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CARDIOLOGY
Research Article

Episodes of T-Wave and QRS Complex Alternans in Haemodialysis Patients

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Received: July 13, 2015; **Published:** August 17, 2015

Abstract

Objective: To detect occurrence of T-wave and QRS alternans, to evaluate their independent predictors, and to estimate alternans change during haemodialysis (HD).

Methods: We studied 58 patients, mean age 59 ± 13 years, 52% males. We performed 1-minute ECG-recording before and after HD determining episodes of alternans.

Results: T-wave alternans episodes were present in 21% and 28% of patients pre-HD and post-HD, respectively, without significant change during the procedure. Pre-HD values were independently predicted by body mass index (BMI) (negative correlation) and number of cigarettes smoked (positive correlation). Post-HD values were predicted by usage of acetyl salicylic acid (ASA) and ferric substitutes (negative correlation) and baseline heart rate (positive correlation).

Episodes of QRS alternans were evident in 7 patients pre-HD and one post-HD: significant decrease during HD (from 0.26 ± 0.85 to 0.07 ± 0.53 number of alternans episodes, $p = 0.015$). Independent predictors for baseline QRS alternans values were BMI and ASA usage (negative correlation), baseline heart rate and calcium channel blocker usage (positive correlation).

Conclusion: Both T-wave and QRS alternans are present in HD-patients. T-wave alternans episodes did not change significantly during HD-procedure, while episodes of QRS alternans showed significant decrease. Regression analysis suggested protective effects for higher BMI and ASA usage in this group.

Keywords: *Electrocardiogram; Haemodialysis; QRS complex alternans; QRS alternans; T-wave alternans*

Abbreviations: ASA: Acetyl salicylic acid; BMI: Body mass index; CAD: Coronary artery disease; CCB: Calcium channel blockers; ECG: Electrocardiogram; HD: Haemodialysis; IQR: Inter quartile range; PCA: Principal Component Analysis; SCD: Sudden cardiac death; SD: Standard deviation; TWA: T wave alternans

Introduction

Repolarization abnormalities are a major risk factor for sudden cardiac death (SCD). Although many methods have been developed to assess the degree of repolarization heterogeneity, the optimal ECG characterization of ventricular repolarization is still a matter of debate. There are static measurements and dynamic repolarization markers. Electrical alternans belongs to the latter group and is defined as alternating patterns in QRS (QRS alternans) or ST segment and/or T wave (T-wave alternans) in consecutive cardiac beats. Electrical alternans occurs at the level of a single cardiomyocyte and is the result of intracellular disturbance in calcium handling. QRS and T-wave alternans reflect instability of cardiac depolarization and repolarization, respectively [1]. T-wave alternans is a continuous variable with higher values implementing greater risk for cardiovascular death and SCD [2,3]. The current recommendation is that it is reasonable to consider TWA evaluation whenever there is suspicion of vulnerability to lethal cardiac arrhythmias [4]. Electrical alternans of the QRS complex is an electrocardiographic phenomenon seen in different clinical situation - mainly supraventricular and ventricular tachyarrhythmia [5, 6]. Its clinical significance however has been less well studied [5-8].

A variety of algorithms and particular signal processing methods for detecting and quantifying TWA have been proposed, employing techniques as spectral analysis, complex demodulation, zero-crossings counting in a series of correlation coefficients, Karhunen - Loève transform, low-pass Capon filtering, Poincaré mapping, periodicity transforms, statistical tests, modified moving average, Laplacian likelihood ratio, etc. A review by Martínez and Olmos [9] highlights the need for methodological systematization effort in characterization and comparison of the different methods. But it remains very difficult to validate or to compare any of these algorithms, even the commercially available ones, since no generally accepted objective criteria exist for measuring TWA, and no generally available set of validation data exists as a basis for comparison. In an attempt to investigate this problem, PhysioNet and Computers in Cardiology organized a Challenge in 2008: "Detecting and quantifying T-wave alternans" [10].

Haemodialysis (HD) is the most commonly applied method used to treat end-stage renal disease patients. It removes waste products and free water from the blood, restoring the homeostasis with a proper balance of electrolytes. The process is related to a significant shift in extracellular water and blood volume and consequently to substantial changes in the electrical activity of the heart, observed by analysis of ECG. Before HD some of the patients present with significant electrolyte abnormalities which is an accepted risk factor for ventricular arrhythmias. Also there is epidemiological evidence that risk of SCD is increased immediately after HD [11]. Our aim was to evaluate T-wave and QRS complex alternans episodes in HD patients and to compare electrical alternans before and after an HD procedure.

