Increased Repolarization Heterogeneity is Associated with Increased Mortality in Hemodialysis Patients

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Abstract

Arrhythmic death is the leading cause of mortality among End-Stage Renal Disease patients but determining which of these patients are at sufficient risk to warrant defibrillator therapy remains an open question. To test whether ECG parameters reflecting ventricular repolarization could help risk stratify these patients, we performed a prospective observational study involving 50 chronic hemodialysis patients. Entrance criteria included age over 40 and the presence of either diabetes or hypertension. Holter recordings were performed at the onset of a dialysis treatment and continued for 48 hrs (until the next session) and ECG parameters were derived from this data. During the 13 month follow up period, 8 patients died, 3 of cardiac causes. Despite the small numbers in this pilot study, significant increases in VPC frequency and T-wave complexity were observed between survivors and non-survivors during dialysis while significant increases in QTc interval and QRS-T angle were seen between these groups in the hours following treatment. If these results can be confirmed in larger trials, they may contribute importantly to risk stratification in these patients.

1. Introduction

There are approximately 400,000 people in the US with End-Stage Renal Disease (ESRD) receiving dialysis. ESRD is a costly and disabling condition that disproportionately affects racial/ethnic minority populations and is associated with a high mortality rate (230 per 1000 patient-years) [1]. Cardiac disease is implicated in as many as 43% of these deaths and, amongst those, cardiac arrhythmias account for 64%.

It has been suggested that implantable cardiac defibrillators (ICDs) are significantly underutilized in this population and that they have great potential for improvement of long term survival [2]. A retrospective cohort study, based on Medicare data demonstrated that ICDs confer a 42% relative risk reduction of all-cause mortality [3]. On the other hand, complications, including infections and bleeding, are more common in ESRD patients receiving ICDs [4].

It is therefore of great importance to determine which ESRD patients are at greatest risk for fatal cardiac arrhythmias. While a number of clinical factors (age, diabetes, hypertension, myocardial infarction, congestive heart failure), biochemical markers (cardiac troponins), echocardiographic parameters (decreased left ventricular ejection fraction and left ventricular hypertrophy) and ECG parameters have been investigated, none have high sensitivity and specificity for detecting arrhythmic risk [5]. Given the increased precision in measuring repolarization features using novel ECG signal analysis [6], we will test whether measurement of cardiac repolarization heterogeneity from Holter derived ECG recordings performed during dialysis (an "arrhythmogenic stress test") can be used to stratify ESRD patients for arrhythmic risk. .

2. Methods

We enrolled ESRD patients at an outpatient hemodialysis centre located in proximity to the University of Rochester Medical Center. The study protocol was accepted by the local Research Subject Review Board. The patients were enrolled after being presented a consent form describing the study objectives and enabling the use of their medical information for research after appropriate de-identification following HIPAA requirements.

2.1. Study protocol

Enrolment criteria were chosen in order to select ESRD patients at relatively high risk for cardiac arrhythmias: age >40yrs and history of treatment for hypertension or diabetes. We excluded patients on class I antiarrhythmics, those with pacemakers, implantable defibrillators or cardiac resynchronization devices and childbearing women.

Patients were enrolled at the hemodialysis centre, and started the study protocol at their next session. Upon arrival, a Holter monitor (Global Instrumentation LLC,

Syracuse, NY, USA) was placed. They then followed their usual hemodialysis routine. The monitors were set up to record for 48 hours, from the onset of the first hemodialysis session until the start of the next session.

2.2. Clinical factors and electrocardiographic measurements

The 12-lead Holter recorders provide ECG signals using the Mason-Likar lead configuration. ECG signals were acquired at 1000Hz with 16 bit resolution. The data was exported from the Telemetric and Holter ECG Warehouse (THEW) [7] in ISHNE format including ECG signal and signal annotation that were manually reviewed and adjusted.

All the computerized measurements were realized using the academic version of the COMPAS software (University of Rochester, Rochester, NY) [6]. Each measurement was calculated using eigenvectors from applying principle component analysis (PCA) to the 8 leads (I, II, V1-V6). COMPAS provided the end of the T-wave by calculating the intersecting point between the baseline and the descending slope of the T-wave. Baseline wander was corrected by the cubic spline interpolation method. T roundness (T-wave complexity) was computed based on the ratio of the two first eigenvalues. QRS-T angle was measured in the referential defined by the three first eigenvectors.

In addition to ECG measurements, we recorded hemodialysis parameters such as treatment time volume of fluid removed, weights (pre- and post-dialysis), pre-dialysis systolic and diastolic blood pressure, and serum electrolytes (K^+, Ca^{+2}, and phosphate)

3. Results

3.1. Clinical, hemodialysis and electrocardiographic factors

We enrolled 50 patients during a period of 16 months, from 2/13/2009 to 6/18/2010, and followed them for 13 months after the completion of their enrolment. Nineteen percent of the population (8/42) died during the follow up period. Three cases were confirmed as cardiac death while the cause of death for the others could not be determined. The clinical characteristics of the groups are provided in Table 1. No statistically significant differences were found between groups.

