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Analysis of T-wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in patients initiating haemodialysis

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Abstract

Background. Cardiovascular disease remains the most common cause of death in end-stage renal disease (ESRD). Recently, novel descriptors of T-wave morphology have been suggested as measures of repolarization heterogeneity and adverse prognosis in non-uraemic populations. However, whether these T-wave descriptors provide prognostic information in uraemic populations has not been examined. The present study aimed to determine the prognostic value of novel T-wave morphology variables in predicting total, cardiovascular and arrhythmia-related mortality in ESRD patients initiating haemodialysis.

Methods. The study was a retrospective cohort of adult ESRD patients starting haemodialysis between 1998 and 2005; follow-up was until September 2006. A total of 325 patients were studied. Novel ECG variables characterizing repolarization and the T-wave loop were analysed.

Results. Of 325 patients with technically analysable data, 154 (47.4%) died after a mean follow-up of 25.5 ± 21.7 months. Direct comparison between cardiovascular death and non-cardiovascular death patients showed that the relative T-wave residuum (TWR) predicted cardiovascular mortality ($0.20 \pm 0.21\%$ *vs* $0.24 \pm 0.17\%$, $P = 0.005$). In Cox modeling, relative TWR was an independent predictor of cardiovascular [relative risk (RR) = 1.86; $P = 0.013$] and arrhythmia-related mortality (RR = 2.102; $P = 0.012$).

Conclusions. The heterogeneity of myocardial repolarization, measured by the relative T-wave residuum in the ECG, appears to be an independent predictor of cardiovascular and arrhythmia-related mortality in patients initiating haemodialysis.

Keywords: cardiovascular mortality; end stage renal disease; relative T-wave residuum; T-wave morphology; ventricular repolarization

Introduction

Cardiovascular diseases continue to be the predominant cause of death among patients with end-stage renal disease (ESRD). Half of the patients receiving chronic haemodialysis therapy die of cardiovascular diseases, with myocardial infarction, heart failure and sudden death comprising most of these deaths [1]. Reported rates of sudden death in this population range from 1.4% to 25%, most sudden deaths result from hyperkalaemia or arrhythmia [2].

Increased dispersion of ventricular repolarization has been implicated in the genesis of ventricular arrhythmias [3–4]. Therefore, non-invasive assessment of the repolarization abnormalities to identify patients at increased risk for sudden cardiac death is of great clinical importance. Several data processing methods have been proposed to detect T-wave pattern abnormalities. T-wave alternans (the identification of which requires an exercise test) is an effective non-invasive risk predictor for patients with congestive heart failure [5]. From the resting 12-lead surface ECG, QT interval dispersion (QTd) was proposed as a simple marker for ECG assessment of heterogeneity of ventricular repolarization [6,7]. Despite encouraging early reports [8–11], new evidence has shown a lack of predictive value for QTd [12–18]. The utility of QTd further confounded by methodological problems of poor reproducibility and lack of standardization [17,18]. A more practical and more electrophysiologically precise description of ventricular

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repolarization is therefore needed. More recently, other approaches to measure repolarization more accurately based on the spatial T-wave vector loop have been suggested, including analysis of the T-wave axis [19], T-wave morphology analysis [20–22], and T-wave residuum (TWR), a parameter indicative of cardiac repolarization heterogeneity [23,24]. These novel T-wave parameters have been proved to be important prognostic parameters for cardiovascular disease.

With the high prevalence of cardiovascular disease in ESRD patients, identifying high-risk patients vulnerable to fatal cardiac arrhythmias is important. Although recent studies have demonstrated that corrected QTd is an independent prognostic predictor for cardiovascular death in uraemic patients [10,11], cardiac repolarization abnormality calculated by novel T-wave analysis methods has not been examined in uraemic patients. The present study is designed to test the hypothesis that cardiac repolarization abnormality detected by novel T-wave analysis methods are important prognostic predictors for overall mortality, cardiovascular mortality, and arrhythmia-related mortality in patients initiating haemodialysis.