Materials and Methods

Patient group

We studied 58 patients on chronic HD at a mean age of 59 years. Baseline characteristics of the study group are presented in table 1. Medical therapy is described in table 2. Digital ECGs (1-minute duration, 12-standard leads, and 500 Hz sampling rate) were recorded before and after HD sessions. Serum electrolytes (potassium-K, sodium-Na, phosphorus-Ph and calcium-Ca), urea and creatinine levels were evaluated before and after HD. We calculated also mean HD clearance.

Alternans detection

The method for T-wave alternans detection successfully participated in the Physionet/Computers in Cardiology Challenge, 2008, reaching the best score [12-14]. Further it was expanded for QRS alternans detection and quantification. First the ECG signals were preprocessed to eliminate or suppress the power line interference [15], the drift [16] and the electromyographic noise [17]. QRS detection was applied [18], onsets and offsets of the QRS complex and T wave were automatically delineated [19].

Later a multi-lead approach has been followed in order to extract single indices of the amplitude and the morphology of the wave from the entire ECG record. We used the ratio $2^{nd}/1^{st}$ eigenvalues of the Principal Component Analysis (PCA) for quantifying the complexity morphology index. The amplitude index was measured from the 3-D spatial vector calculated from the X, Y and Z vectors derived by the standard 12-leads. The PCA and amplitude indices were computed for the QRS and T wave intervals. The alternans detection was performed in an overlapping time window of 60 hearth beats (overlapping step = 10 beats) by separation of the parameters from odd and even RR intervals and the consequent statistical analysis on the two series with the non parametric paired-sampled Wilcoxon signed rank test. The 5% significance level of that statistical test is the threshold to determine the episode as alternans 'yes/no'. The process is repeated for every interval and the result is the number of the detected episodes with alternans. All the RR intervals were analyzed, independently of the presence of noise or artifact, and the heart rate was not considered.

Ethics

All patients signed an informed consent for personal data analysis. The study protocol was approved by the local ethical committee (Protocol No 3/30.03.2010) and is in accordance with the Declaration of Helsinki.

Variable	Distribution
Age (years) - mean ± SD	59.3 ± 12.5
Gender: male/female - number (%)	30 (52%)/28 (48%)
BMI (kg/m^2) - mean ± SD	25 ± 4.2
Duration of renal disease (years) - mean ± SD	9.7 ± 6.7
Duration of HD (years) - mean ± SD	5.2 ± 4.4
Arterial hypertension - number (%)	55 (95%)
Systolic blood pressure (mmHg) - mean ± SD	139.5 ± 15.8
Diastolic blood pressure (mmHg) - median (IQR)	80 (80-90)
Heart rate (beats per minute) - mean ± SD	78.2 ± 15
Hemoglobin (g/l) - mean ± SD	92.5 ± 10.6
Hematocrit (%) - mean ± SD	26.3 ± 4.6
Erythrocytes (x10^{12}/l) - mean ± SD	2.82 ± 0.4
Albumin (g/l) - mean ± SD	35.7 ± 3.5
Urea (mmol/l) - mean ± SD	19.6 ± 4.5
Creatinine (µmol/l) - mean ± SD	699.2 ± 155.2
Sodium (mmol/l) - mean ± SD	136.4 ± 3.4
Potassium (mmol/l) - mean ± SD	5.24 ± 0.72
Calcium (mmol/l) - mean ± SD	2.27 ± 0.19
Phosphorus (mmol/l) - mean ± SD	2.01 ± 0.52
Diabetes mellitus - number (%)	7 (12%)
Dyslipidemia - number (%)	16 (28%)
Present smokers - number (%)	20 (35%)
Ex-smokers - number (%)	11 (19%)
Years of smoking history - mean ± SD	26.9 ± 12.8
Number of cigarettes per day - mean ± SD	14.9 ± 7.9
Family history of CAD - number (%)	6 (10%)
CAD - number (%)	8 (14%)
History of myocardial infarction - number (%)	7 (12%)
History of coronary intervention - number (%)	5 (9%)
History of heart failure - number (%)	7 (12%)
History of peripheral artery disease - number (%)	3 (5%)
History of cerebrovascular disease - number (%)	5 (9%

Table 1: *Baseline characteristics of the study group.*

SD: standard deviation; IQR: interquartile range; BMI: body mass index; CAD: coronary artery disease.

Statistical analysis

We tested the distribution of continuous variables using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD), whereas non-normally distributed data - as median and interquartile range (IQR) (the difference between the 25th and 75th percentile). Categorical variables were presented in percentage terms. QRS and T-wave alternans were considered as continuous variables, as well as transformed to categorical variables based on the presence or absence of alternans. We compared patients' characteristics and baseline laboratory parameters between groups with and without QRS and T-wave alternans using one sample t test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. We performed a multivariable analysis using Linear Regression Model with the stepwise procedure with a criterion to enter ≤ 0.05 and criterion to remove ≥ 0.1. To determine independent predictors for post-HD T-wave alternans we both pre- and post-HD values of electrolytes, heart rate and blood pressure, along with other possible confounding variables. A two-tailed p value < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS statistical software for Windows version 13.0.

