Original Research

Heart rate variability at rest and in response to stress: Comparative study between hemodialysis and peritoneal dialysis patients

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Impact statement

Cardiac arrhythmias and sudden death are the leading causes of cardiovascular mortality in end-stage kidney disease. This study showed for the first time that the autonomic nervous system (ANS) responses (as assessed by heart rate variability) at rest and during mental stress did not differ between hemodialysis (HD) and peritoneal dialysis (PD) patients. Although no differences were observed between HD and PD during handgrip exercise (a sympathetic stimulation test), recovery from sit-to-stand (a functional test used for baroreflex sensitivity measurement) was more impaired in HD patients. These results suggest that ANS function is rather not affected by the type of dialysis therapy received and that patients from both dialysis modalities are prone to the development of ANS-modulated arrhythmogenic background. However, the impaired ability of the ANS to return to baseline after sit-to-stand test suggests a possible further impairment of HD patients in recovering normal ANS function after a stress test compared to patients on PD.

Abstract

Cardiac arrhythmias and sudden death are the leading causes of mortality in end-stage kidney disease (ESKD). Autonomic nervous system (ANS) dysfunction contributes to this arrhythmogenic background. This study compared heart rate variability (HRV) indices between hemodialysis (HD) and peritoneal dialysis (PD) patients, both at rest and in response to mental and physical stimulation maneuvers. Thirty-four HD and 34 PD patients matched for age, sex, and dialysis vintage, and 17 age- and sex-matched controls were studied. ANS function was examined by linear and non-linear HRV indices. Heart rate was recorded continuously (Finometer-PRO) at rest and during ANS maneuvers (orthostatic, mental-arithmetic, sit-to-stand, handgrip exercise tests). At rest, no significant differences between HD and PD were observed in HRV (root mean square of successive differences [RMSSD]: HD = 57.1 ± 81.1 vs PD = 69.6 ± 113.4 ms; $P = 0.792$), except for detrended fluctuation analysis (DFA-α1) (HD = 0.87 ± 0.40 vs PD = 0.70 ± 0.20; $P = 0.047$). DFA-α1 was significantly lower in PD than controls (1.00 ± 0.33; $P < 0.05$). All HRV indices during the mental-arithmetic test (RMSSD: HD = 128.2 ± 346.0 vs PD = 87.5 ± 150.0 ms; $P = 0.893$) and the physical stress tests were similar between HD and PD. The standard deviation along the line-of-identity (SD2)/the standard deviation perpendicular to the line-of-identity (SD1) ratio during mental-arithmetic was marginally lower in HD and significantly lower in PD than controls (PD = 1.31 ± 0.47 vs controls = 1.79 ± 0.64; $P < 0.05$). Both dialysis groups presented similar patterns in HRV responses during orthostatic and handgrip exercise tests. After the sit-to-stand, RMSSD, SD1, SD2, and DFA-α2 were higher compared to rest only in HD (RMSSD = 57.1 ± 81.1 vs 126.7 ± 185.7 ms; $P = 0.028$), suggesting a greater difficulty of HD patients in recovering normal ANS function in response to physical stress. In conclusion, HRV indices at rest and after mental and physical stimulation did not differ between HD and PD; however, the ANS responses following the sit-to-stand test were more impaired in HD. These findings suggest that ANS dysfunction is not largely affected by dialysis modality, but small differences in normal ANS recovery may exist.

Keywords: Heart rate variability, autonomic function, hemodialysis, peritoneal dialysis, arrhythmias, chronic kidney disease

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Introduction

Cardiovascular disease is the predominant cause of mortality in patients with end-stage kidney disease (ESKD) receiving kidney replacement therapy with hemodialysis (HD) or peritoneal dialysis (PD).[1,2] Cardiac arrhythmias and sudden cardiac death are the leading causes of cardiovascular mortality in these patients, with almost half of the deaths attributed to these phenomena.[1] This substantially high cardiovascular mortality observed in ESKD can be only partially explained by the presence of traditional risk factors (i.e. advanced age, hypertension, diabetes, etc.); non-traditional factors, including but not limited to inflammation, arterial stiffness, endothelial dysfunction, and autonomic nervous system (ANS) dysregulation, are significant contributors toward this increased burden of cardiovascular disease,[3] with ANS dysfunction playing a major role in the arrhythmogenic background of these patients.[4,5]