Materials and methods

Patients

A retrospective cohort study was done using data from medical records of a dialysis center in En Chu Kong Hospital, for all patients initiating long-term haemodialysis between January 1998 and October 2005, with follow-up until death or till September 2006. Patients were eligible for the study if they were older than 18 years, required long-term dialysis, and had a digital 12-lead surface ECG recorded within 1 month before starting dialysis. Exclusion criteria included incomplete patient information, pacemaker implantation, treatment with digoxin or class I or III antiarrhythmics, and technically unanalysable surface ECG (e.g. because of excessive noise).

Baseline data collection

Baseline data, including medical history, serum biochemistry, ECG and clinical assessment had been collected routinely on all patients on admission to the dialysis program. Information from medical records included age, gender, body weight, height, body surface area (BSA) calculated according to Mosteller's formula, body mass index (BMI), history of diabetes (defined as a fasting plasma glucose $\geq$126mg/dl or a 2 h post-lucose load plasma glucose $\geq$200mg/dl) or hypertension (defined as a systolic pressure $>$140mmHg and/or with a diastolic pressure $>$90mmHg), smoking habit, cardiovascular medications, (β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, digoxin and anti-arrhythmic agents), history of coronary artery disease (CAD) (angina pectoris, myocardial infarction, prior coronary artery bypass graft surgery, coronary angioplasty or receiving nitrate therapy), peripheral vascular disease (non-traumatic limb amputation or claudication), prior cerebrovascular disease (stroke or transient ischaemic attack) and predialysis biochemistry (potassium, albumin, calcium and phosphate). Fasting cholesterol, bicarbonate and haemoglobulin were not recorded because data were unavailable for most patients. Echocardiograms were reviewed if available. Reports were reviewed for left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), and septal and free wall thickness. LVEF was calculated by Simpson's method. Left ventricular mass index (LVMI) was calculated according to the Penn convention [25]. Left ventricular hypertrophy (LVH) was defined as LVMI $>131\,g/m^2$ in men and $100\,g/m^2$ in women [26]. Left ventricular dilation was defined as LVEDD >55 mm or evidence of cardiomegaly on chest radiograph (cardiothoracic ratio >0.5).

Outcomes

The causes of death were determined by review of dialysis records, review of death certificates, and from the Taiwan Death Registration Database. It was performed by two independent observers who were unaware of the other study data. The cause of mortality was identified as fatal arrhythmia when patients died because of documented ventricular tachyarrhythmia, as sudden death in cases of unwitnessed, unexpected death without clinical or postmortem evidence to support another cause, and as cardiovascular death (CVD) when patients died because of cerebrovascular accident, myocardial infarction, heart failure, fatal arrhythmia or sudden death. Patients who underwent kidney transplantation were censored at the time of organ replacement. Patients who received peritoneal therapy were censored at the time of transfer to this alternative renal replacement therapy.

ECG analysis for QT interval and QT dispersion

In all patients, a surface ECG sampled at 250 Hz was recorded using a PC-based 12-lead digital ECG instrument (BEST-ECG-12; BioEngineering Sense Tek Corp, Taipei, Taiwan) and stored in the digital patient file system in En Chu Kong Hospital. QT interval measurements were performed using a program written in MATLAB (version 6.5, The Mathworks Inc., Natick, MA, USA). Briefly, QT interval was measured from the onset of the QRS complex to the end of the T wave (defined as return to T-P baseline in all leads). When the T-wave amplitude was $<5\,\mu V$, the lead was excluded from the analysis. QT intervals were corrected using Bazett's formula. When U waves were present, the QT interval was measured to the nadir of the curve between the T and U wave. If the end of the T wave was not clear, the lead was excluded from analysis.