Drug Class	Distribution n (%)
Beta blockers	26 (45%)
CCB	26 (45%)
ACE inhibitors	10 (17%)
ARB	7 (12%)
Centrally acting antihypertensive agents	28 (48%)
Thiazide diuretics	2 (3%)
Loop diuretics	3 (5%)
Ferric substitutes	48 (83%)
Phosphate binders	8 (14%)
Vitamin D supplements	31 (53%)
Calcium supplements	18 (31%)
Erythropoietin	44 (76%)
ASA	45 (78%)
Folic acid	3 (5%)

Table 2: *Medical therapy in the studied population.*

CCB: calcium channel blockers; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; ASA: acetyl salicylic acid.

Results

T-wave alternans

Before HD T-wave alternans episodes were present in 12 patients (21%) and absent in 46 (79%). After HD we found episodes of T-wave alternans in 16 patients (28%). In the group of 12 patients with pre-HD T-wave alternans episodes, such episodes of electrical alternans persisted after HD in 5 of them (9% of the whole group and 42% of the subgroup with T-wave alternans before HD) and disappeared in 7 (12% of the whole group and 58% of the subgroup). T-wave alternans episodes as a new finding after haemodialysis appeared in 11 subjects (19% of the whole group). The mean value of all local episodes of detected T-wave alternans did not change significantly during HD: from 0.5 ± 1.84 to 0.78 ± 1.62 detected episodes, p = 0.17 table 3.

	Pre-HD	Post-HD
T-wave alternans - n (%)		
1 episode	9 (16%)	4 (7%)
2 episodes	1 (2%)	4 (7%)
3 episodes	0	4 (7%)
4 episodes	0	3 (5%)
≥ 5 episodes	2 (4%)	1 (2%)
T-wave alternans mean number of episodes	0.5 ± 1.84	0.78 ± 1.62
T-wave alternans presence	12 (21%)	16 (28%)

Table 3: *Prevalence and distribution of T wave alternans before and after HD.*

When we compared baseline characteristics and laboratory values between two subgroups of patients with presence (12 subjects) or absence (46 subjects) of T-wave alternans episodes before HD, we found that the two groups are very similar to each other. The only differences in the baseline characteristics were the following: patients with episodes of T-wave alternans had lower BMI (22.2 ± 3.2 vs 25.7 ± 4.2 kg/m^2, p = 0.008) and systolic blood pressure (123.3 ± 18.1 vs 140.1 ± 23.2 mmHg, p = 0.019) as compared to those without T-wave alternans episodes.

Multivariable regression analysis showed that independent predictors for pre-HD T-wave alternans value were number of cigarettes smoked per day and BMI (R Square for the model combining both parameters - 0.308). The correlation with the number of cigarettes per day was positive (i.e. the more cigarettes smoked, the higher T-wave alternans) while with BMI there was a negative correlation (i.e. the lower the BMI, the higher T-wave alternans values). Post-HD T-wave alternans values were independently predicted by the use of acetyl salicylic acid (ASA), ferric substitutes and heart rate before initiation of HD (R Square for the model combining all parameters - 0.721). There was a negative correlation for the use of ASA and ferric substitutes with T-wave alternans (i.e. those who used them had lower T-wave alternans values), while heart rate was positively correlated (i.e. the higher pre-HD heart rate, the higher T-wave alternans).

QRS alternans

Seven patients (12%) had episodes of QRS alternans before HD, mean number of episodes for the whole group - 0.26 ± 0.85. After HD QRS alternans episodes diminished significantly to a mean value of 0.07 ± 0.53, p = 0.015) and disappeared in all but one of the previously positive patients table 4.

	Pre-HD	Post-HD
QRS alternans - n (%)		
1 episode	3 (5%)	0
2 episodes	2 (4%)	0
3 episodes	1 (2%)	0
4 episodes	0	1 (2%)
5 episodes	1 (2%)	0
QRS alternans mean number of episodes	7 (12%)	1 (2%)
QRS alternans presence	0.26 ± 0.85	0.07 ± 0.53

Table 4: *Prevalence and distribution of QRS complex alternans before and after HD.*

When we compared groups with or without pre-HD QRS alternans episodes, there was not a significant difference in any of the demographic characteristics, renal disease or HD duration, risk factors for or evidence of cardiovascular disease, baseline hemodynamic parameters, electrolyte concentration, urea and creatinine levels. There was, however, difference in the uptake of some medication classes: patients with episodes of QRS alternans were less likely to take ASA (p < 0.001) and more likely to receive centrally acting antihypertensive agents (p = 0.048) and angiotensine-receptor blockers (p = 0.032) compared to those without episodes of QRS alternans.

