

Hemodialysis Procedure—Associated Autonomic Imbalance and Cardiac Arrhythmias: Insights From Continuous 14-Day ECG Monitoring

Nichole M. Rogovoy, BS; Stacey J. Howell, MD; Tiffany L. Lee, BA; Christopher Hamilton, BA; Erick A. Perez-Alday, PhD; Muammar M. Kabir, PhD; Yanwei Zhang, MS; Esther D. Kim, MPH; Jessica Fitzpatrick, PhD; Jose M. Monroy-Trujillo, MD; Michelle M. Estrella, MD, MHS; Stephen M. Sozio, MD, MHS, MEHP; Bernard G. Jaar, MD, MPH; Rulan S. Parekh, MD; Larisa G. Tereshchenko, MD, PhD

Background—In patients with end-stage kidney disease, sudden cardiac death is more frequent after a long interdialytic interval, within 6 hours after the end of a hemodialysis session. We hypothesized that the occurrence of paroxysmal arrhythmias is associated with changes in heart rate and heart rate variability in different phases of hemodialysis.

Methods and Results—We conducted a prospective ancillary study of the Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease cohort. Continuous ECG monitoring was performed using an ECG patch, and short-term heart rate variability was measured for 3 minutes every hour (by root mean square of the successive normal-to-normal intervals, spectral analysis, Poincaré plot, and entropy), up to 300 hours. Out of enrolled participants ($n=28$; age 54 ± 13 years; 57% men; 96% black; 33% with a history of cardiovascular disease; left ventricular ejection fraction $70\pm 9\%$), arrhythmias were detected in 13 (46%). Nonsustained ventricular tachycardia occurred more frequently during/posthemodialysis than pre-/between hemodialysis (63% versus 37%, $P=0.015$). In adjusted for cardiovascular disease time-series analysis, nonsustained ventricular tachycardia was preceded by a sudden heart rate increase (by 11.2 [95% CI 10.1–12.3] beats per minute; $P<0.0001$). During every-other-day dialysis, root mean square of the successive normal-to-normal intervals had a significant circadian pattern (Mesor 10.6 [95% CI 0.9–11.2] ms; amplitude 1.5 [95% CI 1.0–3.1] ms; peak at 02:01 [95% CI 20:22–03:16] AM; $P<0.0001$), which was replaced by a steady worsening on the second day without dialysis (root mean square of the successive normal-to-normal intervals -1.41 [95% CI -1.67 to -1.15] ms/24 h; $P<0.0001$).

Conclusions—Sudden increase in heart rate during/posthemodialysis is associated with nonsustained ventricular tachycardia. Every-other-day hemodialysis preserves circadian rhythm, but a second day without dialysis is characterized by parasympathetic withdrawal. (*J Am Heart Assoc.* 2019;8:e013748. DOI: 10.1161/JAHA.119.013748.)

Key Words: electrocardiography • heart rate/heart rate variability • hemodialysis • trigger clusters • ventricular arrhythmia

Sudden cardiac death (SCD) is the most common cause of death in end-stage kidney disease (ESKD) patients receiving dialysis.^{1,2} Both tachy- and bradyarrhythmias may

play a causative role in SCD in ESKD.^{3–5} Importantly, the phases of hemodialysis relate to the rate of SCD.^{6–9} Mortality increases after a long interdialytic interval, within 6 hours after the end of a hemodialysis session.^{6–8} The dialysis procedure itself triggers multiple mechanisms that can increase the propensity to cardiac arrhythmias.¹⁰ Oscillations in electrolyte levels and fluid volume, a pro-inflammatory state, repetitive myocardial injury from uremia and other toxins,¹⁰ and myocardial stunning¹¹ are hemodialysis-specific risk factors for SCD. A SCD event exemplifies a perfect storm, requiring both a susceptible substrate and a trigger.¹² Together the exposure to SCD risk factors related to fluctuating hemodialysis sessions and traditional SCD triggers can explain the extremely high rate of SCD in dialysis patients.

Autonomic imbalance of the heart is traditionally associated with SCD. Under normal conditions, the autonomic system controls heart rate and rhythm via a balance between the parasympathetic and sympathetic systems. Heart rate

From the Oregon Health & Science University, Portland, OR (N.M.R., S.J.H., T.L.L., C.H., E.A.P.-A., M.M.K., Y.Z., L.G.T.); The Hospital for Sick Children, The University of Toronto, Ontario, Canada (M.M.K., E.D.K., J.F., R.S.P.); Johns Hopkins University, Baltimore, MD (E.D.K., J.M.M.-T., M.M.E., S.M.S., B.G.J., R.S.P., L.G.T.); Kidney Health Research Collaborative, University of California San Francisco, CA (M.M.E.); San Francisco VA Health Care System, San Francisco, CA (M.M.E.).

Accompanying Tables S1 through S8 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013748>

Correspondence to: Larisa Tereshchenko, MD, PhD, 3181 SW Sam Jackson Park Rd, UHN62, Portland, OR 97239. E-mail: tereshch@ohsu.edu

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Clinical Perspective

What Is New?

- Nonsustained ventricular tachycardia is more frequent during hemodialysis or within 6 hours posthemodialysis.
- In incident hemodialysis patients, heart rate sharply increases before nonsustained ventricular tachycardia events, suggesting a triggered ventricular tachycardia mechanism.
- Every-other-day hemodialysis preserves physiological circadian rhythm in heart rate and heart rate variability, whereas the extension of the interdialytic period for the second day abolishes circadian rhythm and shows a steady deterioration in autonomic disbalance.

What Are the Clinical Implications?

- The harmful effect of the 2-day interval without hemodialysis suggests that more frequent dialysis should be considered the preferred prescribed treatment schedule.
- Improvement of patient adherence—avoiding missing hemodialysis sessions—can improve patient outcomes.
- Diagnosis of autonomic imbalance in end-stage kidney disease patients presenting with bradycardia is difficult. In end-stage kidney disease, an autonomic disbalance is manifested by parasympathetic withdrawal and impaired baroreflex sensitivity, and use of β -blockers attenuates association of heart rate with nonsustained ventricular tachycardia, suggesting potential treatment benefit of β -blocker use, which should be studied further.

variability (HRV) is a measure of fluctuations in the autonomic system and baroreflex sensitivity.^{13,14} Parasympathetic withdrawal and increased sympathetic input decreases HRV and triggers SCD.¹² Previous studies using 24-hour Holter electrocardiogram recordings reported the association of depressed HRV¹⁵ with increased mortality in ESKD patients.^{16–18} However, 24- or even 48-hour Holter ECG recordings are too short to study the association of fluctuating autonomic tone with the standard 7-day hemodialysis schedule. Whether autonomic imbalance associates with both the dialytic cycle and cardiac arrhythmias in dialysis patients remains unknown. Longitudinal changes in autonomic tone before, during, and after hemodialysis procedures, along with their association with brady- and tachyarrhythmias, have not been previously studied.

To address this knowledge gap, we conducted an ancillary prospective study in a subset of incident hemodialysis patients, enrolled in the PACE (Predictors of Arrhythmic and Cardiovascular Risk in End Stage Renal Disease) study.^{2,19} We hypothesized that in incident hemodialysis patients, clinical characteristics and paroxysmal arrhythmias are associated

with periodic changes in heart rate and HRV in different phases of hemodialysis.

Methods

Developed for the data analysis, software code is available at GitHub and can be accessed at <https://github.com/Tereshchenkolab/HRV>. In order to minimize the possibility of unintentionally sharing information that can be used to re-identify private information, a subset of the deidentified data generated for this study is available at GitHub.²⁰

Study Population

We conducted a prospective ancillary study within PACE.¹⁹ Both the parental PACE study and this ancillary study were approved by the Johns Hopkins Institutional Review Board, and all participants provided written informed consent.

The PACE study design has been previously described.^{2,19} Briefly, the study enrolled adult ESKD patients who had started in-center hemodialysis within 6 months of enrollment. Patients on home hemodialysis, peritoneal dialysis, in hospice or skilled nursing facility, and patients with an implanted pacemaker or cardioverter-defibrillator were not eligible. At enrollment, participants underwent comprehensive cardiovascular evaluation, which included several types of ECG, echocardiogram, cardiac computed tomography, and coronary angiography.

This ancillary study included randomly selected PACE participants who underwent baseline cardiovascular evaluation and agreed to undergo continuous ECG monitoring for at least 7 days.

Clinical Covariates

Prevalent coronary artery disease (CAD), cerebrovascular disease (CVD), congestive heart failure (CHF), hypercholesterolemia, hypertension, and diabetes mellitus were determined by participant's self-report and physician's diagnosis recorded in the medical record. Participants were asked to bring in their medications, and medication use was recorded during the baseline visit. To assess subjective postdialysis recovery time, participants answered the question: "How long does it take you to recover from a dialysis session?" during a telephone interview, conducted within 30 days of ECG monitoring.

Echocardiography was performed at the PACE echocardiographic core laboratory,¹⁹ where left ventricular ejection fraction, left ventricular dimensions, and left ventricular mass index were measured as previously described.¹⁹ Left ventricular hypertrophy was defined as an echocardiographic left ventricular mass index ≥ 116 g/m² in males or ≥ 104 g/m² in females.

Changes in weight and sitting systolic and diastolic blood pressure before and after each dialysis session were recorded for this study's participants.

Dialysis bath (dialysate concentrations of calcium and potassium) data are reported as a 3-month average. All participants received a dialysate Mg concentration of 1.0 mEq/L, and a dialysate bicarbonate concentration of 40 mmol/L. Three-month averaged intradialytic weight change was calculated. Serum calcium and potassium were assessed as a 3-month average of predialysis measures before the study clinic visit.

Continuous ECG Monitoring Using ECG Patch

Continuous ECG monitoring was performed using an ECG patch (Zio Patch, iRhythm Technologies, Inc., San Francisco, CA). During the study visit, a study coordinator applied the device over the left pectoral region,²¹ and instructed the participant to activate a trigger button in the event of cardiac symptoms (presumed arrhythmia). Participants were instructed to wear the adhesive ECG patch for as long as possible, with the goal of obtaining at least 7 days of continuous ECG recording. After completion of the ECG recording, participants mailed the ECG patch to iRhythm Technologies, Inc, which provided their standard US Food and Drug Administration–approved report to the study investigators—via a secure website. The Zio Patch report was reviewed within 24 hours by the study investigators, and clinically important findings were communicated with participants and their healthcare providers. In addition, continuously recorded raw digital ECG signal was provided by iRhythm Technologies, Inc for further analyses.

Diagnosis of cardiac arrhythmias

Per the standard iRhythm Technologies protocol, the following arrhythmias were diagnosed: atrial fibrillation (AF) or flutter (>4 beats), supraventricular tachycardia (>4 beats), pause >3 s, atrioventricular block of the second or the third degree, ventricular tachycardia (VT, >4 beats), or polymorphic VT/ventricular fibrillation. All arrhythmic events captured by the Zio Patch report were reviewed and validated by at least 2 study investigators (LGT, RSP, SH).