For any particular ECG, exclusion criteria for QT dispersion analysis included bundle-branch block, aberrant conduction on ECG, atrial fibrillation, pre-excitation and more than three leads excluded from analysis. Out of 325 participants, 277 (85.2%) fulfilled the criteria and were included for analysis. QT dispersion was defined as the difference between the maximal and minimal QT interval. Corrected QTd (QTdc) was calculated as the difference between the maximal and minimal QTc intervals. The cut point of abnormal QTdc was set at $>74\,ms/s^{1/2}$ on the basis

of one previous study [10]. Interobserver and intraobserver reliability of QTd were assessed. The second observer was blinded to all clinical data. The intraobserver mean difference was 1.4 ms, and the relative error was 11%. The interobserver mean difference and relative error were 3.5 ms and 15%, respectively.

Analysis of novel T-wave morphology descriptors

Analysis of the digital ECG recordings was performed blindly (i.e. by coworkers who did not have access to the clinical and follow-up data) using a program written in MATLAB (version 6.5, Mathworks Inc., Natick, MA, USA) as previously described [16,20–22]. Flow chart of algorithm is shown in Figure 1. Briefly, 10 s recordings of the ECG were acquired, and the median beat obtained for each lead of the recording was used in the analysis. Using singular value decomposition of the eight independent leads from the standard 12-lead ECG, a minimum three-dimensional space that captures most of the ECG energy was defined. All repolarization descriptors were derived using the ECG vectors in the constructed three-dimensional space. The new descriptors were classified into three categories: temporal variation, wavefront direction descriptors, and spatial variation [20]. The temporal variation descriptors included the normalized T-loop area (NTLA) and lead dispersion (LD). The NTLA was the area covered by the T-wave loop. The LD was the measure of temporal variations in interlead relationship during the inscription of the T loop. The wavefront direction descriptor, the total cosine between QRS and T wave (TCRT), measures the difference between the directions of propagation of depolarization versus repolarization. T-wave morphology (TMD) is a measure of the spatial T-wave morphology variation.

Relative and absolute TWR (RTWR and ATWR, respectively) were also determined in the present study [23,24]. In brief, after singular decomposition, the first three orthogonal components represent the signal of the traditional 3D T-wave vector or dipolar signal contents, and the remaining 4 th–8 th orthogonal lead components, the so-called non-dipolar components, reflect repolarization signals not contained within the global reconstructed T-wave vector and are expected to represent true heterogeneity of ventricular repolarization. The ATWR and RTWR were defined as the sum of squares of the 4 th–8 th eigenvalues of the T-wave signal and as the proportion of this sum to the sum of squares of all (i.e. 1st–8th) eigenvalues.

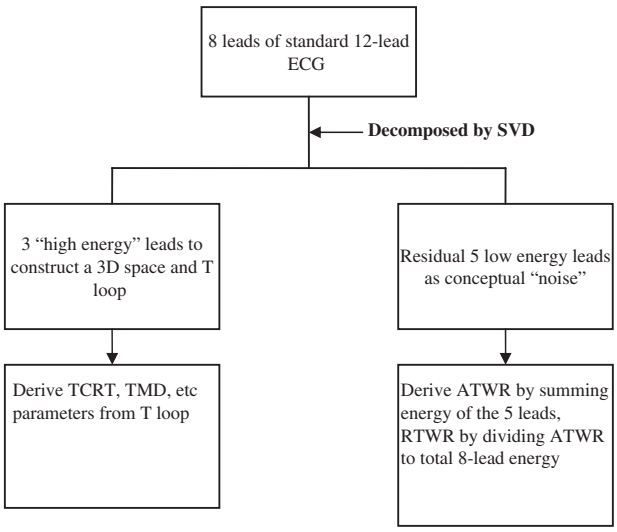

Fig. 1. Flow chart of algorithm.

Statistical analysis

SPSS for Windows (version 11.0, SPSS Inc., Chicago, IL, USA) was used. Continuous values are presented as mean ± SD. Patients with and without events were compared, and the relation of ECG variables to categorical clinical variables was tested using the Mann–Whitney U test. Distributions of categorical variables were performed using the chi-square test. Kaplan–Meier event-probability curves were computed. Different groups were stratified by the median value of each variable and compared using the log-rank test. The independent correlation of multiple variables with event status (total, cardiovascular and arrhythmia-related mortality) during follow-up was determined using Cox regression analysis. Continuous variables were described as medians. A value of $P < 0.05$ was considered statistically significant.

