T. However, if more detailed clinical prospective studies confirm our results, QRS-T may become a useful parameter, particularly helpful in CV risk estimation in dialysis patients, while the possible clinical
importance of the higher QRS-T in PD patients remains to be confirmed in further studies.

In conclusion, the QRS-T is high in PD patients compared with healthy controls and is mainly associated with coronary artery calcium burden, atherosclerosis and troponin T elevation.

Conflict of interest statement. None declared.

References


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