Phases of Hemodialysis

To determine the association of the intermittent hemodialysis sessions with heart rate and HRV time-series, we used hemodialysis phases accepted in the nephrology field relative to their proximity to a hemodialysis treatment (Figure 1). Every study participant underwent hemodialysis (4–5 hours, phase 1), postdialysis (6 hours immediately after hemodialysis, phase 2), between-hemodialysis (variable length, phases 3, 3–5, and 3–7), and predialysis (6 hours preceding dialysis,

phases 4, 6, and 8) phases. Over the course of the 7-day cycle, dialysis treatment–adherent study participants were dialyzed every other day for 5 days (either Monday/Wednesday/Friday or Tuesday/Thursday/Saturday; a total of 3 treatments weekly) and then experienced a 2-day-long interdialytic interval. For example, for an adherent Monday–Friday schedule, the regular interdialytic period was ≈32 hours, and the length of the prolonged interdialytic period over the weekend was much longer at about 56 hours. Nonadherent participants (n=4) did not follow this standard dialytic pattern. Their treatment schedule was interrupted by missed hemodialysis treatments, leading to a variable prolonged interdialytic period of at least 72 hours or longer.

HRV Measurements

A raw single-lead digital ECG signal (sampling rate 200 Hz; amplitude resolution 4.88 μV) was analyzed in the Tereshchenko laboratory at the Oregon Health & Science University. Figure 2 shows examples of the ECG signal and detected cardiac arrhythmia. A custom MATLAB (The MathWorks, Inc, Natick, MA) software application was developed (NMR, EAPA, MMK; provided at <https://github.com/Tereshchenkolab/HRV>) to automatically detect QRS complexes and select a single 3-minute normal sinus rhythm epoch for each hour of recording. The algorithm automatically eliminated epochs with premature R₂ beats if the R₁R₂ interval was shorter than the preceding R₀R₁ interval by 15% or greater. The algorithm similarly eliminated epochs with a sudden pause, if subsequently the R₁R₂ interval was longer than the preceding R₀R₁ interval by 15% or greater, to remove epochs with blocked premature atrial or His extrasystoles, or intermittent sinoatrial or atrioventricular block. Traditionally, in Holter ECG analysis, the premature atrial beat was defined by a coupling interval of <80% of the mean RR interval.²² We applied a more stringent threshold after manually reviewing our ECG data with thresholds ranging from 2% to 20%. A sliding 3-minute window approach was used to scan the entirety of the data: when a premature beat (or sudden pause) was detected, the premature beat and subsequent compensatory pause were skipped, and a new 3-minute window search started thereafter again. If the algorithm did not find a continuous 3-minute epoch of sinus rhythm in an entire hour, the software would change the R-peak detection algorithm²³ and repeated all steps described above. The first R-peak detection algorithm used was a Pan-Tompkins,²⁴ followed by principal component analysis,²⁵ and then parabolic fitting.²⁶ Because the magnitude of R and S peaks varied within and between patients, the dominant peak of the QRS complex varied during this ECG monitoring. We paid special attention to ensure consistent signs of the dominant QRS peak for the entire 3-minute epoch. The greatest average Manhattan distance from baseline to the highest positive (R)

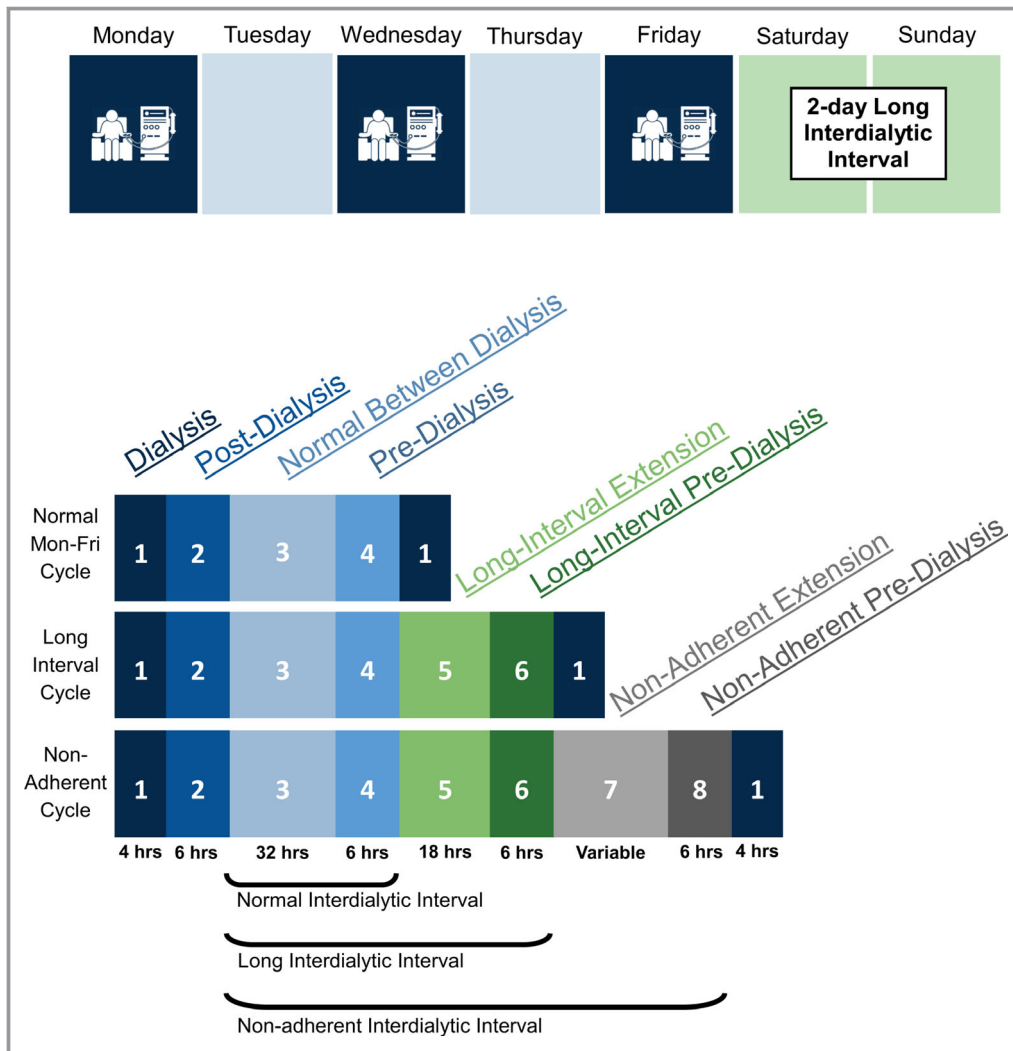


Figure 1. A schematic presentation of the dialytic cycles used for analysis. Blue color indicates phases within 48 hours of the last treatment, green color highlights the phases included to analyze the extra 24 hours between treatments in the 2-day-long interdialytic interval, and gray color symbolizes the phases that were included to analyze >72-hour interdialytic intervals for those who were nonadherent.

peak and highest negative (S) peak was calculated to identify the best dominant peak for each 3-minute epoch. The accuracy of consistent dominant (R or S) peaks detection, and accuracy of the selection of consecutive normal sinus beat were validated on a data subset by the investigator (NMR), with the aid of a graphical display.

HRV was measured according to the Standards.^{27,28} Developed (by MMK) MATLAB (the MathWorks, Inc, Natick, MA) software code is provided at <https://github.com/Tere shchenkolab/HRV>.

Time-domain HRV measures

Heart rate and the root mean square of the successive normal sinus to normal sinus (NN) intervals differences (rMSSD) were calculated for each 3-minute epoch selected per hour.

Frequency-domain HRV measures

The low-frequency (LF; 0.04–0.15 Hz) power, high-frequency (HF; 0.15–0.4 Hz) power, and LF/HF ratio of powers were calculated for each 3-minute epoch.

Nonlinear HRV measures

Quantitative analysis of the Poincaré plot was performed.²⁸ The Poincaré plot was derived from every 3-minute NN data epoch by plotting the values NN_{n+1} against the values of NN_n . SD_1 was calculated as the SD of the cloud of points in the direction perpendicular to the line-of-identity. SD_2 was calculated as the SD of the cloud of points in the direction of the line-of-identity. SD_1/SD_2 ratio was called SD_{12} .

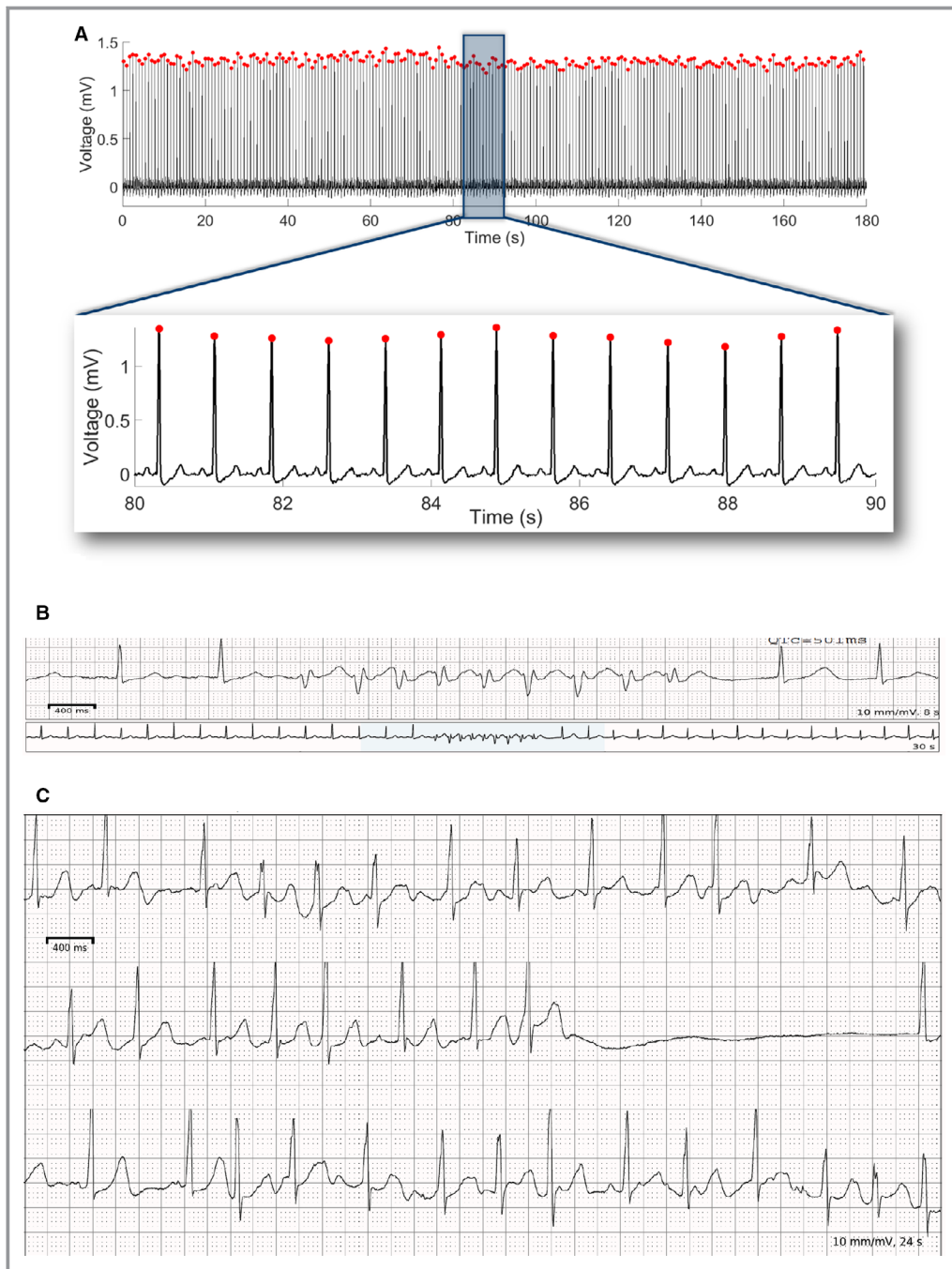


Figure 2. A representative example of (A) a single-lead ECG with detected R-peaks and measured RR' intervals. A 3-minute epoch is shown, with mean heart rate 78 bpm, rMSSD of 11.5 ms, LF power of 2.4 s^2 , HF power of 6.3 s^2 , LF/HF ratio of 0.38, SD_1 of 8.2 ms, SD_2 of 19.7 ms, SD_{12} ratio of 0.41, sample entropy of 2.0, and Renyi entropy of 1.4. A 10-s portion is displayed for closer examination of ECG morphology. B, Polymorphic ventricular tachycardia, and (C) atrial fibrillation and a pause in a study participant. bpm indicates beats per minute; HF, high frequency; LF, low frequency; rMSSD, root mean square of the successive normal sinus to normal sinus intervals differences.