Results

Demographic and follow-up data

Of 354 patients eligible for the study, 29 were excluded for the following reasons: pacemaker implantation in two patients, anti-arrhythmic drugs in 11 patients, and technically unanalysable surface ECG in 16 patients. A total of 325 patients were included in the final data analysis. The mean age at the beginning of haemodialysis was 64.1 ± 13.7 (18–92) years. There were seven patients censored for transplant and zero censored for peritoneal dialysis (PD) during follow-up. After a mean follow-up (mean dialysis duration) of 25.5 ± 21.7 (3–101) months, there were 154 (47.4%) deaths from all causes with median survival of 18.6 months (Table 1), including 79 (24.3%) cardiovascular deaths, 59 (18.1%) arrhythmia-related deaths (fatal arrhythmia and sudden death) and infections in 42 (12.9%) patients. Fifteen patients for whom death was

Table 1. Cause of death of 154 ESRD patients (total 325 patients) in this study

Cause of death	*n*(%)
Total mortality	154(47.4%)
Total cardiovascular mortality	79(24.3%)
Cerebrovascular event	16(4.9%)
Total cardiac mortality	63(19.4%)
Myocardial infarction	3(0.9%)
Heart failure	1(0.3%)
Fatal arrhythmia	15(4.6%)
Sudden death	44(13.5%)
Infection	42(12.9%)
Treatment withdrawal	2(0.6%)
Unidentified	15(4.6%)
Other	16(4.9%)

Table 2. Clinical characteristic according to survival status

Variables	Survivors ($n=171$)	All-cause death ($n=154$)	*P* values	Survivors and non-CVDs ($n=246$)	CVDs ($n=79$)	*P*-values
Age (years)	60.5 ± 14.2	68.2 ± 11.9	<0.001*	63.2 ± 14	66.8 ± 12.4	0.044*
Sex (%, female)	56.1	55.8	0.957	54.9	59.5	0.472
Body mass index (kg/m^2)	24.5 ± 4.8	23.2 ± 5.1	0.002*	24.2 ± 5	23.2 ± 4.5	0.074
Hypertension (%)	72.5	75.3	0.565	70.3	84.8	0.011*
Diabetes (%)	53.8	61	0.188	55.7	62	0.322
Prevalent CAD (%)	14.6	23.4	0.044*	15.4	29.1	0.007*
Smoking (%)	14	16.2	0.580	15	15.2	0.974
Albumin data available	152	146		221	72	
Albumin (mg/dl)	3.38 ± 0.67	3.15 ± 0.66	0.003*	3.29 ± 0.7	3.22 ± 0.6	0.384
Echocardiogram performed	95	113		146	58	
LVEF (%)	64.7 ± 14	59.6 ± 15	0.009*	63.6 ± 14.4	58.1 ± 15.1	0.014*
LVMI (g/m^2)	179.3 ± 59.2	187.4 ± 61.9	0.201	181.6 ± 63.2	191.9 ± 54.6	0.094
LVH (%)	81.9	88.7	0.175	82.6	92.9	0.065
Left ventricular dilation (%)	46.7	55.8	0.102	47.5	62	0.025*

Values represented as mean $\pm$ SD or number or percent.
CAD,coronary artery disease; CVD, cardiovascular death; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.
*$P < 0.05$.

ascertained from the Taiwan Death Registration Database, but no definite cause of death could be established, were classified as unidentified.

