Circadian Modulation of Electrocardiographic Alternans in Kidney Failure Patients on Dialysis

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Abstract

Circadian rhythm (periodicity: 24 h) can modulate trends of indices based on the electrocardiogram (ECG), as ECG alternans (ABAB fluctuation of ECG waves; ECGA). This work aims to verify if circadian rhythm modulates ECGA in kidney failure patients - to our knowledge, not investigated yet - and to study the effect of dialysis treatment. ECGA was analyzed on 51 long-term (48 h on average) 12-lead ECG from end-stage renal disease (ESRD) patients. Acquisitions included dialysis, night after, and following day and night. Measures of P-wave, QRS-complex and T-wave alternans (PWA, QRSA, and TWA, respectively; μV) were obtained using the enhanced adaptive matched filter method. Results indicate that, in dialysis-free days, ECGA trend was affected by circadian modulation. PWA/QRSA/TWA trends reached their minima during the night and their maxima during the day (lead average, 7/9/16 μV and 11/16/20 μV, respectively; $p<0.05$). Dialysis interrupted ECGA circadian periodicity, reducing daytime PWA/QRSA/TWA (lead average, 8/12/17 μV). Generally, ECGA values increased from dialysis to 24 h after, by +39%, +31% and +20% for PWA, QRSA, and TWA, respectively. Thus, in our ESRD population, circadian modulation affected ECGA, and dialysis treatment interrupted its periodicity, causing a decrement of ECGA.

1. Introduction

Biological rhythms are repetitive phenomena happening in living organisms (including humans) to adapt to the environment. Each biological rhythm has its own periodicity. Circadian rhythm is one of the most studied, with a periodicity of 24 h. The 24-h periodicity essentially lays on the day alternation between activity, typical of the diurnal period, and rest, typical of the nocturnal period. The dynamics of the human cardiovascular system are modulated by the circadian rhythm, so that it can optimize resources according to the person's condition. This adapting ability is reflected into the indices extracted from the electrocardiogram (ECG), *e.g.*, heart rate, heart-rate variability, or QT dispersion [1]. Given the clinical role of ECG indices for the diagnosis of cardiovascular diseases, knowing their circadian modulation is important.

Circadian modulation affects ECG alternans (ECGA) and, specifically, T-wave alternans (TWA) [1]. TWA is the most known manifestation of ECGA. It is an electrophysiological phenomenon manifesting in the ECG as the fluctuation of the morphology, amplitude, and/or shape of the T wave according to an every-other-beat pattern [2]. Analogously, the fluctuation of the other waves/complex, as P wave and QRS complex (*i.e.*, P-wave alternans - PWA - and QRS-complex alternans - QRSA), looms on ECGA. ECGA clinical role is to unmask cardiac instabilities possibly leading to severe or even malignant arrhythmias. Hashimoto et al. studied TWA circadian modulation in a healthy population for a period of 24 h, and observed maximum TWA between 12:00 am and 6:00 pm, and minimum TWA between 00:00 am and 6:00 am [3]. Analogous trends were found out by Martín-Yebra et al. analyzing chronic heart failure patients and by Kanazawa et al. analyzing patients with implanted cardioverter defibrillator [4,5].

Given the link between the cardiovascular system and the urinary system, some anomalies, or simply variations, affecting one of the two systems can have indirect consequences on the other. Kidney failure patients show ECGA, and dialysis treatment seems to have consequences on ECGA dynamics, although its link with the clinical outcome is still unclear [6-8]. ECGA evidence associated with dialysis treatment could be interpreted considering that dialysis treatment involves ion rebalancing and ECGA is driven by ion passage across cardiocyte membrane. To our knowledge, circadian rhythm effect on kidney failure patients' ECGA around the dialysis treatment hasn't been investigated yet.

This work aims to verify if circadian rhythm modulates ECGA in a population of end-stage renal disease (ESRD) patients considering an observation period of 2 days (the day of dialysis session and the day after) and to study the effect of dialysis treatment on ECGA daily trend.

2. Clinical data

The analyzed data belong to the "E-HOL-12-0051-016" database of Telemetric and Holter ECG Warehouse (THEW; http://thew-project.org/). Data consist of continuous long-term (48 h on average) 12-lead ECG from ESRD patients. Acquisitions included dialysis, which lasted 4 h on average (possible start times: early morning, 6:00 am - 8:00 am; late morning, 10:00 am – 12:00 am; early afternoon, 14:00 am – 16:00 am), following night, and following day and night. ECG sampling frequency was 1000 Hz, and ECG amplitude resolution was 0.5 μV. R-peak positions were available as annotations.