Entropy

To quantify the entropy rate on a short-length NN series, we elected to measure sample entropy²⁸ and Renyi entropy for each 3-minute epoch. Renyi entropy was calculated as

described by Cornforth et al.²⁹ We used an α value equal to 4 because of previous data suggesting that positive α (1–5) provides the best discrimination of cardiac autonomic neuropathy, and based on the sampling rate of our data.³⁰

Statistical Analysis

Normality of the distribution of continuous variables was evaluated using standardized normal probability plots. For comparison of clinical characteristics in participants with versus without detected arrhythmia, normally distributed continuous variables were presented as means±SD and were compared using a *t* test. Fisher exact test was used to compare categorical variables.

The main data set was structured as a panel of time-series, as HRV was measured at the beginning of each hour (assuming equal intervals between 3-minute epochs). The assumption of equal intervals between 3-minute epochs was confirmed for 81% of epochs starting in the first second (44%), within the first 10 minutes (76%), or within the first 15 minutes (81%) of each hour. The assumption of equal intervals between 3-minute epochs was violated for 10% of epochs starting in the second half of an hour. To test the robustness of our findings, we conducted a sensitivity analysis after exclusion of epochs that violated the equal intervals assumption required for time-series analysis.

Within-subject and between-subjects SDs were reported for each phase of dialysis. Paired comparison of HRV in different phases of the dialytic cycle was performed using analysis of variance within subjects (for repeated measures). As previous studies reported an increased risk of SCD in the postdialysis phase after the long interdialytic weekend,³¹ we performed paired comparisons of HRV in the postdialysis phase that followed: (1) normal hemodialysis versus (2) 2-day-long interdialytic interval versus (3) longer than 72-hour interdialytic interval in nonadherent participants.

To determine whether demographic and clinical characteristics, paroxysmal cardiac arrhythmias, and dialytic and circadian (24-hour) cycles are associated with time-series of heart rate and HRV metrics, we constructed autoregressive conditional heteroscedasticity (ARCH) and generalized autoregressive conditionally heteroscedastic (GARCH) panel models.³² In ARCH time-series analysis, both the mean and variance of the HRV metric were modeled as time dependent, which allowed modeling volatility that can arise in response to the dialysis procedure or other unmeasured factors. Time series of heart rate and HRV metrics (1-by-1) served as an outcome. To identify our ARCH/GARCH model, we first explored the autocorrelation function (ACF) and partial autocorrelation (PACF) function of the HRV time-series, and ACF/PACF of squared HRV variables' values. Because the ACF and PACF of heart rate and HRV time-series represented white noise, but ACF/PACF of squared series tapered (autoregressive of order 1), we constructed ARCH(1/1)/GARCH(1) models.

To determine whether demographic and clinical characteristics (including use of β -blockers) are associated with heart

rate and HRV time-series, age, sex, race, prevalent CAD, CHF, CVD, history of AF, diabetes mellitus, Charlson comorbidity index, and postdialysis recovery time were included in each ARCH model.

To determine whether paroxysmal cardiac arrhythmias are associated with time-series of heart rate and HRV metrics, separate ARCH models were constructed for each type of paroxysmal arrhythmia (VT, AF, supraventricular tachycardia, and pause). ARCH models were adjusted for age, sex, race, prevalent CAD, CHF, CVD, AF, Charlson comorbidity index, and postdialysis recovery time.

To describe the circadian (24-hour) rhythm—while accounting for multiple 24-hour cycles analyzed for the same patient (longitudinal/panel data structure)—we constructed periodic regression models with fixed (within) estimators. We used periodic regression to analyze the behavior of heart rate and HRV, which vary in a circular-scale 24-hour cycle. We converted the circular variable “hour in a 24-hour cycle” from cyclic (hours of the day) to angular (radians) format, and then to trigonometric format (paired units sine and cosine). We studied whether heart rate and HRV time-series responded in a periodic way to the 24-hour cycle. We estimated the periodic mean (Mesor) for heart rate and HRV metrics, and calculated an amplitude (A) of variation about the Mesor in the modeled cycle:

$$\begin{aligned} 24\text{-hour HR/HRV range} &= \text{Amplitude } A \\ &= 2 \times \sqrt{\sin^2\beta + \cos^2\beta} \end{aligned}$$

We calculated phase angle (acrophase ϕ) as a time within the 24-hour cycle when heart rate/HRV is maximized (peak location): $\phi = \arctan(\sin\beta/\cos\beta)$. The minimum is located 12 hours (0.5 cycles) away from the maximum. Because dialysis and the immediate postdialytic phase are well known to significantly affect heart rate and HRV,^{31,33} dialysis (phase 1) and postdialytic phase 2 were excluded from periodic regression analyses. We stratified circadian rhythm analyses by the type of interdialytic phase: in a regular dialytic schedule (phases 3–4), second-day interdialytic extension (phases 5–6), and interdialytic extension above 72 hours (phases 7–8 in nonadherent participants missing dialysis), as shown in Figure 1.

To determine whether the dialytic cycle is associated with the heart rate and HRV time-series after removal of the effect of circadian rhythm, we constructed periodic panel ARCH/GARCH models to determine a change in HRV per hour of remoteness from the first dialysis hour. ARCH/GARCH models were adjusted for age, sex, race, prevalent CAD, CHF, CVD, AF, diabetes mellitus, Charlson comorbidity index, and postdialysis recovery time. In addition, circadian 24-hour cycles (paired units sine and cosine) were included

in each ARCH model and served to adjust for circadian periodicity.

Sensitivity analyses

To test the robustness of our findings, we excluded 10% of epochs that violated the equal intervals assumption that is required for time-series ARCH models. Furthermore, we adjusted ARCH models for weight and sitting systolic and diastolic blood pressure changes before and after every hemodialysis session during ECG monitoring.

Statistical analysis was performed using STATA MP 15.1 (StataCorp LP, College Station, TX).

Results

Study Population

The study population (Table 1) included 28 PACE participants (mean age 54 ± 13 years; 57% men; 96% black). Approximately one third of the population had a history of structural heart disease with normal left ventricular ejection fraction. The average dialysis recovery time was 16 minutes. All study participants had hypertension and used antihypertensive medications; 83% were on β -blockers. Most of the study participants received identical dialysate: >70% participants received dialysate concentration of potassium equal to 2 mmol/L and calcium equal to 2.5 mmol/L.

Cardiac Arrhythmia Events

Almost half of the participants ($n=13$, 46%) had arrhythmias detected during monitoring (Table 2; Figure 2). Except for 1 patient with 46% paroxysmal AF burden, all detected events were nonsustained (NS), lasting <30 seconds, and asymptomatic. NSVT occurred more frequently during hemodialysis or within 6 hours posthemodialysis, as compared with pre- or between-hemodialysis (63% versus 37%, $P=0.015$). Supraventricular tachycardia occurred more frequently pre- or between-hemodialysis as compared with during hemodialysis or posthemodialysis (84% versus 16%, $P=0.015$). All patients with NSVT were free from CAD at baseline.

Dynamic Time Series of Heart Rate and HRV

The average duration of analyzed continuous ECG recording was 6.5 ± 2.3 days. All 28 participants had at least 1 ECG recording over a 2-day-long interdialytic interval, and 4 participants missed 1 to 2 dialysis sessions during ECG monitoring.

Average heart rate was fastest within the first 6 hours postdialysis (Table 3) and gradually slowed down afterward. Short-term HRV (rMSSD, HF power, Poincaré SD_1) decreased

Table 1. Clinical Characteristics of Study Participants With and Without Any Clinically Significant Cardiac Arrhythmias Diagnosed During ECG Monitoring

Characteristic	Total (n=28)
Age (SD), y	53.9 (12.5)
Male, n (%)	16 (57.1)
Black, n (%)	27 (96.4)
Body mass index (SD), kg/m ²	29.4 (7.4)
Cause of ESKD:	
Glomerulonephritis, n (%)	3 (10.7)
Hypertension, n (%)	5 (17.9)
Diabetes mellitus, n (%)	12 (42.9)
HIV/other/genetic/obstruction, n (%)	7 (25.0)
Unknown, n (%)	1 (3.6)
Hypertension, n (%)	28 (100)
Diabetes mellitus, n (%)	16 (57.1)
Coronary artery disease, n (%)	8 (28.6)
Heart failure, n (%)	9 (32.1)
Cerebrovascular disease, n (%)	8 (28.6)
History of atrial fibrillation, n (%)	10 (35.7)
Hypercholesterolemia, n (%)	19 (67.9)
Smoker current or former, n (%)	15 (53.6)
Drinker current or former, n (%)	23 (82.1)
Use of β -blockers, n (%)	19/23 (82.6)
Charlson comorbidity index (SD)	5.5 (2.2)
Dialysis recovery time (SD), min	15.9 (3.3)
LV ejection fraction (SD), %	70.3 (9.3)
LV internal dimension diastole (SD), cm	5.3 (0.7)
LV internal dimension systole (SD), cm	3.1 (0.7)
LV mass index (SD), g/m ²	146.0 (53.2)
LV hypertrophy, n (%)	17 (70.8)
3-mo averaged calcium (SD), mg/dL	8.52 (0.65)
3-mo averaged potassium (SD), mEq/L	4.34 (0.39)
3-mo averaged intradialytic weight change (SD), kg	2.09 (0.97)
3-mo averaged dialysis bath calcium concentration (SD), mmol/L	2.4 (0.2)
3-mo averaged dialysis bath potassium concentration (SD), mmol/L	2.2 (0.4)

Three-month-averaged values are from the start of dialysis. ESKD indicates end-stage kidney disease; HIV, human immunodeficiency virus; LV, left ventricular.

posthemodialysis, then recovered by the time of the next regular hemodialysis session. However, if hemodialysis was not performed within the next 72 hours, short-term HRV gradually diminished further. In an unadjusted paired comparison, there were no statistically significant differences in

Table 2. Cardiac Arrhythmia Events Timeline

	Events 6-h Predialysis, n (%)	Events During Dialysis, n (%)	Events 6-h Postdialysis, n (%)	Events Between Dialysis, n (%)	Number of Patients (% of population)
Total number of events, n=47	12 (26)	8 (17)	9 (19)	18 (38)	13 (46)
VT, n=8	1 (13)	2 (25)	3 (38)	2 (25)	4 (15)
SVT, n=17	5 (29)	1 (6)	2 (12)	9 (53)	9 (32)
AF, n=21	6 (29)	4 (19)	4 (19)	7 (33)	2 (7)
Pauses >3 s, n=1	0	1 (100)	0	0	1 (3.5)

AF indicates atrial fibrillation; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

HRV posthemodialysis after different durations of the preceding interdialytic interval (Table S1).