Multivariable linear regression analysis showed that independent predictors for the number of pre-HD QRS alternans episodes were the use of ASA and calcium channel blockers (CCB), baseline heart rate and BMI. Again there was negative correlation between ASA usage and BMI and QRS alternans (i.e. protective effect of ASA and higher BMI). Correlation of QRS alternans with CCB usage and baseline heart rate was a positive one (i.e. subjects who took CCB and had higher baseline heart rate, had higher QRS alternans values).

History of CAD was present in 8 patients (14%). None of the patients had evidence of acute myocardial ischemia during haemodialysis, as evidenced by ECG and absence of symptoms. Presence of CAD did not correlate significantly with, and was not an independent predictor of, episodes of T-wave or QRS complex alternans pre- or post-haemodialysis.

Discussion

Analyzing a group of HD patients we were able to find that T-wave alternans episodes are present in a considerable number of subjects but did not change significantly after an HD session. Independent predictors for higher pre-HD T-wave alternans values were more cigarettes smoked per day and lower BMI, and for higher post-HD T-wave alternans values - higher baseline heart rate and non-usage of ASA and ferric substitutes. Episodes of QRS alternans diminished significantly after HD as compared to pre-HD values. Higher baseline QRS alternans values were independently predicted by lower BMI, increase in baseline heart rate, non-usage of ASA and usage of CCB.

Our results are in accordance with a study of Green., *et al*. [20] - in a group of 19 HD-patients the authors found that TWA did not change significantly after HD, nor did it correlate with any laboratory or echocardiographic parameters. Other studies have found high prevalence of T-wave alternans in HD subject (higher than what we have found in our analysis) but without variability between recognized periods of variable risk [21]. We were not able to find any studies evaluating QRS alternans during HD and in chronic kidney disease patients. There is, however, a significantly small study (15 participants) by Ojanen., *et al*. [22] showing that QRS vector difference and ST segment vector magnitude change significantly during HD, giving a false impression of myocardial ischemia. Simova., *et al*. [23] have also reported a significant increase of the QRS area and maximal vector in VCG as result of HD. These VCG dynamics were related mostly to a change in extracellular water and blood volume.

The positive correlation between microvolt T-wave alternans and heart rate is well known. In the present study we found a similar positive correlation between QRS alternans and heart rate. This means that until data of the exact relation of QRS alternans and heart rate in different populations (especially in those with established risk of sudden death) become available, the clinical interpretation of QRS alternans remains unknown.

An interesting finding in our study (and also persistent in different settings) was the protective effect of higher BMI - predicting lower T-wave and QRS alternans values. Obesity of course is a well-known and accepted risk factor for cardio-vascular disease but probably in the setting of advanced disease (such as end-stage renal disease) increased body weight could play a protective role. This is in line with the so called “obesity paradox” hypothesis that has been largely discussed in several other disease settings [24,25].

“Obesity paradox” has received a lot of attention recently. On one side there are indisputable evidence and impressive consistency on the effects of obesity on the incidence of diabetes [26], cardiovascular disease [27], and much other morbidity [26], which could be involved in the pathogenesis of chronic kidney disease. On the other hand there are data that for patients with chronic kidney disease, end-stage renal disease and on HD having more fat mass results in better survival, i.e. obesity paradox [28,29]. Our study however is too small to have a significant influence in confirming the presence of obesity paradox in this population.

The other consistent finding that ASA usage is related to lower T-wave and QRS alternans values is not a surprise, since ASA has been proven long ago to protect against cardiovascular mortality, including SCD, in secondary and also in many primary prevention settings [30]. We did not, however, find any studies evaluating the effect of ASA usage on T wave or QRS complex alternans.

Limitations

This is a single center study and we have included only patients on a maintenance HD in a single HD center. That explains the relatively small study group (58 subjects). Multivariable linear regression analysis was carried out on even smaller subgroups of patients (12 patients - 21% with T-wave alternans episodes before HD, 16 patients - 28% with T-wave alternans episodes after HD and 7 patients - 12% with episodes of QRS alternans before HD) which could compromise the reliability of our results.

Another limitation is the fact that MMA alternans measurement was done on one-minute ECG recordings instead of the more accepted method of 24 (48)-hour ambulatory Holter ECG recording.

Conclusion

Electrical alternans is present in a significant number of patients undergoing HD. Number of patients with episodes of T-wave alternans did not change significantly during HD, while episodes of QRS alternans showed a significant decrease after an HD procedure. Regression analysis suggested protective effects (lower T-wave and QRS alternans values) for higher BMI and ASA usage in this group.

Acknowledgements

The study is supported by the "Short Term Mobility 2014" Program of CNR, Italy.

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Volume 2 Issue 1 August 2015