Criteria of patients' enrollment were: 1) being high-risk ESRD patient for cardiac arrhythmias and sudden cardiac death; 2) being over 40 years old; and 3) having a confirmed history of hypertension or diabetes requiring treatment. Criteria of exclusion were: 1) being with class-I antiarrhythmic; 2) having a pacemaker or an implanted cardioverter defibrillator; 3) being with cardiac resynchronization therapy; 4) having a history of chronic atrial fibrillation; 5) being female subject of childbearing potential not using medically prescribed contraceptive measures; 6) being a participant of other trials; 7) being unable to cooperate with the designed protocol due to dementia, psychological or similar reasons. According to these criteria, 51 ESRD patients (30/21 male/female, 40 to 95 years old) with significant risk for cardiac arrhythmias and sudden cardiac death were enrolled in one of the University of Rochester Medical Center affiliated out-patient dialysis centers.

Enrolled patients gave their informed consent to participate. The consent forms were communicated and signed by the patients prior to ECG acquisition.

3. Methods

3.1. Analysis by the enhanced adaptive matched filter

Measures of PWA, QRSA and TWA were obtained using the enhanced adaptive matched filter (EAMF) method [9]. The analysis was performed on each available lead and on 128-heartbeat ECG windows recursively extracted every second.

According to the EAMF-based analysis procedure, firstly, the ECG window was resampled to 200 Hz, band-pass filtered using a 6^{th} order bidirectional Butterworth filter with cut-off frequencies of 0.3 Hz and 35 Hz, and deprived of the baseline. From R-peak positions (annotations were optimized as needed), mean RR interval was computed, and heartbeat fiducial points were localized. Fiducial points are the major ECG waves endpoints: specifically, the onset points of P wave and Q wave (Pon and Qon, respectively), and the end of QRS complex and T wave (J and Tend, respectively). They were exploited to identify three adjoining sections of each heartbeat: the heartbeat portion from Pon to Qon, called P section, the heartbeat portion from Qon to J, called QRS section, and the heartbeat portion from J to Tend, called T section. Starting from these sections, three signals were determined through the ECG signal enhancement. It consists in forcing to the baseline value the signal amplitude of all sections except the one of interest. EAMF processes in parallel the resulting signals (P, QRS and T signals) if the ECG window from which they are derived satisfies two suitability conditions: RR-interval standard deviation does not exceed 10% of the mean RR; ectopic or noisy beats are at most 10. Ectopic or noisy beats are defined as the ones that have the QRS and/or T sections that correlate less than 0.85 with the corresponding sections of the reference beat (computed as the median over the 128 heartbeats) and they are replaced by the reference beat if they are 10 or less. If both suitability conditions are satisfied, the P, QRS and T signals are computed and processed by the EAMF, otherwise ECGA analysis cannot be performed.

EAMF is implemented as a 6^{th} order bidirectional Butterworth bandpass filter, with a narrow passing band centered around alternans frequency (AF), which is equal to half heart rate, by definition. Specifically, the passing band is included between AF-0.06 Hz and AF+0.06 Hz [9]. The filter output is a pseudosinusoid and the double of its amplitude defines the local PWA, QRSA and TWA amplitude (one value per heartbeat; μV) according to the input signal (P signal, QRS signal and T signal, respectively). Eventually, median alternans amplitude was computed for each ECG window.

3.2. Statistics

ESRD population was divided into three groups based on the time at which dialysis session started: 20 patients (39%) belonged to the early morning group (EM); 20 patients (39%) to the late morning group (LM); 11 patients (22%) to the early afternoon group (EA). Median PWA, QRSA and TWA were computed for each lead every 10 min. For each group, cumulative (with respect to the patients) PWA, QRSA and TWA lead trends (representative of the three groups) were computed. Each trend was further fitted by a polynomial of order 14 to cancel possible local rapid changes, hardly attributable to physiological phenomena. Then, the mean among the 12 lead PWA/QRSA/TWA trends (representative of the three groups) was computed, obtaining an overall trend for each group (and for each ECGA kind).