Association of Clinical Characteristics With Heart Rate and HRV Time Series

During the regular hemodialysis schedule (phases 1–4), prevalent cardiovascular disease and its risk factors were associated with faster heart rate and further depressed HRV (Figure 3 and Table S2). History of AF and use of β -blockers were associated with slower heart rate.

In contrast, during the second day without hemodialysis (phases 5–6), traditional cardiovascular risk factors were associated with slower heart rates. Female sex and prevalent CAD were associated with increased SD_2 and LF power, suggesting greater sympathetic predominance. Interestingly, diabetes mellitus was associated with a smaller SD_2 and LF power.

In our study, 4 participants (100% black; 2 males and 2 females) missed hemodialysis for >72 hours. They were CAD- and CHF-free, with a high Charlson comorbidity index (6.8 ± 1.2). During missed hemodialysis (phases 7–8), diabetes mellitus and longer perceived dialysis recovery time were associated with greater degree of HRV depression (Table S2 through S4).

Association of Heart Rate and HRV With Cardiac Arrhythmias

In adjusted analysis, significantly increased heart rate in the beginning of an hour (as compared with the preceding hour, by 11.2 [95% CI 10.1 – 12.3] beats per minute [$P < 0.0001$]) was associated with paroxysmal VT events occurring at any time within the same hour. That association remained significant after further adjustment for the use of β -blockers ($+8.5$ [95% CI 7.1 – 9.8] beats per minute; $P < 0.0001$). There was no association of VT events with HRV. There were no associations of other types of observed arrhythmias with heart rate or HRV.

Circadian Rhythm in Heart Rate and HRV During Different Types of Dialytic Cycles

During the interdialytic period in the regular dialytic cycle (phases 3–4), heart rate and all HRV parameters demonstrated a significant circadian pattern—as expected (Figure 4 and Table S5). Short-term HRV ($rMSSD$ and SD_1) peaked at night, whereas heart rate and SD_{12} peaked during the day.

In contrast, the second day of the long interdialytic interval (phases 5–6) abolished circadian rhythms, with few exceptions. Periodic changes in heart rate remained largely unchanged across all interdialytic periods, but its acrophase shifted to the afternoon in the ultralong (missed dialysis >72 hours) interdialytic interval (phases 7–8). In phases 5 to 6, the amplitude of circadian rhythm in Renyi entropy and SD_2 increased, whereas circadian rhythm in other HRV metrics dissipated. During phases 7 to 8, we observed a distorted periodic pattern in short-term HRV ($rMSSD$, SD_1) with acrophase in the afternoon, whereas circadian rhythm in other HRV metrics remained eliminated.

Association of the Phases of Hemodialysis With Heart Rate and HRV Time-Series

In fully adjusted ARCH models (Figure 5 and Table S6), phase 1 dialysis and postdialytic phase 2 were characterized by gradual improvement of parasympathetic tone (increasing $rMSSD$ and SD_1). During the regular interdialytic interval in every-other-day hemodialysis cycle (phases 3–4), we observed very few significant trends: a slight decrease in $rMSSD$ and SD_1 , and the increase in SD_2 and sample entropy. In contrast, during the second day of a 2-day-long interdialytic interval (phases 5–6), there were significant and meaningful changes in all HRV parameters: heart rate gradually increased, short-term HRV ($rMSSD$, HF power, SD_1) and SD_{12} decreased, whereas intermediate HRV (SD_2 , LF/HF ratio, Renyi entropy) increased, suggesting depressed parasympathetic and increased sympathetic influences.

Table 3. Heart Rate and HRV in Different Phases of the Dialytic Cycle

HRV Measure	Phase 1 N=323; n=26 T=12.4	Phase 2 N=480; n=26 T=18.5	Phase 3 N=2554; n=28 T=91.2	Phase 4 N=438; n=27 T=16.2	Phase 5 N=428; n=28 T=15.3	Phase 6 N=135; n=26 T=5.2	Phase 7 N=221; n=4 T=55.3	Phase 8 N=15; n=3 T=5	Within ANOVA P
Heart rate (SD), bpm	74.1 (11.3)	81.3 (13.4)	77.2 (12.2)	75.9 (11.5)	77.6 (14.1)	73.9 (12.2)	70.8 (8.0)	71.0 (5.4)	<0.0001
SD between	10.4	11.3	10.1	10.3	12.9	13.2	9.8	5.3	
SD within	6.1	7.6	7.7	6.0	6.0	4.4	4.3	3.1	
rMSSD (SD), ms	12.6 (7.8)	9.7 (5.2)	11.0 (6.4)	11.1 (6.7)	11.1 (5.6)	11.8 (5.6)	11.3 (4.1)	9.2 (2.3)	<0.0001
SD between	6.1	3.7	4.1	5.2	3.7	4.3	2.7	2.1	
SD within	4.6	3.7	5.1	5.1	4.4	4.2	3.6	1.7	
HF power (SD), s ²	4.6 (2.0)	4.1 (1.8)	4.3 (1.9)	4.4 (2.0)	4.5 (2.0)	4.6 (2.2)	5.8 (2.2)	5.1 (2.9)	<0.0001
SD between	1.5	1.3	1.4	1.5	1.5	1.7	1.9	2.9	
SD within	1.3	1.4	1.4	1.4	1.3	1.4	1.4	0.9	
LF power (SD), s ²	3.1 (1.0)	3.0 (1.0)	3.1 (1.0)	2.9 (0.9)	3.0 (1.0)	3.0 (1.0)	3.1 (1.0)	3.0 (0.8)	0.068
SD between	0.6	0.6	0.6	0.5	0.6	0.7	0.8	0.3	
SD within	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.7	
LF/HF ratio (SD)	0.82 (0.46)	0.89 (0.48)	0.87 (0.46)	0.84 (0.45)	0.84 (0.47)	0.80 (0.43)	0.66 (0.39)	0.88 (0.58)	0.006
SD between	0.36	0.36	0.35	0.37	0.36	0.33	0.37	0.61	
SD within	0.27	0.31	0.32	0.32	0.29	0.26	0.24	0.16	
Poincaré SD ₁ (SD), ms	9.0 (5.6)	6.9 (3.7)	7.8 (4.6)	7.9 (4.8)	7.8 (4.0)	8.4 (3.9)	8.0 (2.9)	6.5 (1.6)	<0.0001
SD between	4.3	2.6	2.9	3.7	2.6	3.0	1.9	1.5	
SD within	3.3	2.6	3.6	3.6	3.1	2.9	2.6	1.2	
Poincaré SD ₂ (SD), ms	25.8 (18.7)	21.6 (15.9)	23.8 (18.4)	23.7 (17.2)	22.4 (16.5)	24.4 (16.5)	20.3 (15.3)	23.5 (17.0)	0.002
SD between	15.2	11.1	14.9	19.6	12.1	12.5	13.7	16.6	
SD within	11.1	11.6	13.5	11.4	12.2	10.7	10.1	7.4	
SD ₁₂ (SD), %	0.44 (0.25)	0.42 (0.25)	0.43 (0.24)	0.43 (0.27)	0.46 (0.28)	0.45 (0.27)	0.56 (0.33)	0.47 (0.32)	0.461
SD between	0.20	0.19	0.19	0.20	0.20	0.20	0.34	0.33	
SD within	0.16	0.17	0.18	0.20	0.19	0.18	0.20	0.12	
Sample Entropy (SD)	1.49 (0.40)	1.39 (0.46)	1.39 (0.44)	1.43 (0.44)	1.42 (0.44)	1.43 (0.47)	1.52 (0.43)	1.25 (0.62)	0.0004
SD between	0.25	0.26	0.21	0.24	0.23	0.29	0.23	0.73	
SD within	0.35	0.40	0.39	0.38	0.37	0.38	0.38	0.30	
Renyi entropy (SD)	1.31 (0.31)	1.33 (0.28)	1.31 (0.30)	1.33 (0.29)	1.31 (0.31)	1.29 (0.31)	1.23 (0.33)	1.30 (0.36)	0.758
SD between	0.17	0.13	0.09	0.17	0.12	0.15	0.13	0.31	
SD within	0.27	0.26	0.29	0.27	0.29	0.28	0.31	0.24	

bpm indicates beats per minute; HRV, heart rate variability; N, number of epochs; n, number of participants; rMSSD, root mean square of the successive normal sinus to normal sinus intervals differences; SD₁, Poincaré plot SD perpendicular the line of identity; SD₂, Poincaré plot SD along the line of identity; T, average number of hours.

Missing dialysis for >72 hours was associated with a steady increase in SD₁₂ ratio and HF power (Table S6).

Sensitivity analysis, after exclusion of 3-minute epochs that started in the second half of an hour and thus violated the equal intervals assumption, provided consistently similar results (Table S7). Further adjustment for changes in weight and sitting systolic and diastolic blood pressure before and after dialysis yielded similar results (Table S8).

Discussion

This continuous ECG-monitoring study of incident in-center hemodialysis patients revealed several important findings. First, we observed an association of the phases of dialysis with cardiac arrhythmias; specifically, NSVT events were more frequent during hemodialysis or within 6 hours posthemodialysis. In the time-series analysis adjusted for cardiovascular disease and risk factors, we demonstrated a

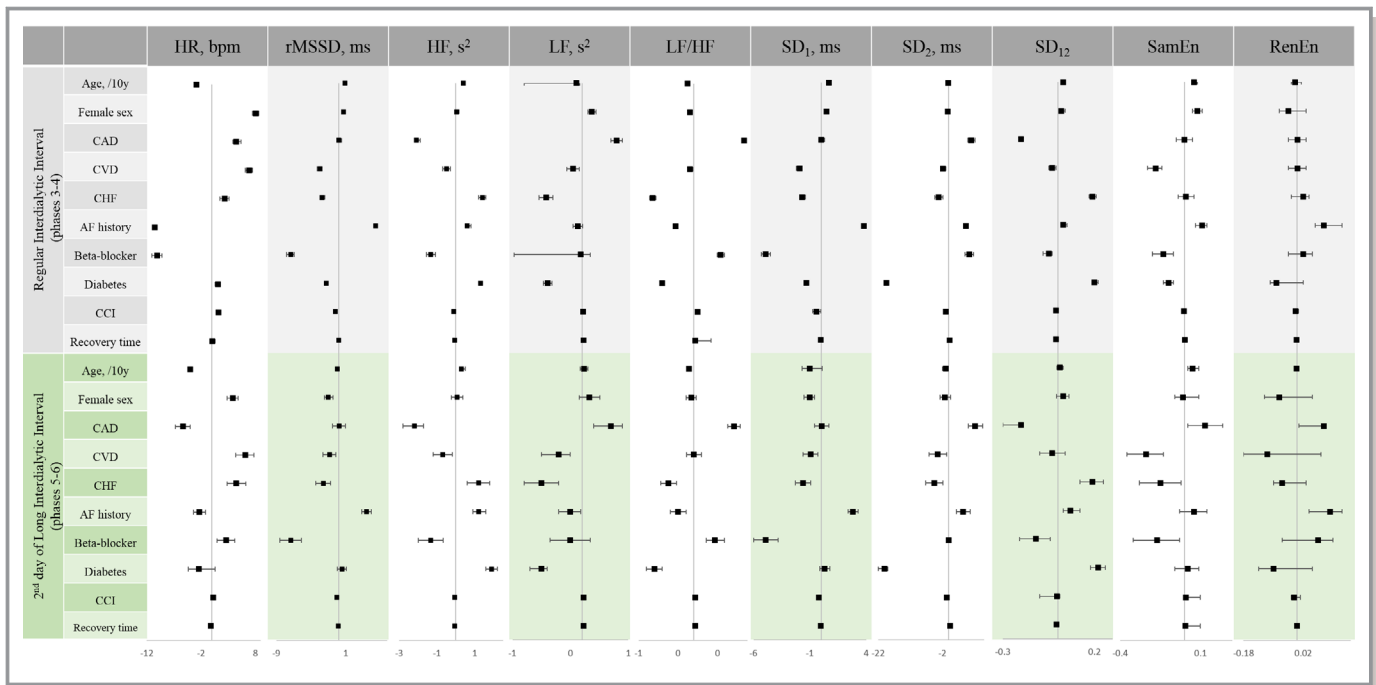


Figure 3. Association of demographic and clinical characteristics with heart rate and short-term HRV in ARCH models, stratified by the type of dialytic cycle. Beta-coefficient with 95% CI is shown. AF indicates atrial fibrillation; bpm, beats per minute; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CVD, cerebrovascular disease; HF, high-frequency power; HR, heart rate; HRV, heart rate variability; LF, low-frequency power; RenEn, Renyi entropy; rMSSD, root mean square of the successive normal sinus to normal sinus intervals differences; SamEn, sample entropy; SD₁, the SD of the Poincare plot cloud of points in the direction perpendicular to the line-of-identity; SD₂, SD₁/SD₂ ratio; SD₂, the SD of the cloud of points in the direction of the line-of-identity.