The characteristics of the dialysis sessions are reported in Table 2. The only factor showing statistically significant differences between groups was the dialysis treatment time. Patients who experienced cardiac death underwent shorter delivered hemodialysis sessions on average than survivors (3 hrs vs. 4 hrs) although the volume of fluid removed for each group was not statistically different.

Table 3 provides the values for the ECG parameters at the times when they were the most significantly different between groups. At 30 min into the dialysis session, the number of VPCs was statistically higher in patients who died a cardiac death than in survivors. T-wave complexity, a marker for increased heterogeneity of repolarization, also showed a strong trend toward higher values during the hemodialysis session (at 130 min) in the all-cause mortality group.

Table 1. Clinical characteristics of the study population.

	Survivors	All death	Cardiac death
N	42	8	3
Race	34-8	4-4	2-1
Age (yrs)	63±12	60±12	56±10
Gender (m/f)	17/25	3/5	1/2
Hypertension	41 (98%)	6(75%)	3 (100%)
Diabetes type I	2	0	0
Diabetes type II	14	3	0
LVEF(%)	59±15	58±22	60±24

LVEF: Left Ventricular Ejection fraction. Race: African American-White

Table 2. Hemodialysis factors

	Survivors	All death	Cardiac death
N	42	8	3
Treatment (min.)	240±29	**203±24***	**180±17***
Fluid removed (L)	2.9±1.3	2.7±1.2	3.8±1.0
Pre-H weight (Kg)	89±22	87±18	77±16
Pre-H SBP (mmHg)	142±26	144±27	130±20
Pre-H DBP(mmHg)	74±16	76±21	57±30
Serum Ca^{2+} (mg/dl)	8.8±1.7	8.6±1.2	7.4±1.4
Serum K^+ (mg/dl)	5.1±1.5	5.7±1.1	6.3±0.4
Kt/V_{urea} [n.u.]	1.42±0.24	1.42±0.27	1.27±0.14
K bath (mM)	2.0±0.8	2.0±0.6	2.0±0.6

Pre-H; pre-hemodialysis; SBP: systolic blood pressure; DBP: diastolic blood pressure; Kt/V_{urea}: dialysis treatment adequacy; * $p \leq 0.05$ with reference to survivors.

Table 3. ECG factors

	T (min.)	Survivors	All death	Cardiac death
N		42	8	3
RR (ms)	390	733±125	780±212	933±232
QTc (ms)	390	444±45	475±47	**524±45#**
VPCs (n/hr)	30	2±37	22±23	**33±35***
QRS-T (deg)	390	78±46	**115±30***	97±36
T complexity	130	.13±.15	**.29±.17#**	.32±.14

T complexity: T-wave complexity; *P≤0.05 and # p=0.07 in reference to survivors

Finally, the repolarization parameters QRS-T angle and QTc were increased (significantly and near significantly,

respectively) at 6.5 hrs. after the onset of dialysis (i.e. 2.5-3.5 hrs. after the dialysis session) in the all-cause mortality and cardiac mortality groups respectively.

We used linear mixed effect models (LME) with autoregressive covariance structure to investigate the differences in ECG trends during and after hemodialysis between survivors and the all-cause mortality ("All death") group. During dialysis, the LME showed a significant increase in T-wave complexity (0.29±0.15 vs. 0.23±0.17, p=0.05) for the group of patients who died during the 13-month follow-up. During the 44 hours following the end of the hemodialysis session, this group had lower heart rate (RR interval: 775±134 vs. 855±91 msec, p=0.01), increased QTc interval (449±43 vs. 458±38, p=0.003), and a trend toward less acute QRS-T angle (63±45 vs. 94±38 degrees, p=0.09).

Figure 2 shows the QTc interval duration during the first ~12 hrs after the start of the dialysis session for survivors and all-cause mortality groups (upper panel) and survivors vs. cardiac mortality (lower panel).

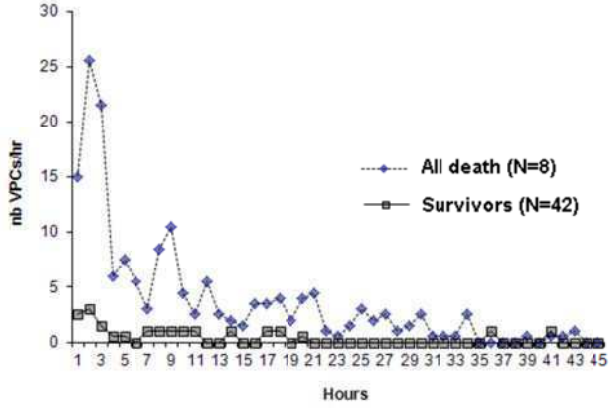

Figure 1: Monitoring of occurrence of the average number of ventricular ectopic beats per hour during and after the hemodialysis session.