Nighttime was defined as the period from 7:00 pm to 7:00 am, while daytime was defined as the period from 7:00 am to 7:00 pm. Specifically, two nighttime/daytime couples were determined: one in the first day (N1 and D1,

respectively) and one in the second day (N2 and D2, respectively). The time (t1) at which N1 and N2 minima were more frequent among the 12 leads, and the time (t2) at which D1 and D2 maxima were more frequent among 12 leads were evaluated. Values registered at t1 in both N1 and N2 (mN1 and mN2, respectively) and at t2 in both D1 and D2 (MD1 and MD2, respectively) were extracted from the 12 lead PWA/QRSA/TWA trends. Also, values registered 2 h after the dialysis start time (and, thus, during dialysis, DD) and 24 h later (and, thus, post dialysis, PD) were extracted. Then, median values and interquartile ranges (IQR= $75^{th} - 25^{th}$ percentiles) were computed over the 12 leads to characterize MD1, MD2, mN1, mN2, DD, and PD distributions. Statistical differences of MD1 vs. mN1, MD2 vs. mN2, and DD vs. PD were tested for each group by the Wilcoxon signed-rank test, setting the statistical significance (p) to 0.05.

4. Results

Results about the ECGA overall trends are shown in Figure 1, where D1/D2, N1/N2 and dialysis session periods are on white, gray, and red backgrounds, respectively. Excluding the red area, PWA fluctuates around 9/10/10 µV, QRSA around 13/12/11 µV, and TWA around 16/18/19 µV in EM/LM/EA groups, showing 2 couples of local maximum/minimum equally distributed (12 h away from each other) along the 48 h of observation (t1= 3:50 am; t2= 3:50 pm). Maximum values extracted in D1 and D2 (*i.e.*, MD1, MD2) and minimum values extracted in N1 and N2 (*i.e.*, mN1, mN2) are reported in Table 1, while ECGA values extracted during the dialysis session and 24 h later are reported in Table 2. In Tables 1 and 2, total values were computed as the median over the features of the three distributions.

5. Discussion and conclusion

In our ESRD population, ECGA revealed a higher cardiovascular risk than in healthy population. This confirms the known increased risk of mortality (linked to the function decline of kidneys) due to cardiovascular complications occurring in chronic kidney disease [10]. Several studies have investigated the effect of dialysis on daily ECGA trends (TWA in particular), reaching rarely concordant results [6-8,11], but, as far as we know, there are no published ones that also integrate the evaluation of the circadian rhythm modulation.

Figure 1 indicates that, in dialysis-free days, ECGA trend was modulated with a periodicity of 24 h: in general, PWA, QRSA and TWA decreased in nighttime and increased in daytime. This is confirmed by ECGA amplitudes in Table 1. The definition of N1/N2 and D1/D2 is arbitrary since conditioned by many factors. Here, we decided to divide the 24-h day into two equal periods that would likely correspond to the periods of higher patient's activity (7:00 am-7:00 pm) and rest (7:00 pm-7:00 am). In these periods, time at which

