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Repolarisation Descriptors and Heart Rate Variability in Hemodialysed Patients

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Summary

T wave morphology (TWM) descriptors derived from Holter electrocardiograms during hemodialysis (HD) are of potential value for cardiac risk assessment in HD patients. Our knowledge on autonomic regulation of TWM descriptors is limited. The purpose of this study was to investigate the association between TWM parameters and heart rate variability (HRV) during intradialytic monitoring. In each of 81 patients on maintenance HD, continuous electrocardiograms were recorded 5 times during HD on alternate weeks. TWM descriptors were calculated every 5 s in overlapping 10-s ECG segments and Low Frequency (LF) (0.04 Hz to 0.15 Hz), High Frequency (HF) (0.15 Hz to 0.40 Hz) powers of the spectrum of HRV were calculated every five min. The calculated values of TWM and HRV were averaged during the first hour of the recordings and subsequently over all recordings in each subject. Analyzable data for HRV and TWM were available in 71 HD patients (aged 61±15, 36 % diabetics, 32 % females). LF in normalized units correlated positively with Total Cosine R to T (r=0.374, p=0.001) and negatively with T wave morphology dispersion (r=−0.253, p=0.033) after adjusting for heart rate. A heart rate independent association between repolarisation descriptors and HRV exists in HD patients. Autonomic modulation needs to be considered when using TWM characteristics for risk profiling of HD patients.

Key words

TMD • TCRT • QRS-T angle • HRV • Autonomic • Hemodialysis

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Introduction

Uremic cardiomyopathy and autonomic imbalance are important predisposing factors of ventricular arrhythmias observed, at particularly high rates, in patients with advanced chronic kidney disease (Herzog *et al*. 2008, Poulikakos *et al*. 2014a). Descriptors of repolarisation aberration derived from surface 12 lead electrocardiogram (ECG) have shown promising results for risk stratification purposes not only in cardiac patients (Zabel *et al*. 2000) but also in small cohorts of hemodialysis (HD) patients (Lin *et al*. 2007, de Bie *et al*. 2013, Poulikakos *et al*. 2014b). Abnormal cardiac autonomic modulation has been consistently reported in patients with advanced chronic kidney disease (Poulikakos *et al*. 2014a) and autonomic abnormalities are also known to carry prognostic information both in cardiac patients (Bigger *et al*. 1993) and in patients on maintenance HD (Fukuta *et al*. 2003, Oikawa *et al.* 2009, Suzuki *et al.* 2012).

The autonomic system plays a role in synchronizing naturally existing electrical differences between ventricular myocytes (Conrath and Opthof 2006) both directly at the cellular level *via* autonomic receptors

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that influence ionic channels and regulate the spatiotemporal electrical and contractile performance of the heart (Ogrodnik and Niggli 2010), and indirectly by controlling heart rate (HR).

Although it has been shown that selected descriptors of repolarisation aberration are HR dependent (Smetana *et al.* 2004) it is not known whether and if yes, by which mechanisms autonomic system affects repolarisation heterogeneity independent of HR changes. At the cellular level, it is difficult to differentiate the pure chronotropic effect from the adrenergic effect as they occur concomitantly. However this distinction is important and may have clinical implications. Chronic adrenergic stimulation may result in increased repolarisation heterogeneity *via* heart rate independent mechanisms relating to the distribution and the signalling of adrenoreceptors (Nikolaev *et al.* 2010). Increased repolarisation heterogeneity predisposes to ventricular tachycardias (Kuo *et al.* 1983, Chauhan *et al.* 2006). Combination of factors predisposing to repolarisation heterogeneity and of sympathetic overdrive may thus lead to particularly increased risk of ventricular arrhythmias and of arrhythmic death.

Consequently, we aimed at investigating the relationship between the T wave morphology (TWM) descriptors and cardiac autonomic modulation in HD patients. We have previously shown that selected TWM descriptors (Poulikakos *et al.* 2013) from continuous intradialytic electrocardiograms demonstrate intra-subject stability and reproducibility in stable patients on maintenance hemodialysis. In this study we measured spectral parameters of heart rate variability (HRV) and studied their associations with TWM descriptors.