The comparisons of clinical characteristics between survivors whose deaths were from all causes, and the CVDs and non-CVDs are summarized in (Table 2). Compared with survivors, the 154 non-survivors were older, had lower BMIs, lower albumin levels, lower LVEF, and a greater prevalence of CAD, but did not differ with respect to gender, smoking status, LVMI, prevalence of hypertension, left ventricular dilation or diabetes. Similarly, compared with non-CVDs, the 79 CVDs were older, had lower LVEF and greater prevalence of left ventricular dilation, hypertension and CAD, but did not differ with respect to gender, BMIs, albumin level, smoking status, LVMI or prevalence of diabetes. Angiotensin-converting enzyme inhibitors or angiotensin-II receptor antagonist were taken by 56 of 325 (17.2%) patients, calcium channel blockers by 187 of 325 (57.5%) patients, β-blockers by 82 of 325 (25.2%) patients.

T-wave analysis data

The comparison of cardiac repolarization measurements between survivors and non-survivors and between CVDs and non-CVDs are summarized in (Table 3). Both all-cause and cardiovascular mortality were associated with lower LD. The most striking difference was found for relative 'TWR', indicating a higher degree of repolarization heterogeneity in patients who died from cardiovascular causes during long-term follow-up.

Correlations between T-wave morphology measurements, conventional repolarization parameters and clinical variables

Pearson correlation coefficients were determined among T-wave morphology measurements, conventional repolarization parameters and clinical variables. Among T-wave morphology variables, intermediate inverse relationship was found between TCRT and relative TWR ($r = 0.313$, $P < 0.0001$). All other correlation coefficients were <0.25 and were of no clinical relevance. Moreover, conventional QTd variables and QRS width were weakly related to the T-wave morphology variables (both $r < 0.25$, $P > 0.05$).

Survival analysis: Kaplan–Meier curves and Cox regression

As shown in (Figure 2), patients with a relative TWR above the median (i.e. > 0.145%) had worse arrhythmia-related survival rates ($P = 0.0011$, Figure 2A), cardiovascular survival rates ($P = 0.0014$, Figure 2B), and all-cause survival rates ($P = 0.0319$). Stratification of patient by QT dispersion, QTc dispersion, LD, TCRT, TMD, NTLA and ATWR did not show a difference in survivals.

Cox regression analysis was performed using a stepwise backward removal of least significant variables. Clinical variables [age, LVEF, BMI, hypertension, CAD, presence of left ventricular dilatation, serum albumin level and T-wave morphology descriptors (relative TWR, LD)], which were univariately predictive of events, were entered as independent variables. Continuous variables were described by medians. The results showed age and serum albumin levels but neither LD nor relative TWR were independent predictors for all-cause mortality, whereas age, presence of CAD and low serum albumin just before dialysis were significant predictors for CVD and arrhythmia-related mortality (Table 4). Relative TWR was the only independent T-wave analysis measurement remaining in the final regression equation for CVD and arrhythmia-related mortality.

Table 3. Repolarization complexity and abnormality measurements according to survival status

Variables	Survivors ($n=171$)	All-cause deaths ($n=154$)	P values	Survivors and non-CVDs ($n=246$)	CVDs ($n=79$)	P-values
HR (bpm)	84.47 ± 15.41	86.25 ± 19.85	0.546	84.96 ± 16.83	86.42 ± 20.06	0.78
QTc ($ms/s^{1/2}$)	422.78 ± 38.19	426.38 ± 40.79	0.532	422.65 ± 40.73	430.22 ± 37	0.197
QTd checked	146	131		210	67	
QTd (ms)	39.48 ± 17.94	44.59 ± 25.74	0.205	41.30 ± 20.93	43.77 ± 25.47	0.687
QTdc ($ms/s^{1/2}$)	46.36 ± 21.49	53.2 ± 31.37	0.277	48.73 ± 25.05	52.3 ± 31.69	0.704
QTdc > 74 $ms/s^{1/2}$ (%)	5.5	10.7	0.11	7.6	9.0	0.725
TCRT	-0.29 ± 0.24	-0.29 ± 0.25	0.894	-0.29 ± 0.24	-0.31 ± 0.24	0.412
NTLA	0.56 ± 0.13	0.56 ± 0.13	0.947	0.56 ± 0.13	0.56 ± 0.13	0.884
LD	34.51 ± 3.24	33.54 ± 3.66	0.019*	34.36 ± 3.35	33.1 ± 3.71	0.015*
TMD (degree)	58.61 ± 18.12	57.26 ± 18.39	0.564	58.63 ± 18.07	55.93 ± 18.7	0.286
ATWR (tu)	417.21 ± 628.9	502.64 ± 792.99	0.628	423.51 ± 689.73	474.45 ± 730.25	0.752
RTWR (%)	0.21 ± 0.18	0.22 ± 0.20	0.275	0.20 ± 0.21	0.24 ± 0.17	0.005*