The Figure 3 presents the time course of T-wave complexity for ~8 hrs after the start of hemodialysis for the group of patients who survived and for the group of patients who did not.

4. Discussion

We have used ECG signal analysis of 48-hr Holter data to identify parameters that may contribute to risk stratification of hemodialysis patients for sudden cardiac death (SCD). Neither conventional clinical risk factors (advanced age, HTN, diabetes and reduced LVEF) nor were dialysis risk factors more prevalent in the cohort of non-survivors in our study, highlighting the need for additional markers.

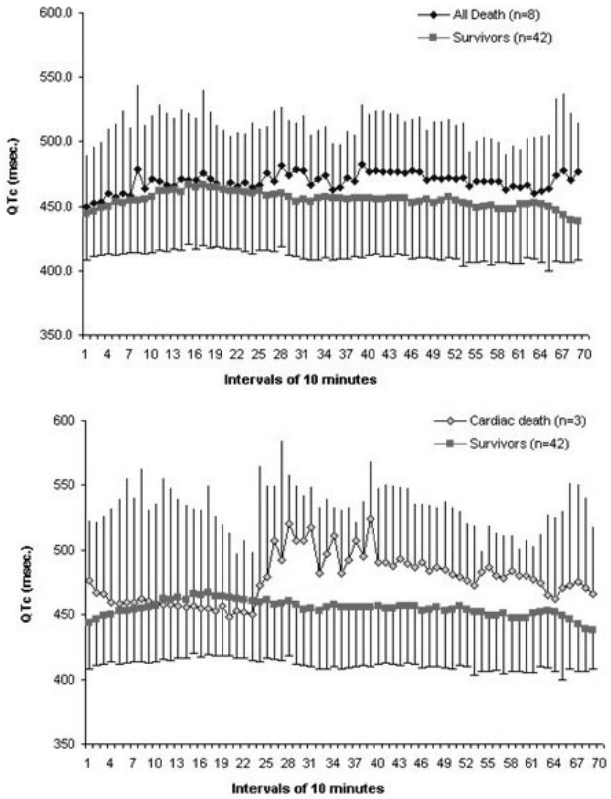

Figure 2: QTc interval duration for the first ~12 hours after the onset of the hemodialysis session for survivors vs. all-death groups (upper panel), and survivors vs. cardiac death groups (lower panel). Ten-minute-based mean and standard deviation are shown.

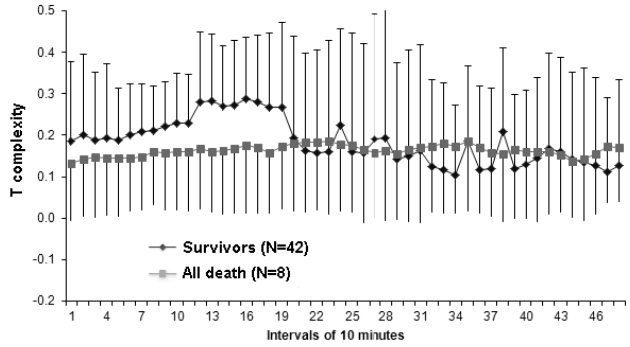

Figure 3: T-wave complexity within all death and survival groups for the 8 hours following the start of dialysis (mean and standard deviation). The graph reveals the trend toward increased T-wave complexity during the hemodialysis session confirmed by the general mixed linear model.

Our results suggest that both increased VPC frequency and T-wave complexity during dialysis may be associated with increased risk. Since SCD during dialysis per se is an uncommon event [8], this risk would presumably manifest itself in an event in the post-dialysis period. Our data also raised the possibility that increased QTc and

QRS-T angle as measured a few hours following dialysis may predict risk. This is consistent with the results of Severi et al [9] who showed increased T-wave complexity during the last hour of dialysis correlated with increased VPC frequency, a surrogate marker for malignant arrhythmias.

While the QTc increase did not quite reach statistical significance (p=0.07) for the very small cardiac death cohort, the markedly prolonged mean of 524 msec is notable. The timing of the QTc measurement is critical (see Fig. 2) and may explain why its prolongation has not been consistently shown to correlate with cardiac events in this population. The increased QTc in the hours post dialysis is somewhat surprising since one would expect an efflux of K+ from the intracellular to extracellular compartments which would tend reduce QTc.

In conclusion, we report more frequent ventricular ectopic beats during the dialysis session in ESRD who did not survive during the 13 months following their enrollment in the study. Moreover, there was no significant change in repolarization features during the dialysis, but a significant increased QTc interval and T complexity was measured during the 48 hours following the HD, these changes may play a role in the predisposition of ESRD patients to cardiac death.

Acknowledgements

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