Materials and Methods

Study population

Eligible patients in sinus rhythm from the HD population of St George's Hospital NHS Trust were recruited to undergo digital intradialytic ECGs. The recordings were performed during dialysis on the same day of the week on weekdays and were repeated 5 times in each patient, with 2-week periods between repetitions. Patients with infections or malignancies were excluded. Patients with obstructive coronary artery disease were eligible if they had been asymptomatic and free of any cardiac events for at least 12 months before the first recording. Patients with fasting plasma glucose ≥7.0 mmol/l and/or A1C≥6.5 percent (48 mmol/mol) and/or those receiving anti-diabetic medications were classified as diabetics. Patients received 4 h sessions of regular HD treatment three times weekly and delivered dialysis treatment adhered to national guidelines (Shaw *et al.* 2012). The study was approved by the local Ethics Committee and all participants consented in writing.

ECG acquisition and analysis

Using the Mason Likar electrode positions, continuous 12-lead ECGs were started approximately 30 min before the HD session and finished after the end of the HD session. CardioMem® CM 3000-12 (Getemed, Teltow, Brandenburg Germany) recorders were used programmed to capture the signals at 1024 Hz.

TWM parameters

The calculation of the TWM descriptors has been previously described (Acar *et al.* 1999) and included the Total Cosine R to T (TCRT), the T Wave Morphology Dispersion (TMD) and the Principal Component Analysis ratio (PCA). Using a custom developed software package, the 12-lead digital electrocardiographic signal is reconstructed by singular value decomposition into an orthogonal eight-lead system in which the first three leads contain most of the non-redundant information. In these dominant three leads, the detection points of the QRS complex and T wave is made in the representative median beats of each 10-s ECG segments. The total cosine R-to-T (TCRT) represents the spatial angle between repolarisation and depolarization propagation 3-dimensional loop. Increased angle indicates global repolarisation heterogeneity. T wave morphology dispersion (TMD) is the measure of the differences of the projections of the 3-dimensional T wave loop into different leads of the standard electrocardiogram. It reflects regional repolarisation heterogeneities. The principal component analysis (PCA) ratio is the ratio of the second to the first determinant of the reconstructed spatial T wave vectors. It measures the scale of the T wave loop between a narrow band and a broad pattern. It is a measure of the repolarisation complexity.

These descriptors were calculated in representative QRS-T complexes of each 10-s ECG segments with moving the segments in 5-s steps.

HRV parameters

HRV parameters were calculated using the software of the analyzer (Anonymous 2006). Every 5-min

window the absolute (denoted with the subscript a) and normalized (denoted by the subscript n) values, of the Low Frequency (LF) (0.04 Hz to 0.15 Hz) and High Frequency (HF) (0.15 Hz to 0.40 Hz) powers of the spectrum and the HR were computed. The normalized values were calculated automatically by the software of the analyzer using the formulas $LF_n = LF_a$ / (Total Power − Very Low Frequency) x 100 and $HF_n = HF_a$ / (Total Power − Very Low Frequency) x 100. Very low frequency corresponded to less than 0.04 Hz power of the spectrum. Although the principal calculation was based on Fast Fourier Transform, the calculation of the normalized components corresponded fairly to the established HRV standards (Anonymous 1996).

The absolute difference between the HR during the last and first 5-min of the first hour was also calculated and denoted ΔHR.

Statistical analysis

We used the single recording average values during the first hour of separate recordings to investigate the reproducibility of TWM and HRV parameters, and overall averaged values of all completed recordings (i.e. averages of the first hour of all repeated recordings in the same patient) to characterize individual patients and to examine relationship between HRV and TWM. For the purposes of this analysis LF_a and HF_a were used after decadic logarithmic transformation. Repeated measures Anova was used to test reproducibility.

Two sided independent-sample t-tests and chi square tests were used for comparison of numerical means and of categorical values, respectively. Pearson correlation coefficient was used to investigate correlations between variables; partial correlation was used to measure the correlation after adjusting for other variables. For the final analysis, IBM SPSS statistics 19 was used for the statistical analysis; p value <0.05 was considered statistically significant.

Results

Baseline characteristics

The study population has been described previously (Poulikakos *et al.* 2013). In brief, we obtained 350 intradialytic recordings; analyzable data for HRV and TWM parameters were available in 348 and 319 recordings respectively.

Data for both HRV and TWM during the first hour were available in 72 HD patients. One patient who had excessive ΔHR (35) was excluded from the analysis. All calculated HRV and TWM parameters showed intrasubject stability (p>0.05).

Baseline characteristics of the population of this study are shown in Table 1.

Table 1. Baseline characteristics, TWM and HRV parameters according to the presence or absence of diabetes mellitus.