Values represented as mean ± SD or number or percent.
ATWR, absolute T-wave residuum; CVD, cardiovascular death; HR, heart rate; LD, lead dispersion; NTLA, normalized T-loop area; QTc, corrected QT interval; QTd, QT dispersion; QTdc, corrected QT dispersion; RTWR, relative T-wave residuum; TCRT, total cosine of R- to T-wave; TMD, T-wave morphology dispersion; tu, technical units.
*$P < 0.05$.

Discussion

To our knowledge, this study is the first one to demonstrate that the heterogeneity of ventricular repolarization measured by calculating relative TWR is an independent non-invasive predictor for cardiovascular death in patients initiating haemodialysis. Relative TWR, is available within a single beat of the ECG and can be measured automatically, instantaneously, and with a practically acceptable reproducibility [16].

The annual death rate in our study group was 22.3% during a mean follow-up of 25.5 months, which was 7.7% higher than data published by the United State Renal Data System from 2000–2004 [27]. This high mortality rate may be due to a higher prevalence of diabetes (57.2% *vs* 36.7%), older age (64 *vs* 58) and high percentage of LVH in our study population [10]. Our population also had a lower prevalence of CAD as compared with other studies [28]. This discrepancy might be contributed to fewer smokers (15.1% *vs* 40%) and fewer males (44% *vs* 53%). Also, a patients in the present study had a higher prevalence of diabetes (57.2% *vs* 43%); it is possible that some CAD patients were clinically silent, thus, not detected using our clinical definition of CAD [29].

Non-invasive assessment of ventricular repolarization and its role in risk prediction

Increased heterogeneity of ventricular repolarization, clearly linked to the genesis of ventricular arrhythmias [3,4] may be accurately measured using invasive electrophysiological [30] and complex body surface mapping techniques [31]. However, these approaches do not lend themselves to routine clinical application, leading to a search for accurate and applicable non-invasive measures based on the standard 12-lead ECG. QTd, another marker of heterogeneity of ventricular repolarization, despite encouraging early reports [8–11], is insufficiently accurate for clinical risk stratification in prospective studies [12–14]. Recent analysis suggest that varying T-loop morphology and the magnitude of differences in interlead projection of the T-wave loop may account for QTd [15–17]. Moreover, accuracy and reproducibility of QTd measurements are limited by the unreliability of T-wave offset detection [16,18]. Recently, a technique that previously had been developed for technical engineering to quantify ventricular repolarization was used. This method was based on a mathematical technique called singular value decomposition. The eight independent leads of the 12-lead ECG (I, II, and V1 to V6) were decomposed into a three-lead subspace and several new descriptors of T-wave morphology were calculated. One such approach has been to apply to the so-called principal component analysis (PCA) (relative weight of the first two components or eigenvectors of repolarization). The first demonstration of clinical usefulness was shown in patients with congenital long QT syndrome [32] and arrhythmogenic right ventricular dysplasia [33]. Beyond the approach of PCA, Acar *et al.* [21–22] developed a set of novel T-wave morphology descriptors to quantify various abnormal temporospatial repolarization indices which are potent predictors of adverse outcome in survivors of acute myocardial infarction. In 2001, it was realized that not only the T-wave loop but also the ratio of the energy of the T-wave loop to the energy of the non-dipolar TWR is a valid electrophysiological parameter. The rationale of this approach is that repolarization signals not reflected by a common 3D T-wave vector mirror the true heterogeneity of ventricular repolarization. These non-dipolar signal contents (termed ATWR and RTWR) can be expressed in absolute terms or relative to the overall