sharp increase in heart rate preceding NSVT events, suggesting a triggered VT mechanism,³⁴ likely because of sympathetic activation. Second, we found that the hemodialysis schedule dramatically influenced the autonomic tone. An every-other-day dialysis schedule preserved physiological circadian rhythm in heart rate and HRV, whereas the extension of the interdialytic period for the second day abolished circadian rhythm and displayed a steady deterioration. The 2-days-off dialysis led to progressively decreasing parasympathetic tone.

Dialysis Phase and Paroxysmal Cardiac Arrhythmias During ECG Monitoring

SCD is more frequent after the long interdialytic interval, during hemodialysis, or within 6 to 12 hours after the end of a hemodialysis session.⁶⁻⁸ Our observation was consistent with implantable loop recorder studies³⁵ that confirmed the same pattern: NSVT events were more frequent during and postdialysis, and the reasons could be multifactorial.¹⁰ We must emphasize that NSVT events are not equivalent to SCD. The predictive value of NSVT for SCD in ESKD remains unknown. NSVT is associated with SCD in many,³⁶⁻³⁹ but not all⁴⁰ populations.

Importantly, after rigorous adjustment for cardiovascular disease and associated risk factors, including use of β -blockers, we observed that suddenly increased heart rate precedes subsequent NSVT events. Such clinical manifestation is typical for triggered VT, which can manifest as polymorphic VT (Figure 2). The triggered VT mechanism can potentially^{41,42}—at least partially—explain recent results of the ICD2 trial, which showed that prophylactic ICD therapy did not reduce the rate of SCD or all-cause mortality in ESKD patients.⁴³

Use of β -blockers⁴⁴ can be a potential preventive intervention in such patients.³ Of note, we observed an attenuated association of heart rate with VT events even after adjustment for the use of β -blockers, in spite of 83% of participants taking β -blockers, which highlights the possible importance of appropriate β -blocker dose titration.

Dynamic Changes in Autonomic Tone in the Dialytic Cycle

Despite multiple studies reporting unfavorable effects of the long 2-day interdialytic interval⁶⁻⁸, in-center hemodialysis is typically prescribed 3 times per week. Our study is the first longitudinal study of heart rate and HRV time-series across

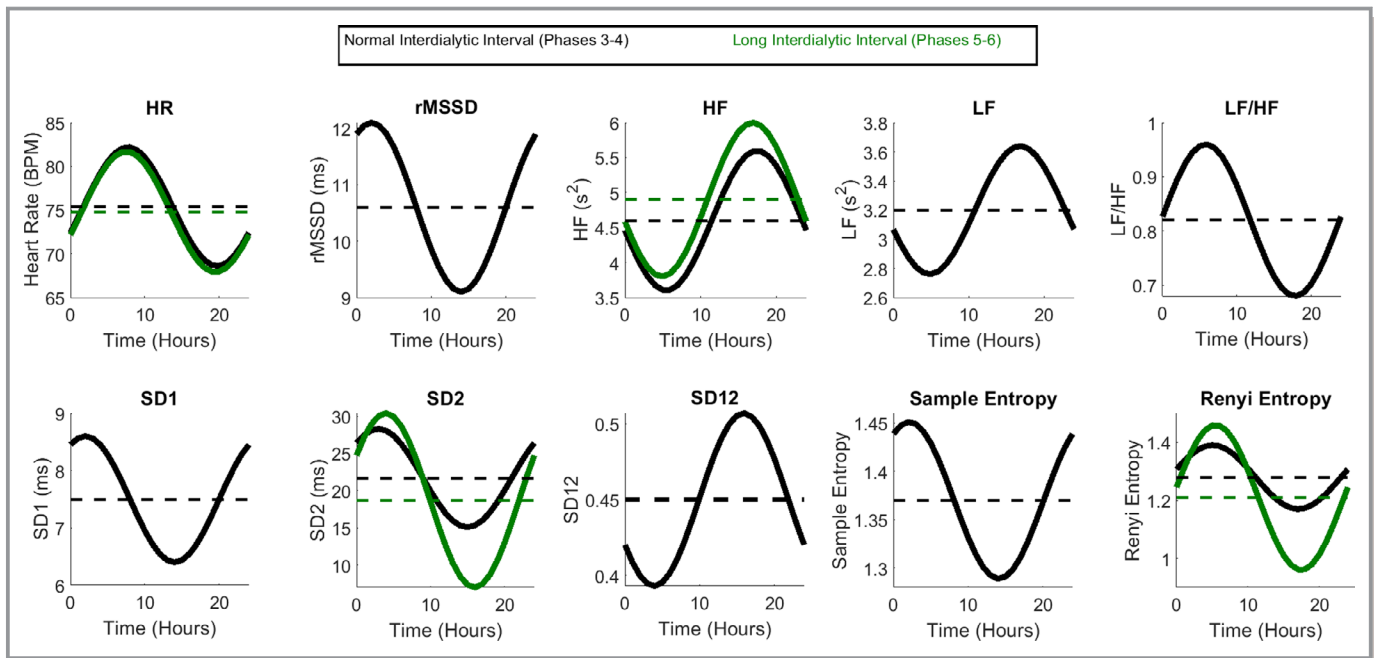


Figure 4. Circadian rhythm in heart rate and HRV during a 1-day- (black) and 2-day-long (green) interdialytic interval. Mesor is shown as a dashed line. BPM indicates beats per minute; HF, high-frequency power; HR, heart rate; HRV, heart rate variability; LF, low-frequency power; rMSSD, root mean square of the successive normal sinus to normal sinus intervals differences; SD₁, the SD of the Poincaré plot cloud of points in the direction perpendicular to the line-of-identity; SD₁₂, SD₁/SD₂ ratio; SD₂, the SD of the cloud of points in the direction of the line-of-identity.

multiple hemodialysis sessions, allowing direct paired comparison of the effect of the 2-day interdialytic interval. Our findings add to the growing evidence of the harmful

consequences of a prolonged interdialytic interval. While every-other-day hemodialysis preserved relatively normal cardiovascular autonomic tone, a second day without

HR/HRV Metric	Dialysis & Post-dialysis (phases 1-2)		Regular Interdialytic Interval (phases 3-4)		2 nd day Interdialytic Extension (phases 5-6)	
	per 24-h remoteness from 1st dialysis hour	P	per 24-h remoteness from 1st dialysis hour	P	per 24-h remoteness from 1st dialysis hour	P
HR, bpm	-0.76(-0.95 to -0.57)	<0.0001	+0.02(-0.05 to 0.11)	0.495	+0.57(0.26-0.87)	<0.0001
rMSSD, ms	+0.20(0.12-0.29)	<0.0001	-0.05(-0.09 to -0.001)	0.044	-1.41(-1.67 to -1.15)	<0.0001
HF Power, s ²	+0.04(-0.002 to 0.09)	0.061	-0.006(-0.03 to 0.02)	0.588	-0.38(-0.50 to -0.25)	<0.0001
LF Power, s ²	+0.02(-0.002 to 0.05)	0.073	+0.002(-0.010 to 0.02)	0.703	-0.02(-0.08 to 0.05)	0.639
LF/HF	-0.004(-0.01 to 0.003)	0.246	-0.001(-0.005 to 0.003)	0.504	+0.04(0.01 to 0.06)	0.002
SD ₁ , ms	+0.14(0.08-0.21)	<0.0001	-0.03(-0.07 to -0.001)	0.043	-1.00(-1.19 to -0.81)	<0.0001
SD ₂ , ms	-0.04(-0.26 to 0.18)	0.706	+0.27(0.17-0.37)	<0.0001	+0.87(0.37-1.37)	0.001
SD ₁₂	-0.003(-0.008 to 0.002)	0.219	-0.0006(-0.003 to 0.002)	0.597	-0.06(-0.07 to -0.05)	<0.0001
SamEn	+0.006(-0.005 to 0.018)	0.287	+0.01(0.005 to 0.02)	<0.0001	+0.007(-0.022 to 0.037)	0.624
RenEn	+0.002(-0.002 to 0.005)	0.345	+0.004(-0.0005 to 0.008)	0.088	+0.02(0.002 to 0.04)	0.030

Figure 5. Association of the phase of dialysis with heart rate and HRV after adjustment for circadian rhythm and clinical characteristics. bpm indicates beats per minute; HF, high-frequency power; HR, heart rate; HRV, heart rate variability; LF, low-frequency power; RenEn, Renyi entropy; rMSSD, root mean square of the successive normal sinus to normal sinus intervals differences; SamEn, sample entropy; SD₁, the SD of the Poincaré plot cloud of points in the direction perpendicular to the line-of-identity; SD₁₂, SD₁/SD₂ ratio; SD₂, the SD of the cloud of points in the direction of the line-of-identity.

hemodialysis was characterized by parasympathetic withdrawal and a steady increase in sympathetic predominance, which may explain the previously observed increased rate of SCD after the long interdialytic interval.^{6–8} Mounting evidence of the harmful effect of the 2-day interval without hemodialysis suggests that more frequent^{45,46} dialysis should be considered the preferred prescribed treatment schedule. Whether more frequent hemodialysis attenuates arrhythmic propensity remains to be determined.