Heart rate variability (HRV) analysis is a valuable tool for assessing cardiac autonomic regulation in both short-term (minutes) and long-term (24 h) intervals and is traditionally quantified in time-domain and frequency-domain analyses.[6,7] More modern indices, such as non-linear measures of HRV (Poincaré Plot, Entropy, and Detrended Fluctuation Analysis [DFA]), have recently drawn widespread attention,[8] providing additional prognostic information for cardiovascular risk and enabling recording HRV alterations both at rest and during physiological maneuvers.[9,10] Previous studies in HD patients have shown strong associations between abnormal HRV responses and adverse outcomes, including intradialytic hypotension episodes,[10] cardiovascular-related hospitalizations,[11] and cardiovascular death.[12,13] HRV responses in patients receiving PD, although less studied, were also suggested to be an independent predictor of both cardiovascular and total mortality.[14,15]

Potential differences between the effects of the two kidney replacement therapies on autonomic function are not adequately examined; most of the existing evidence centers on the acute effects of HD on conventional resting HRV indices, suggesting that the HD session promotes abnormal HRV responses, which are associated with ultrafiltration.[16–18] Since the intermittent nature of HD renders it a less "physiological" kidney replacement modality compared to PD,[19] it could be hypothesized that individuals on PD would have more favorable HRV responses than HD patients, due to the continuous nature of the modality and the absence of rapid volume and solute changes during treatments. To the best of our knowledge, no study so far has tested this hypothesis. Therefore, the aim of this study was to compare HRV linear and non-linear indices at rest and during mental and physical stress between HD and PD patients.

Materials and methods

Study population

A total of 68 ESKD individuals (34 on HD and 34 on PD, matched in 1:1 ratio for age, sex, and dialysis vintage) from the Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Greece and affiliated Units were included in this study. The study protocol (NCT05278702) was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki (approval no. 2433) and the Institutional Review Board of Hippokration Hospital, Thessaloniki, Greece (approval no. 444). All procedures were performed according to the Declaration of Helsinki (2013 Amendment) and all participants provided informed written consent prior to study enrollment.

Inclusion criteria were as follows: (1) age >18 years, (2) ESKD treated with HD or PD for >3 months, and (3) for patients undergoing HD: standard schedule of thrice-weekly sessions. Exclusion criteria were as follows: (1) changes in antihypertensive, cardiovascular, or neurological treatment one month prior to enrollment, (2) history of hereditary or degenerative neurological disorders (e.g. Parkinson's disease, multiple sclerosis) that cause primary ANS dysfunction, (3) history of ANS dysfunction due to acquired disorders (e.g. diabetes mellitus, amyloidosis, autoimmune diseases, spinal cord injuries, etc.), (4) active malignant disease or other comorbidity with poor prognosis, (5) active infection or relevant intercurrent illness, and (6) history of drug or alcohol abuse or severe mental disorder.

Seventeen individuals without chronic kidney disease (CKD) (i.e. healthy individuals or patients with mild hypertension and/or dyslipidemia) matched for age and sex in 2:1 ratio with each group of ESKD patients were also studied as controls.

Study design and data collection

Patients undergoing HD were evaluated on a non-dialysis day, with the measurements taking place in a random order at our research center either 24 h prior or 24 h after the middle of a mid-week HD session. Patients on PD were evaluated at the same premises on the day of their routine assessment at the PD Unit. Prior to ANS function measurements, baseline demographics, anthropometric characteristics, medical history, and concomitant medications were obtained, and a detailed physical examination was performed. Blood samples for routine laboratory tests were obtained, immediately before the HD session that preceded or followed the day of the measurements for the HD patients or immediately before the study assessments for the PD patients and the control group. All procedures were performed in a room with an ambient temperature of 23–24°C. The same procedures were followed for the control group.