	Diabetes		
	Present (n=26)	**Absent (n=45)**	**P value**
Age (years)	67±10	58±16	0.007
Females	35 %	30 %	0.715
Beta blocker use	29 %	33 %	0.768
Mean Beta Blocker dosing (% of maximum dose)	8±18	12±24	0.480
Alpha 1 receptor antagonist use	23 %	11 %	0.167
K	4.7±0.6	4.9±0.7	0.136
P	1.6±0.4	1.6±0.4	0.944
Ca	2.3±0.14	2.3±0.15	0.225
CRP	9±8	11±17	0.559
PTH	37±30	47±34	0.270
LF_a	−5.32±0.55	−5.13±0.33	0.078
HF_a	−5.47±0.62	−5.50±0.42	0.852
LF_n	47±12	59±12	<0.001
HF_n	37±6	32±7	0.002
TCRT	−0.03±0.46	0.19±0.60	0.092
TMD	37±25	27±20	0.088
PCA ratio	0.17±0.07	0.16±0.07	0.562
HR	74±11	78±11	0.124
HRD	−1±5	−2±6	0.532

Ca = adjusted calcium (mmol/l), CRP = C-reactive protein (mg/l), HF_a = high frequency component (0.15 Hz to 0.40 Hz) of Heart Rate Variability (HRV) in absolute values, HF_n = high frequency component (0.15 Hz to 0.40 Hz) of Heart Rate Variability (HRV) in normalized units, HR = Heart Rate (beats per minute), HRD = difference between heart rate during the last and first five minutes (L-F) of the first hour of recording, K = potassium (mEq/l), LF_a = low frequency component (0.04 Hz to 0.15 Hz) of HRV in absolute values, LF_n = low frequency component (0.04 Hz to 0.15 Hz) of HRV in normalized units, n = number of subjects, P = phosphate (mmol/l), PTH = Parathyroid hormone in pmol/l, PCA ratio = Principal component analysis (PCA) ratio, TCRT = Total Cosine of R to T, TMD = T wave Morphology Dispersion; LF_a and HF_a values are presented after decadic logarithmic transformation. All numerical data are expressed as mean ± SD. Shaded areas highlight statistically significant differences.

There was no difference in mean LF_a, HF_a, LF_n, HF_n, HR and TCRT, TMD and PCA values between patients receiving and not receiving beta blockers and between patients receiving and not receiving alpha adrenergic blocker.

There was a difference in LF_n and HF_n but no difference in LF_a and HF_a between diabetics and non-diabetics (Table 1).

Females had higher values of LF_a and HF_a compared to males (−5.01±0.43 vs. −5.29±0.41 p=0.009 and −5.32±0.43 vs. −5.57±0.51 p=0.047 respectively) but there was no sex difference in normalized values. As expected, females had higher TCRT values (Smetana *et al.* 2002) compared to males (0.49±0.38 vs. −0.07±0.54 p<0.001) but there was no sex difference in TMD and PCA ratio.

Associations between TWM and HRV indices

In the total study population, LF_n correlated positively with TCRT (r=0.374, p=0.001) and negatively with TMD (r=−0.253, p=0.033) after adjusting for HR (Fig. 1). HF_a correlated positively with TMD (r=0.235, p=0.048). There was no correlation between the PCA ratio and any of the calculated HRV indices.

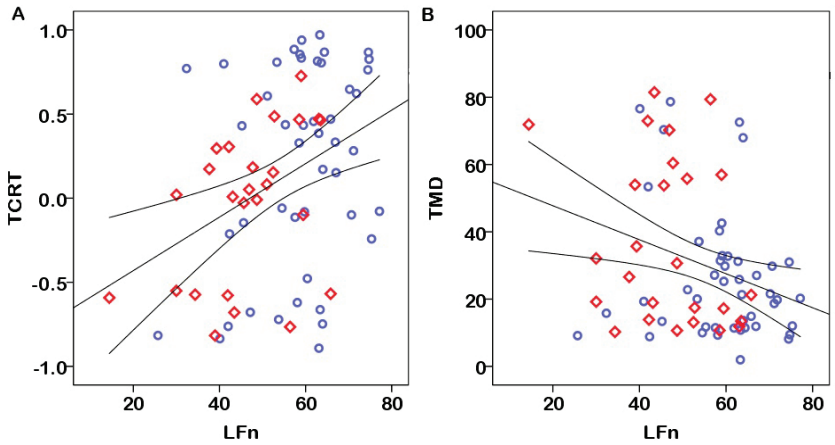

Fig. 1. Scatter diagrams showing the relationship between LF_n and TCRT (**A**, left panel) and TMD (**B**, right panel). Patients with and without diabetes are shown with red diamonds and blue circles respectively. Linear regression line is plotted with its 95 % confidence interval (curved lines). LF_n = the low frequency (0.04 Hz to 0.15 Hz) component of Heart Rate Variability in normalized units, TMD = T wave morphology dispersion, TCRT = Total Cosine of R to T

Discussion

The study shows heart rate independent association between TCRT, TMD and LF_n in hemodialysed patients.