HRV in ESKD Patients on Hemodialysis, and Effect of Missing Dialysis

In addition to the work in previous implantable loop recorder studies—which similarly detected arrhythmias—we also analyzed time-series of heart rate and HRV, which allowed us to shed light on the underlying mechanisms. HRV reflects a dynamic bidirectional interaction between the heart and the respiratory system, regulated by the autonomic nervous system¹⁴ and estimating sympathovagal balance.^{47,48} Our study highlights the unique features of the HRV-manifestation of autonomic imbalance in ESKD patients presenting with bradycardia because of direct negative chronotropic and dromotropic effects of hyperkalemia, hypocalcemia, and possible uremic toxins. Autonomic imbalance can diminish the cholinergic anti-inflammatory pathway, leading to an exaggerated cytokine response and inflammation⁴⁹. Similar to other studies,⁵⁰ we observed that heart rate increases during and immediately after hemodialysis.⁵¹ In our study participants, autonomic imbalance was manifested largely by parasympathetic withdrawal. Unlike in CHF studies,^{52,53} we observed LF/HF ratio <1, likely because of impaired baroreflex sensitivity, or a blunted sympathetic response in our study participants. Moak et al¹³ showed that LF power reflects baroreflex-mediated changes in cardiovagal and sympathetic noradrenergic outflows. In the case of baroreflex failure, LF power is reduced, regardless of the status of cardiac sympathetic innervation. Normally, acute removal of fluid during a hemodialysis session activates the baroreflex. Several groups of investigators^{54–57} observed worse clinical outcomes in ESKD patients with a blunted sympathetic response and a low (<1) LF/HF power ratio, which was characteristic of our patient population. Blunted sympathetic response on volume removal can be genetically determined by the polymorphism in the gene for angiotensin-converting enzyme.⁵⁰ Inadequate baroreflex sensitivity can cause intradialytic hypotension,⁵⁸ a well-known risk marker of adverse clinical outcomes in ESKD.

In participants who missed 1 to 2 hemodialysis sessions during ECG monitoring, as expected, heart rate further slowed, HRV progressively diminished, and circadian rhythm in HRV remained vanished or distorted—all because of

deepened autonomic imbalance. Of note, patients who missed hemodialysis were characterized by prominent bradycardia. Several recent studies reported bradyarrhythmias during monitoring,^{5,9,35,59} but did not comment (or possibly did not have available data) on patients' adherence to treatment. Improvement of patient adherence—avoiding missing hemodialysis sessions—can improve patient outcomes.

Circadian Rhythm in Heart Rate and HRV

Our finding of disrupted circadian rhythm aligns with previously reported autonomic dysregulation during the normal wake/sleep cycle in ESKD.⁶⁰ Two mechanisms⁶¹ are responsible for circadian rhythm in heart rate: (1) central circadian clock in the suprachiasmatic nucleus in the hypothalamus, acting via the autonomic nervous system, and (2) a local circadian clock in the heart itself. In our study participants, the circadian rhythm in heart rate remained relatively preserved during the prolonged interdialytic interval, whereas the circadian rhythm in HRV was largely abolished. Changes in the acrophase of the circadian rhythm in heart rate during the ultralong interdialytic (missed hemodialysis) interval—peaking in the afternoon instead of morning hours—may reflect a switch in the circadian clock from central to local regulatory mechanisms. A better understanding of circadian rhythms in heart rate and HRV may help to improve medical management and clinical outcomes in ESKD patients on hemodialysis. Chan et al⁴⁵ studied the effect of daily dialysis versus every-other-day dialysis and found that daily dialysis improved vagal modulation of the heart and increased short-term HRV, which is consistent with our study findings. Further studies of the interplay between circadian rhythm and dialytic cycle are needed to develop an optimal treatment schedule for ESKD patients.

Limitations

The strengths of this study arise from the continuous ECG monitoring, providing an opportunity for our study—with multiple 24-hour and dialytic cycles for the same participants—to significantly improve robustness and reduce error in estimations. Other strengths include the use of advanced statistical modeling of time-series (ARCH/GARCH) and appropriate use of explicit periodic regression.

However, limitations of the study should be considered. Use of a single-lead ECG poses objective challenges for discrimination of supraventricular arrhythmia from normal sinus rhythm. Everyday physical activity manifests through noise and artifacts. To ensure analysis of normal sinus rhythm, we implemented rigorous quality control procedures, which included semi-automated analysis of the data, and manual review of ECGs. To improve the quality of included

ECG data, we elected to study 3-minute epochs of continuously normal (uninterrupted) clean sinus rhythm.

Impaired baroreflex sensitivity can be measured by heart rate turbulence, which was not measured in this study. Further study of heart rate turbulence in ESKD patients on dialysis is needed. Results of frequency-domain HRV should be considered with caution. We measured HRV on each 3-minute segment, which at least partially explains the differences between HF and LF power reported in our study as compared with the 24-hour power spectrum analyses.^{52,53} To overcome limitations of isolated HRV metrics, we evaluated several HRV measures presumably reflecting parasympathetic tone (rMSSD, SD₁, HF power), and sympathovagal balance (SD₂, SD₁₂, LF/HF ratio). Consistent findings across the full set of HRV metrics increase the validity of our results.

The size of this study is relatively small, and participants were predominantly black, which limits generalizability. Nevertheless, these were participants with known structural heart disease and in-depth data for a prolonged period of time to compare using within-person comparison. On average, the study participant had 156±55 hours of data, providing satisfactory power for the analyses of heart rate and short-term HRV (rMSSD, SD₁) using the periodic regression and time-series analysis, in all stratified time intervals. However, the statistical powers of the stratified ARCH analyses of LF/HF power, SD₁₂, and entropy measures were not sufficient in phases 3 to 4 and 5 to 6. Thus, some of the nonsignificant findings might be because of low statistical power.

The assumption of equal intervals between 3-minute epochs was violated for ≈10% of epochs. To address this limitation, sensitivity analyses were performed and epochs that started in the second half of an hour were excluded from ARCH models, which did not change the association of dialytic cycle with HRV time-series. Only 4 study participants missed hemodialysis, and therefore, results of this subgroup analysis should be considered with caution. The reason for the missed hemodialysis sessions was unknown.

Clinical Implications

In summary, this prospective continuous ECG-monitoring study showed that cardiac arrhythmias are common in hemodialysis patients. In time-series analysis, paroxysms of VT are preceded by faster (than in a previous hour) heart rate, suggesting a triggered mechanism of VT. Every-other-day hemodialysis preserves physiological circadian rhythm in heart rate and HRV, while the prolonged interdialytic interval abolishes the circadian rhythm and displays a steadily worsening autonomic imbalance. The armamentarium of devices capable of continuously monitoring ECG is fast-growing. Further studies are needed to develop an individualized prediction of cardiac

arrhythmias based on analyses of heart rate and HRV time-series.

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Disclosures

None.

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Supplemental Material

Table S1. Comparison of heart rate and HRV post-dialysis in a regular dialytic (every other day) cycle, after two-day long interdialytic interval, and after missed dialysis for more than 72 hours.

HRV measure	Post-dialysis in a regular dialytic cycle N=350; n=26 T=13.5	Post-dialysis after the long interdialytic weekend N=122; n=21 T=5.8	Within ANOVA P Compared to phase 2 after the regular vs. weekend-long interdialytic interval	Post-dialysis after missed dialysis > 72h N=9; n=2 T=4.5	Within ANOVA P Compared to phase 2 after regular vs. ultra-long (>72h) interdialytic interval
Heart rate(within SD), bpm	81.4(7.4)	81.8(7.2)	0.439	71.3(2.8)	0.377
rMSSD(within SD), ms	9.6(3.5)	10.1(3.3)	0.109	11.1(1.8)	0.372
HF power(within SD), s ²	4.0(1.4)	4.3(1.1)	0.081	4.0(0.8)	0.777
LF power(within SD), s ²	3.0(0.8)	3.0(0.8)	0.126	3.3(0.8)	0.788
LF/HF ratio(within SD), %	0.9(0.3)	0.9(0.2)	0.615	1.0(0.4)	0.583
Poincaré SD ₁ (within SD), ms	6.8(2.5)	7.1(2.3)	0.109	7.9(1.3)	0.372
Poincaré SD ₂ (within SD), ms	22.2(12.4)	19.7(8.1)	0.401	27.1(6.9)	0.869
SD ₁₂ (within SD), %	0.41(0.16)	0.45(0.15)	0.070	0.33(0.05)	0.820
Sample Entropy(within SD)	1.4(0.4)	1.4(0.3)	0.364	1.6(0.5)	0.990
Renyi Entropy(within SD)	1.3(0.3)	1.3(0.2)	0.192	1.6(0.1)	0.451

N=number of observations; n=number of participants; T=average number of hours; SD=standard deviation; SD₁=Poincaré plot

standard deviation perpendicular the line of identity; SD₂=Poincaré plot standard deviation along the line of identity.

Table S2. Association of demographic and clinical characteristics with heart rate and short-term HRV in ARCH models, stratified by the type of dialytic cycle.

Clinical characteristic	Heart rate (95%CI), bpm	P	rMSSD (95%CI), ms	P	SD1 (95%CI), ms	P	HF power(95%CI), s ²	P	
Regular dialytic cycle (phases 1-4)	Age, /10y	-2.9(-3.1 to -2.7)	<0.0001	+0.9(0.8-1.0)	<0.0001	+0.7(0.6-0.7)	<0.0001	+0.4(0.3-0.5)	<0.0001
	Female sex	+8.1(7.5-8.6)	<0.0001	+0.7(0.4-0.9)	<0.0001	+0.5(0.3-0.6)	<0.0001	+0.05(-0.07-0.17)	0.437
	Black race	+23(-388-433)	0.927	-2(-21 to 17)	0.825	-2(-15 to 12)	0.824	-7(-21 to 6)	0.301
	CAD	+4.5(3.8-5.3)	<0.0001	+0.03(-0.3 to 0.4)	0.849	+0.02(-0.2 to 0.3)	0.846	-2.1(-2.2 to -1.9)	<0.0001
	CVD	+6.8(6.1-7.5)	<0.0001	-2.7(-3.1 to -2.4)	<0.0001	-1.9(-2.2 to -1.7)	<0.0001	-0.5(-0.7 to -0.3)	<0.0001
	CHF	+2.3(1.5-3.1)	<0.0001	-2.4(-2.7 to -2.0)	<0.0001	-1.7(-1.9 to -1.4)	<0.0001	+1.4(1.2-1.6)	<0.0001
	AF history	-10.5(-11.0 to -10.1)	<0.0001	+5.3(5.1-5.6)	<0.0001	+3.8(3.6-4.0)	<0.0001	+0.6(0.5-0.8)	<0.0001
	Beta-blocker	-10.1(-11.1 to -9.2)	<0.0001	-6.9(-7.5 to -6.4)	<0.0001	-4.9(-5.3 to -4.5)	<0.0001	-1.33(-1.57 to -1.08)	<0.0001
	Diabetes	+1.1(0.6-1.5)	<0.0001	-1.8(-2.0 to -1.5)	<0.0001	-1.3(-1.4 to -1.1)	<0.0001	+1.3(1.2-1.4)	<0.0001
	CCI	+1.2(1.1-1.3)	<0.0001	-0.5(-0.6 to -0.4)	<0.0001	-0.4(-0.03 to -0.01)	<0.0001	-0.10(-0.13 to -0.07)	<0.0001
	Recovery time, min	+0.04(0.01-0.6)	0.012	-0.03(-0.05 to -0.01)	<0.0001	-0.02(-0.03 to -0.01)	<0.0001	-0.05(-0.06 to -0.04)	<0.0001
2 nd day interdialytic extension (phases 5-6)	Age, /10y	-4.0(-4.4 to -3.7)	<0.0001	-0.2(-0.4-0.1)	0.265	-1.0(-0.3 to 0.1)	0.274	+0.3(0.2-0.5)	<0.0001
	Female sex	+3.8(2.8-4.8)	<0.0001	-1.5(-2.1 to -0.8)	<0.0001	-1.0(-1.5 to -0.6)	<0.0001	+0.07(-0.24 to 0.38)	0.656
	Black race	-15(-21 to -9))	<0.0001	-8(-13 to -3)	0.003	-5(-9 to -2)	0.004	-7.5(-9.8 to -5.1)	<0.0001
	CAD	-5.3(-6.7 to -4.0)	<0.0001	+0.06(-0.9 to 1.0)	0.906	+0.04(-0.6 to 0.7)	0.903	-2.2(-2.8 to -1.7)	<0.0001
	CVD	+6.1(4.4-7.7)	<0.0001	-1.3(-2.3 to -0.4)	0.007	-0.9(-1.6 to -0.3)	0.006	-0.7(-1.2 to -0.2)	0.004
	CHF	+4.5(2.8-6.2)	<0.0001	-2.2(-3.3 to -1.2)	<0.0001	-1.6(-2.3 to -0.9)	<0.0001	+1.2(0.6-1.8)	<0.0001
	AF history	-2.3(-3.4 to -1.2)	<0.0001	+4.0(3.3-4.7)	<0.0001	+2.8(2.4-3.3)	<0.0001	+1.2(0.9-1.6)	<0.0001
	Beta-blocker	+2.6(0.9-4.2)	0.002	-6.9(-8.5 to -5.4)	<0.0001	-4.9(-6.0 to -3.8)	<0.0001	-1.33(-1.99 to -0.68)	<0.0001
	Diabetes	-2.4(-0.4 to 0.6)	<0.0001	+0.5(-0.2 to 1.1)	0.173	+0.3(-0.1 to 0.8)	0.176	+1.9(1.6-2.2)	<0.0001
	CCI	+0.25(0.05-0.60)	0.100	-0.3(-0.5 to -0.2)	<0.0001	-0.2(-0.3 to -0.1)	<0.0001	-0.05(-0.12 to 0.03)	0.199
	Recovery time, min	-0.23(-0.29 to -0.17)	<0.0001	-0.05(-0.10 to -0.0007)	0.047	-0.03(-0.07 to -0.0002)	0.048	-0.06(-0.08 to -0.04)	<0.0001
Phases 7-8	Age, /10y	-5.3(-5.8 to -4.7)	<0.0001	-0.20(-0.24 to -0.15)	<0.0001	-1.4(-1.7 to -1.0)	<0.0001	+0.5(0.3-0.7)	<0.0001
	Diabetes	-4.8(-6.0 to -3.6)	<0.0001	-1.6(-2.5 to -0.6)	0.001	-1.10(-1.8 to -0.4)	0.001	+2.2(1.8-2.6)	<0.0001
	Recovery time, min	+2.4(2.2-2.6)	<0.0001	+0.4(0.13-0.64)	0.003	+0.3(0.09-0.5)	0.003	+0.3(0.2-0.5)	<0.0001