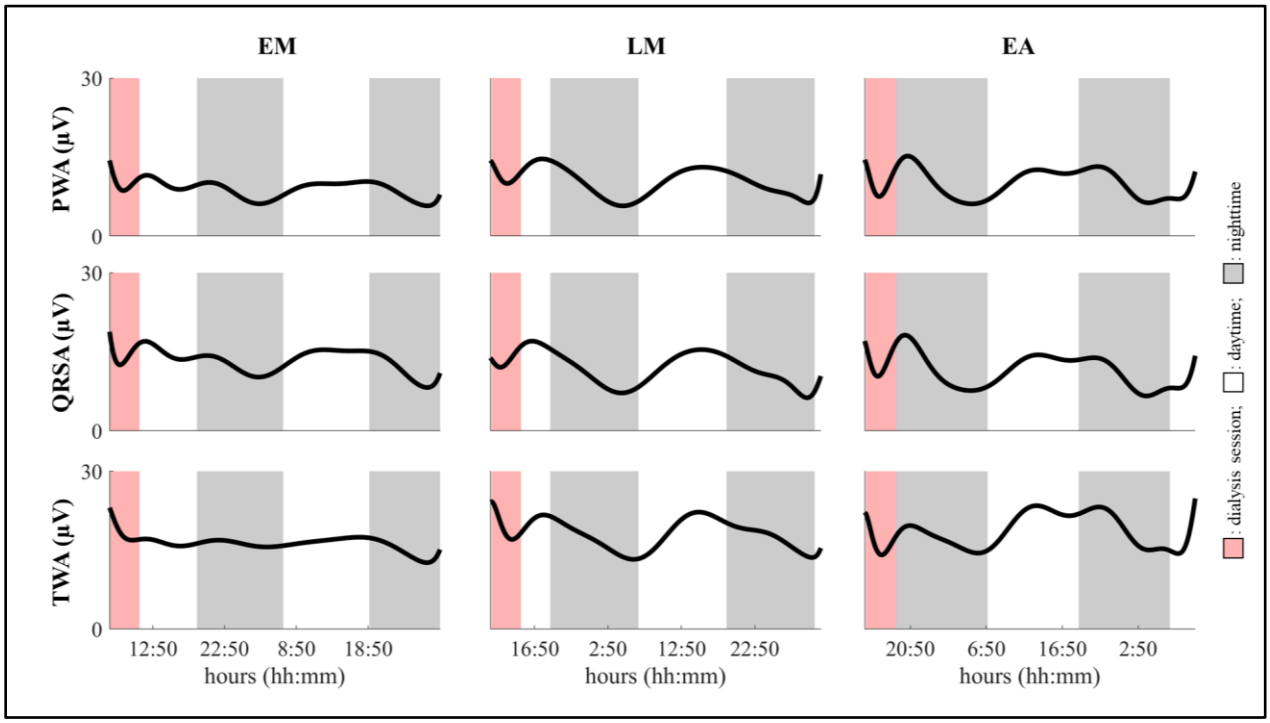

Figure 1. PWA (first row), QRSA (second row) and TWA (third row) overall trends for patients groups with different dialysis starting time: EM (first column), LM (second column) and EA (third column).

Table 1. Median(IQR) ECGA values extracted from the daytime and nighttime of the dialysis day (first acquisition day) and from the daytime and nighttime of the day after (second acquisition day).

	PWA (µV)				QRSA (µV)				TWA (µV)			
	MD1	**mN1**	**MD2**	**mN2**	**MD1**	**mN1**	**MD2**	**mN2**	**MD1**	**mN1**	**MD2**	**mN2**
EM	9(4)	6*(4)	10(4)	6*(4)	15(5)	11*(5)	16(6)	8*(4)	17(7)	16(6)	18(8)	13*(5)
LM	14(3)	7*(4)	13(6)	9*(5)	18(7)	9*(5)	17(6)	10*(5)	21(8)	17*(5)	23(10)	18*(9)
EA	9(5)	6*(4)	13(8)	7*(5)	12(5)	8*(5)	16(8)	9*(7)	17(7)	14*(5)	23(10)	16*(9)
Tot	**10(4)**	**6*(5)**	**13(7)**	**7*(4)**	**15(5)**	**9*(5)**	**17(6)**	**9*(4)**	**17(7)**	**16*(6)**	**22(10)**	**16*(8)**

EA: early afternoon; EM: early morning; LM: late morning; MD1: maximum registered at 3:50 pm in D1; MD2: maximum registered at 3:50 pm in D2; mN1: minimum registered at 3:50 am in N1; mN2: minimum registered at 3:50 am in N2; *: $p<0.05$.

Table 2. Median(IQR) ECGA values extracted from the dialysis session period and 24 h later.

	PWA (µV)		QRSA (µV)		TWA (µV)	
	DD	**PD**	**DD**	**PD**	**DD**	**PD**
EM	8(5)	10(4)	13(6)	16(5)	17(9)	17(7)
LM	10(4)	13(5)	12(5)	16(6)	18(6)	22(8)
EA	8(5)	13*(8)	11(6)	15(7)	16(7)	22*(11)
Tot	**8(5)**	**13*(7)**	**12(5)**	**16*(5)**	**17(7)**	**21*(10)**

DD: 2 h after dialysis start time; EA: early afternoon; EM: early morning; LM: late morning; PD: 24 h after DD; *: $p<0.05$.

maximum/minimum ECGA values were mostly registered (*i.e.*, t1 and t2) are concordant with observations from other studies [3,4]. Dialysis interrupted the circadian periodicity of ECGA, causing a decrement of PWA/QRSA/TWA (lead average, 8/12/17 µV) in daytime. Indeed, in quite all cases, ECGA values increased from dialysis to 24 h after. Maximal increments were +63%, +36%, and +38% for PWA, QRSA and TWA, respectively, and they were registered always in EA group. Thus, during afternoon, when ECGA reaches its highest values, dialysis influence is more perceivable than in periods in which ECGA is already lower. Mean increments of PWA, QRSA and TWA were +39%, +31% and +20%. This may suggest that PWA benefits the most from dialysis ion rebalancing.

In conclusion, in our kidney failure population, ECGA was affected by circadian modulation and dialysis treatment interrupted its periodicity, causing a decrement in all forms (PWA/QRSA/TWA) of ECGA. Further studies, considering more factors influencing ECGA (e.g., comorbidities and medicaments), are needed to possibly confirm and better interpret the observed results.

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