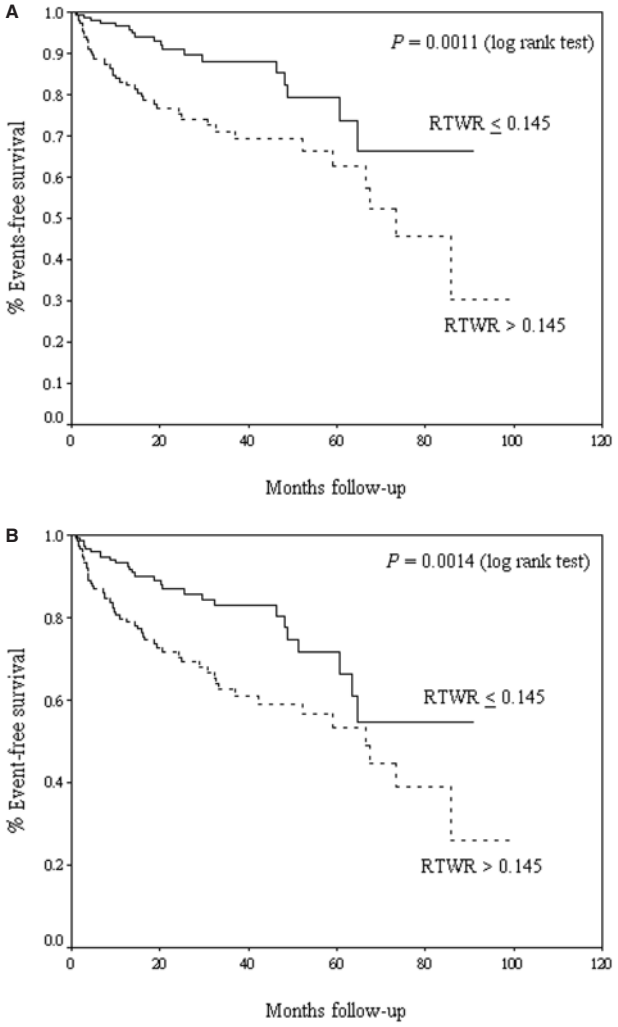

Fig. 2. (**A**) Kaplan–Meier event–probability curves (arrhythmia-related survival) for patient groups stratified by RTWR (relative T-wave residium) above and below median value ($P = 0.0011$ by log-rank test). (**B**) Kaplan–Meier event–probability curves (cardiovascular survival) for patient groups stratified by RTWR (relative T-wave residium) above and below median value ($P = 0.0014$ by log-rank test).

signal power involving dipolar and non-dipolar contents. Zabel and colleagues [23] found that male veterans who died from any cause had substantially higher TWR values. In a population of 1729 American Indian participants, Okin *et al.* [24] found that an abnormal TWR provides additional prognostic information beyond QTc and PCA ratio for prediction of all-cause and CV mortality.

Because the moving cardiac dipole represents only the vectorial sum of all action potential dipoles, it does not reflect the heterogeneity of action potentials through the myocardium. Localized dipoles that are mutually cancelled when summed into the total cardiac dipole influence various ECG leads differently. Those parts of the ECG energy that cannot be attributed to the global dipole represent local myocardial heterogeneity. TWR is not influenced by the global

Table 4. Multivariate Cox predictors of all-cause, cardiovascular and arrhythmia-related mortality