Table S3. Association of demographic and clinical characteristics with intermediate HRV in ARCH models, stratified by the type of dialytic cycle.

Clinical characteristic	LF power(95%CI), s ²	P	LF/HF ratio (95%CI)	P	SD1/SD2 ratio (95%CI)	P	SD2 (95%CI), ms	P	
Regular dialytic cycle (phases 1-4)	Age, /10y	-0.1(-1.0 to -0.04)	<0.0001	-0.08(-0.09 to -0.07)	<0.0001	+0.03(0.03-0.04)	<0.0001	-0.14(-0.17 to -0.11)	<0.0001
	Female sex	+0.17(0.10-0.24)	<0.0001	-0.05(-0.07 to -0.02)	<0.0001	+0.02(0.01-0.04)	<0.0001	-0.3(-0.9 to 0.2)	0.190
	Black race	+3.3(1.0-5.7)	0.005	+2.5(-1.2 to 6.2)	0.182	-0.9(-2.3-0.4)	0.177	+32(-121 to 187)	0.678
	CAD	+0.6(0.5-0.7)	<0.0001	+0.64(0.61-0.68)	<0.0001	-0.2(-0.2 to -0.21)	<0.0001	+7.0(5.9-8.1)	<0.0001
	CVD	-0.15(-0.26 to -0.05)	0.005	-0.05(-0.08 to -0.01)	0.009	-0.03(-0.05 to -0.01)	0.002	-1.8(-2.6 to -1.0)	<0.0001
	CHF	-0.62(-0.74 to -0.50)	<0.0001	-0.52(-0.56 to -0.48)	<0.0001	+0.19(0.17-0.21)	<0.0001	-3.1(-4.3 to -1.9)	<0.0001
	AF history	-0.07(-0.15 to 0.01)	0.102	-0.23(-0.26 to -0.21)	<0.0001	+0.03(0.02-0.05)	<0.0001	+5.3(4.7-5.9)	<0.0001
	Beta-blocker	-0.02(-1.17 to 0.14)	0.810	+0.34(0.30-0.39)	<0.0001	-0.05(-0.08 to -0.03)	<0.0001	+6.4(5.0-7.7)	<0.0001
	Diabetes	-0.59(-0.67 to -0.52)	<0.0001	-0.40(-0.42 to -0.38)	<0.0001	0.20(0.19-0.22)	<0.0001	-19.4(-20.1 to -18.7)	<0.0001
	CCI	+0.02(0.01-0.04)	0.011	+0.05(0.04-0.05)	<0.0001	-0.01(-0.01to-0.01)	<0.0001	-0.9(-1.0 to -0.7)	<0.0001
	Recovery time, min	+0.03(0.02-0.03)	<0.0001	+0.021(0.019-0.22)	<0.0001	-0.01(-0.01to-0.01)	<0.0001	+0.32(0.29-0.35)	<0.0001
2 nd day interdialytic extension (phases 5-6)	Age, /10y	+0.04(-0.03-0.1)	0.265	-0.06(-0.08 to -0.03)	<0.0001	+0.01(-0.004-0.03)	0.139	-1.0(-2.0 to -1.0)	<0.0001
	Female sex	+0.13(-0.05 to 0.31)	0.170	-0.03(-0.10 to 0.03)	0.296	+0.03(-0.008-0.06)	0.133	-1.3(-2.7 to 0.5)	0.058
	Black race	+3.0(1.5-4.5)	<0.0001	+1.8(1.4-2.2)	<0.0001	-1.0(-1.3 to -0.7)	<0.0001	+37(26-47)	<0.0001
	CAD	+0.5(0.2-0.7)	<0.0001	+0.51(0.43-0.59)	<0.0001	-0.2(-0.3 to -0.2)	<0.0001	+8.2(6.0-10.5)	<0.0001
	CVD	-0.4(-0.7 to -0.2)	0.001	+0.001(-0.09-0.10)	0.983	-0.03(-0.1-0.04)	0.426	-3.4(-6.1 to -0.7)	0.015
	CHF	-0.7(-1.0 to -0.4)	<0.0001	-0.32(-0.42 to -0.22)	<0.0001	+0.19(0.12-0.25)	<0.0001	-4.5(-7.2 to -1.8)	0.001
	AF history	-0.2(-0.4 to -0.02)	0.027	-0.2(-0.3 to -0.1)	<0.0001	+0.07(0.03-0.12)	0.001	+4.5(2.3-6.7)	<0.0001
	Beta-blocker	-0.20(-0.55 to 0.14)	0.247	+0.27(0.16-0.39)	<0.0001	-0.12(-0.21 to -0.04)	0.004	-0.1(-0.2 to -0.8)	<0.0001
	Diabetes	-0.7(-0.9 to -0.6)	<0.0001	-0.5(-0.6 to -0.4)	<0.0001	+0.22(0.18-0.26)	<0.0001	-20(-22 to -19)	<0.0001
	CCI	+0.03(0.02-0.05)	0.276	+0.02(0.01-0.04)	<0.0001	-0.004(-0.1-0.01)	0.930	-0.6(-1.1 to -0.2)	0.009
	Recovery time, min	+0.03(0.02-0.05)	<0.0001	+0.02(0.01-0.02)	<0.0001	-0.008(-0.01 to -0.005)	<0.0001	+0.4(0.3-0.5)	<0.0001
	Phases 7-8	Age, /10y	+0.2(0.1-0.3)	0.001	-0.01(-0.10-0.03)	0.740	-0.02(-0.05 to -0.001)	0.041	-0.8(-2.0 to 0.1)
Diabetes		-1.4(-1.6 to -1.2)	<0.0001	-0.47(-0.53 to -0.41)	<0.0001	+0.43(0.39-0.47)	<0.0001	-14.6(-16.0 to -13.3)	<0.0001
Recovery time, min		+0.11(0.06-0.16)	<0.0001	-0.08(-0.09 to -0.06)	<0.0001	+0.03(0.02-0.04)	<0.0001	-4.3(-4.7 to -3.8)	<0.0001

Table S4. Association of demographic and clinical characteristics with entropy in ARCH models, stratified by the type of dialytic cycle

	Clinical characteristic	Sample entropy (95%CI), bpm	P	Renyi entropy (95%CI), ms	P
Regular dialytic cycle (phases 1-4)	Age, per 10y	+0.06(0.05-0.08)	<0.0001	-0.007(-0.02 to 0.003)	0.189
	Female sex	+0.08(0.05-0.11)	<0.0001	-0.03(-0.06 to -0.001)	0.006
	Black race	+0.3(-0.6 to 1.2)	0.530	-0.19(-0.43 to 0.06)	0.138
	CAD	+0.0004(-0.05 to 0.05)	0.988	+0.0005(-0.03 to 0.03)	0.974
	CVD	-0.18(-0.23 to -0.14)	<0.0001	+0.0001(-0.03 to 0.03)	0.992
	CHF	+0.01(-0.04 to 0.06)	0.709	+0.02(-0.02 to 0.06)	0.244
	AF history	+0.11(0.07-0.14)	<0.0001	+0.09(0.06-0.12)	<0.0001
	Beta-blocker	-0.13(-0.20 to -0.07)	<0.0001	+0.02(-0.03 to 0.07)	0.469
	Diabetes	-0.10(-0.13 to -0.07)	<0.0001	-0.07(-0.09 to -0.04)	<0.0001
	CCI	-0.002(-0.01 to 0.005)	0.567	-0.006(-0.01 to 0.0001)	0.052
	Recovery time, min	+0.002(-0.0001 to 0.004)	0.051	-0.003(-0.005 to -0.001)	<0.0001
2 nd day interdialytic extension (phases 5-6)	Age, per 10y	+0.05(0.02-0.09)	<0.0001	-0.003(-0.003 to 0.02)	0.832
	Female sex	-0.01(-0.06 to 0.09)	0.713	-0.06(-0.11 to -0.001)	0.045
	Black race	+0.4(-0.2 to 1.0)	0.200	+0.03(-0.4 to 0.4)	0.914
	CAD	+0.13(0.02-0.24)	0.017	+0.09(0.005-0.18)	0.037
	CVD	-0.24(-0.36 to -0.13)	<0.0001	-0.10(-0.18 to -0.02)	0.018
	CHF	-0.15(-0.28 to -0.02)	0.022	-0.05(-0.02 to 0.05)	0.295
	AF history	+0.06(-0.03 to 0.14)	0.193	+0.11(0.04-0.17)	0.001
	Beta-blocker	-0.17(-0.32 to -0.03)	0.016	+0.07(-0.05 to 0.18)	0.275
	Diabetes	+0.02(-0.06 to 0.09)	0.653	-0.08(-0.13 to -0.02)	0.009
	CCI	+0.01(-0.002 to 0.1)	0.090	-0.01(-0.02 to 0.004)	0.151
	Recovery time, min	+0.005(-0.0002 to 0.10)	0.062	-0.001(-0.005 to 0.003)	0.733
Phases 7-8	Age, per 1y	-0.003(-0.008 to 0.003)	0.360	+0.03(-0.008 to 0.07)	0.116
	Diabetes	-0.51(-0.61 to -0.42)	<0.0001	-0.16(-0.23 to -0.08)	<0.0001
	Recovery time, min	+0.11(0.09-0.14)	<0.0001	+0.006(-0.002 to 0.01)	0.126

Table S5. Comparison of circadian rhythm in heart rate and HRV during different interdialytic phases.