Our results thus suggest that in HD patients a link may exist between chronic autonomic imbalance and repolarisation aberration. Decreased TCRT and increased TMD are known to predict worse outcomes in cardiac patients (Zabel *et al.* 2000, 2002) and the risk of sudden cardiac death in the general population (Porthan *et al.* 2013). Lower LF_n may indicate reduced baroreflex sensitivity which is also a risk factor for adverse outcomes (La Rovere *et al.* 2001). Thus risk profiling in dialysis patients might be served by looking at these two interlinked parameters. Dialysis patients with lower LF_n and TCRT and high TMD might be a good population to investigate prophylactic strategies.

The potential link between chronic autonomic imbalance and repolarisation heterogeneity in dialysis patients warrants further investigation as it may have important clinical therapeutic implications to prevent arrhythmic complications in patients with chronic kidney disease. In patients with ischemic cardiomyopathy sympathetic stimulation increases repolarisation aberration (Vaseghi *et al.* 2012) whereas research in animal models suggests that the underlying pathology may be related to redistribution of β_2 adrenergic receptors with subsequent altered cAMP signalling (Nikolaev *et al.* 2010).

Previous studies have investigated the relationship between descriptors of repolarisation aberration and autonomic nervous system in subjects with structurally normal hearts. TCRT and the ventricular gradient have been shown to decrease in response to autonomic provocations induced by postural changes (sitting, standing) (Batchvarov *et al.* 2002) and ventricular gradient decreased following pharmacological autonomic provocation with isoprenaline infusion (Vahedi *et al.* 2012) beyond the expected HR effects. Our results extend these observations suggesting a potential impact of autonomic system independent of heart rate and are in line with a study in patients with diabetes mellitus showing increased QRS-T angle in patients with depressed HRV (Voulgari *et al.* 2010).

We did not detect differences in absolute values

of spectral parameters of HRV between diabetics and non-diabetics that would normally be seen in other populations. This should be interpreted considering the expected global reduction of HRV in dialysis patients due to chronic sympathetic over activation (Converse *et al.* 1992, Hausberg *et al.* 2002) related to chronic kidney disease irrespective of the diabetic status. Abnormally saturated sympathetic tone leads to decreased HRV components reflecting a decrease of the physiologic oscillations of the autonomic system (Malik and Camm 1993) and is known to predispose to ventricular arrhythmias.

Limitations

The main limitations of the study are related to the small number of the patients and the purely observational nature of the study that did not include autonomic provocations. The physiologic scope of the study would have been increased by including postural provocations that might unveil stronger correlations between the repolarisation characteristics and expressions of cardiac autonomic regulation. However, we found it difficult to include such postural provocations for practical reasons in the given clinical setting.

Heart rate variability is reduced in patients with severe depressive and/or anxiety disorders that are not uncommon in HD patients. However, none of the patients in this study were treated for these disorders and we were thus unable to add relevant sub-analyses.

Echocardiographic examinations are not routinely repeated in HD patients at our institution. We are therefore unable to comment on the possible relationship of our findings with increased left ventricular mass and/or cardiac fibrosis that belong to the possible mechanisms of sudden death in these patients.

We limited our analysis to the first hour of the recordings but we were not able to correct our data for possible electrolyte changes that could potentially have an impact on both TWM and HRV. In addition, for ethical reasons a number of our patients remained on cardiovascular medications that may influence both repolarisation characteristics and HRV parameters. Finally our observations were performed during HD and we do not have data on the circadian patterns on TWM and HRV in these patients that might be of additional value for risk profiling.

Conclusion

In hemodialysed patients, LF_n is associated with decreased TCRT and increased TMD independent of heart rate. Elucidating the electrophysiological link between cardiac autonomic regulation and ventricular repolarisation is likely to be of value for the characterization of high risk profiles in hemodialysed patients.

Conflict of Interest

There is no conflict of interest.

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