Variable	Parameter estimate	Standard error	*P*-value	Risk Ratio	95% CI for Risk Ratio
All-cause mortality					
Age	0.955	0.179	<0.001	2.598	1.83–3.687
Albumin	0.762	0.176	<0.001	2.142	1.519–3.022
Cardiovascular mortality					
Age	0.595	0.245	0.015	1.86	1.138–3.039
Albumin	0.734	0.246	0.003	2.084	1.286–3.378
CAD	0.838	0.261	0.001	2.311	1.386–3.854
RTWR	0.62	0.25	0.013	1.86	1.138–3.039
Arrhythmia-related mortality					
Age	0.554	0.283	0.048	1.741	1.03–3.03
Albumin	0.722	0.285	0.011	2.058	1.178–3.596
CAD	0.881	0.299	0.003	2.414	1.34–4.339
RTWR	0.743	0.297	0.012	2.102	1.175–3.76

All-cause mortality: chi-square = 48.51; cardiovascular mortality: chi-square:35.29; arrhythmia-related mortality: chi-square:29.35.
CAD, coronary artery disease; CI, confidence interval; RTWR, relative T-wave residuum.
P-values and absolute risk ratios are at last regression step.

distribution of action potential durations and by the global orientation of the repolarization sequence; rather, it reflects heterogeneity within the T wave and thus quantifies the localized repolarization inhomogeneity in the ventricular myocardium [16].

The present study demonstrates that relative TWR provides additional prognostic value beyond the previously demonstrated predictive clinical variables in patients initiating haemodialysis. These findings, taken together with the poor correlation of relative TWR with QTc, QTdc and other T-wave morphology descriptors, suggest that the non-dipolar content of the ECG provides independent information regarding ventricular repolarization.

Other T-wave parameters as risk predictors

Unlike recent studies demonstrating that the corrected QT dispersion is an independent predictor for cardiovascular death in ESRD patients [10,11], our study only showed a trend toward this conclusion. A more general population with advanced age, LVH and cardiomegaly at study entry in this study may partially explain the differences. This may imply that TWR is a more sensitive tool than QT dispersion in high risk patients. Moreover, in contrast to QT dispersion [10,11,13,14], there is no need to exclude ECG with BB block, atrial fibrillation and aberrant conduction for T-wave morphology analysis [20–24]. This superiority will broaden the clinical applicability for T-wave morphology parameters in patients under haemodialysis, in which the prevalence of arrhythmia in this group of patients is quite high (15% in our study). Finally, as mentioned earlier, QTd is only a gross and indirect measure of repolarization abnormalities. For good reasons. QTd should be replaced by more precise repolarization descriptors.

Unlike previous studies [21–24], other T-wave morphology parameters such as TCRT, TMD, NTLA and ATWR were not associated with events in the current study. Only LD was univariately associated with events in the current study. Due to higher risk, patients in the present study had lower TCRT, higher NTLA and higher TMD compared with previous ones [23,24]. It is possible that in this higher risk study population, T-wave morphology parameters such as LD, TCRT, TMD and NTLA could not offer additional prognostic information. Moreover, a relatively small study population and shorter follow-up period may also contribute to the discrepancy.

Implications and future directions

Even after taking comorbid diseases into account, ESRD patients have a significant risk of cardiovascular mortality and death. This study shows computerized analysis of relative TWR from the resting 12-lead ECG measured before the initiation of dialysis is an important, independent predictor of cardiovascular mortality and may replace measurement of QTd.

In this study, a digital 12-lead surface ECG was recorded within 1 month before starting dialysis. In this stage of ESRD, most patients are likely to have serum electrolyte imbalance and volume overload, both of which may affect ECG variables. Since many conditions are likely to have changed during the period prior to and after the start of dialysis, further study to investigate ECG at the stable stage of haemodialysis (i.e. 3 or 6 months after initiating dialysis) is warranted and is underway.

Limitations

First, because of the retrospective nature of this study, baseline and outcome measures may be incomplete. The value of T-wave morphology should be confirmed in a prospective manner in future studies. Second, the pathophysiology of the TWR and other new T-wave morphology parameters has not been studied in experimental models, so potential mechanisms underlying these observations could only be discussed from a theoretical perspective. Careful independent validations and verifications of pathophysiological models are seriously needed before any practical applications can be proposed or even considered.

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