HR / HRV metric	Regular interdialytic interval (phases 3-4)				2 nd day of a long interdialytic interval (phases 5-6)				Nonadherent interdialytic extension (phases 7-8)			
	Mesor (95%CI)	24-hour Amplitude (95%CI)	Peak time (95%CI)	P Sin Cos	Mesor (95%CI)	24-hour Amplitude (95%CI)	Peak time (95%CI)	P Sin Cos	Mesor (95%CI)	24-hour Amplitude (95%CI)	Peak time (95%CI)	P Sin Cos
HR, bpm	75.4(74.6-76.3)	6.8(5.6-8.6)	07:44(06:52 - 08:14)	<0.0001	74.8(72.9-76.7)	6.9(5.2-11.1)	07:30(06:08-10:44)	0.008 0.020	73.7(71.9-75.6)	8.3(3.4-13.4)	15:30(14:15-15:48)	0.006 <0.0001
rMSSD, ms	10.6(0.9-11.2)	1.5(1.0-3.1)	02:01(20:22-03:16)	0.342 <0.0001	NS	NS	NS	0.067 0.182	8.7(7.2-10.2)	6.8(2.7-10.9)	05:05(04:47-06:18)	0.001 0.085
HF, s ²	4.6(4.5-4.8)	1.0(0.6-1.5)	17:28(17:04-18:23)	<0.0001 0.166	4.9(4.5-5.3)	1.1(0.2-2.2)	16:54(16:36-22:39)	0.038 0.202	NS	NS	NS	0.604 0.235
LF, s ²	3.2(3.1-3.3)	0.44(0.17-0.72)	16:50(16:38-17:34)	0.001 0.022	NS	NS	NS	0.090 0.163	3.5(3.1-3.8)	1.0(0.1-1.9)	16:16(16:00-16:17)	0.032 0.028
LF/HF	0.82(0.78-0.85)	0.14(0.06-0.24)	05:49(05:11-08:34)	0.003 0.770	NS	NS	NS	0.271 0.246	0.83(0.73-0.93)	0.42(0.14-0.71)	16:31(16:26-16:59)	0.003 0.012
SD ₁ , ms	7.5(7.1-7.9)	1.1(0.7-2.2)	02:00(20:22-03:15)	0.343 0<0.0001	NS	NS	NS	0.067 0.182	6.2(5.1-7.2)	4.8(1.9-7.8)	05:05(04:47-06:18)	0.001 0.085
SD ₂ , ms	21.7(20.2-23.2)	6.6(2.9-10.8)	02:58(00:47-03:31)	0.025 <0.0001	18.7(15.0-22.3)	11.7(1.9-21.9)	03:56(01:53-04:06)	0.032 0.007	NS	NS	NS	0.067 0.784
SD ₁₂	0.45(0.43-0.47)	0.057(0.008-0.12)	15:54(07:58-16:08)	0.088 0.023	NS	NS	NS	0.112 0.078	NS	NS	NS	0.450 0.789
SamEn	1.37(1.32-1.42)	0.081(0.077-0.204)	02:08(18:41-03:30)	0.478 0.014	NS	NS	NS	0.877 0.825	NS	NS	NS	0.631 0.117
RenEn	1.28(1.25-1.31)	0.11(0.02-0.20)	05:03(04:43-08:31)	0.019 0.195	1.21(1.12-1.30)	0.25(0.08-0.48)	05:28(04:54-10:07)	0.022 0.506	NS	NS	NS	0.420 0.163

NS=non-significant (absent circadian rhythm)

Table S6. Association of phase of dialysis with heart rate and HRV after adjustment for circadian rhythm, clinical characteristics.

HR / HRV metric	Dialysis & postdialysis (phases 1-2)		Regular interdialytic phases 3-4		2 nd day interdialytic extension (phases 5-6)		Nonadherent interdialytic extension (phases 7-8)	
	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P
HR, bpm	-0.76(-0.95 to -0.57)	<0.0001	+0.02(-0.05 to 0.11)	0.495	+0.57(0.26-0.87)	<0.0001	+0.20(-0.17 to 0.57)	0.285
rMSSD, ms	+0.20(0.12-0.29)	<0.0001	-0.05(-0.09 to -0.001)	0.044	-1.41(-1.67 to -1.15)	<0.0001	+0.10(-0.41 to 0.60)	0.710
HF power, s ²	+0.04(-0.002 to 0.09)	0.061	-0.006(-0.03 to 0.02)	0.588	-0.38(-0.50 to -0.25)	<0.0001	+0.24(0.06-0.42)	0.010
LF power, s ²	+0.02(-0.002 to 0.05)	0.073	+0.002(-0.010 to 0.02)	0.703	-0.02(-0.08 to 0.05)	0.639	-0.04(-0.04 to 0.12)	0.322
LF/HF	-0.004(-0.01 to 0.003)	0.246	-0.001(-0.005 to 0.003)	0.504	+0.04(0.01 to 0.06)	0.002	-0.01(-0.03 to 0.01)	0.157
SD ₁ , ms	+0.14(0.08-0.21)	<0.0001	-0.03(-0.07 to -0.001)	0.043	-1.00(-1.19 to -0.81)	<0.0001	+0.07(-0.29 to 0.42)	0.709
SD ₂ , ms	-0.04(-0.26 to 0.18)	0.706	+0.27(0.17-0.37)	<0.0001	+0.87(0.37-1.37)	0.001	-0.35(-0.81 to 0.12)	0.148
SD ₁₂	-0.003(-0.008 to 0.002)	0.219	-0.0006(-0.003 to 0.002)	0.597	-0.06(-0.07 to -0.05)	<0.0001	+0.02(0.004-0.04)	0.017
SamEn	+0.006(-0.005 to 0.018)	0.287	+0.01(0.005 to 0.02)	<0.0001	+0.007(-0.022 to 0.037)	0.624	-0.005(-0.047 to 0.036)	0.795
RenEn	+0.002(-0.002 to 0.005)	0.345	+0.004(-0.0005 to 0.008)	0.088	+0.02(0.002 to 0.04)	0.030	-0.01(-0.05 to 0.03)	0.764

Table S7. Sensitivity analysis after exclusion of epochs starting in the 2nd half of an hour: Association of the dialytic cycle with HRV.

HR / HRV metric	Dialysis & postdialysis (phases 1-2)		Regular interdialytic phases 3-4		2nd day interdialytic extension (phases 5-6)		Nonadherent interdialytic extension (phases 7-8)	
	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1st dialysis hour	P	per 24-h remoteness from 1st dialysis hour	P
HR, bpm	-0.60(-0.79 to -0.41)	<0.0001	+0.02(-0.06 to 0.10)	0.612	+1.1(0.63-1.51)	<0.0001	-0.06(-0.55 to 0.45)	0.828
rMSSD, ms	+0.20(0.10 to 0.30)	<0.0001	-0.07(-0.11 to -0.02)	0.006	-1.51(-1.80 to -1.23)	<0.0001	+0.33(-0.24 to 0.91)	0.257
HF power, s ²	+0.04(-0.008 to 0.09)	0.103	-0.01(-0.03 to 0.01)	0.332	-0.36(-0.50 to -0.23)	<0.0001	+0.26(0.06-0.47)	0.013
LF power, s ²	+0.02(-0.008 – 0.05)	0.176	+0.003(-0.010-0.02)	0.665	+0.04(-0.04 to 0.12)	0.319	+0.07(-0.12 to 0.15)	0.093
LF/HF	-0.006(-0.01 to 0.003)	0.180	-0.002(-0.006 to 0.002)	0.349	+0.05(0.02 to 0.08)	0.001	-0.01(-0.04 to 0.01)	0.377
SD ₁ , ms	+0.14(0.07-0.21)	<0.0001	-0.05(-0.08 to -0.01)	0.005	-1.07(-1.28 to -0.87)	<0.0001	+0.23(-0.17 to 0.65)	0.257
SD ₂ , ms	-0.20(-0.43 to 0.04)	0.103	+0.29(0.18-0.39)	<0.0001	+0.52(-0.13-1.18)	0.119	-0.87(-1.62 to -0.12)	0.023
SD ₁₂	-0.004(-0.009-0.0009)	0.111	-0.001(-0.004-0.001)	0.275	-0.06(-0.08 to -0.05)	<0.0001	+0.02(0.004-0.04)	0.017
SamEn	+0.003(-0.009-0.02)	0.595	+0.010(0.004-0.015)	0.001	0.006(-0.028 to 0.040)	0.733	+0.01(-0.033 to 0.055)	0.631
RenEn	+0.002(-0.002-0.006)	0.243	+0.004(-0.0003-0.008)	0.069	+0.02(0.002 to 0.04)	0.030	-0.01(-0.05 to 0.03)	0.764

Table S8. Sensitivity analysis adjusted for weight and blood pressure change: Association of the dialytic cycle with HRV

(N=7). All 7 participants were on beta-blockers.

HR / HRV metric	Dialysis & postdialysis (phases 1-2)		Regular interdialytic phases 3-4		2nd day interdialytic extension (phases 5-6)	
	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P	per 24-h remoteness from 1 st dialysis hour	P
HR, bpm	+0.34(-0.03 to 0.70)	0.071	+0.11(-0.08 to 0.29)	0.272	+0.82(0.44-1.20)	<0.0001
rMSSD, ms	-0.24(-0.45 to -0.20)	0.032	-0.04(-0.11 to 0.03)	0.233	+0.91(-2.30 to 4.10)	0.581
HF power, s ²	-0.001(-0.04 to 0.04)	0.952	-0.0003(-0.05 to 0.05)	0.992	+0.01(-0.04 to 0.06)	0.612
LF power, s ²	+0.01(-0.03 to 0.06)	0.626	-0.04(-0.07 to -0.01)	0.003	-0.03(-0.06 to -0.005)	0.022
LF/HF	-0.004(-0.02 to 0.01)	0.658	-0.007(-0.02 to 0.001)	0.085	-0.008(-0.02 to 0.002)	0.122
SD ₁ , ms	-0.17(-0.32 to -0.01)	0.032	-0.03(-0.08 to 0.02)	0.233	+0.65(-1.63 to 2.92)	0.578
SD ₂ , ms	-0.80(-1.05 to -0.55)	<0.0001	-0.08(-0.39 to 0.23)	0.619	-1.21(-5.32 to 2.91)	0.565
SD ₁₂	+0.002(-0.01 to 0.01)	0.761	+0.0004(-0.0006 to 0.007)	0.903	-0.22(-0.40 to -0.04)	0.015
SamEn	+0.004(-0.006 to 0.01)	0.441	+0.002(-0.01 to 0.02)	0.798	-0.12(-0.45 to 0.21)	0.461
RenEn	+0.02(0.007 – 0.03)	0.001	+0.01(0.002 – 0.02)	0.020	+0.01(0.001-0.02)	0.024