Linear and non-linear HRV indices were assessed in the HD and PD groups of patients and the controls, both at rest and during mental and physical stress induced by specific physiological maneuvers that evoke ANS responses and are described thoroughly below.

ANS testing procedures

Participants were connected to a photoplethysmography apparatus (Finometer-PRO, Finapres Medical Systems, The Netherlands) for continuous measurement of beat-to-beat pulse pressure profiles and heart rate (HR). A semi-reclining position was obtained, and the participants were advised

to relax during the initial equipment's calibration (about 12–15 min). After a 5–min rest (baseline measurement), the patients underwent the following ANS tests:

1. Mental-arithmetic test: the participant performed twice a countdown of consecutive deductions, beginning from 100 and deducting 7, until 0.
2. Physiological maneuvers inducing mild physical stress:

a. Orthostatic test: following a 5-min rest in the supine position with stable breathing, the participant obtained the upright position which he/she maintained for 5 min.
b. Sit-to-stand test: following a 3-min seated rest with the back supported, the participant completed as many full stands as possible within 30 s; the participant was instructed to fully sit between each stand and a 3-min recovery followed. HRV data during this recovery period were evaluated.
c. Handgrip exercise test: initially, the participants' maximal handgrip strength (the highest of three maximal voluntary contractions [MVCs] with a 60-s interval between trials) was determined using a digital dynamometer (K-Force, K-invent). Then, the participant performed a 3-min submaximal intermittent handgrip exercise test at 35% of MVC (6 sets of 30 s handgrip exercise at 35% MVC, with visual feedback in order to maintain the desired force output, and a 3-s rest between sets).

HRV data analysis

HRV analysis was performed with the Kubios software (version 3.5.0, Finland) according to recommendations[7] and by the same researcher to eliminate interobserver variability. The interbeat interval data obtained from the Finapres (using Beatscope-1a software) were exported and analyzed offline. Artifacts were detected with a specific algorithm; then, data were re-scanned by visual inspection for verification. Motion artifacts or single rare ectopic beats were removed, whereas disturbances of physiological origin, such as premature beats and atrial fibrillation induced by the physiological maneuvers (that were not present at rest), were unedited.[20] Premature beats may actually have an important role in the new dynamic analysis of R-R interval behavior, as they represent the real beat-to-beat R-R interval time series and are strong predictors of cardiovascular death in different populations.[20] The linear (Root Mean Square of Successive Differences, RMSSD) and non-linear time-domain (Poincaré plot analysis, Approximate Entropy [ApEn], Sample Entropy [SampEn], Detrended Fluctuation Analysis [DFA]) indices were calculated. The RMSSD is used to assess parasympathetic activity and provides information on a beat-to-beat basis, appropriate for short-term recordings.[7,21] The standard deviation perpendicular to the line-of-identity (SD1), the standard deviation along the line-of-identity (SD2) indices, and their ratio (SD2/SD1) were evaluated for the Poincaré plot analysis. The SD1 index measures short-term HRV reflecting parasympathetic nervous system function (similar to the RMSSD index), the SD2 measures short- and long-term variability, and the SD2/SD1 ratio is an index of sympathetic/parasympathetic function reflecting autonomic balance.[22] ApEn and SampEn quantify the complexity of the R-R interval and are not sensitive to the existence of ectopic beats.[23] The DFA analysis is a scaling analysis method representing the correlation properties of a signal. The short-term scaling component (DFA-α1) provides an estimation of the intrinsic fractal correlation properties in HR dynamics for short-term R-R interval data (4–11 beats), while the long-term component (DFA-α2) is the intermediate-term scaling exponent (>11 beats). The normal fractal behavior of HR for the α-indices is values close to 1.0 (1.0–1.3).[20] Values deviating significantly, either higher or lower, are indicative of a loss of complexity or are correlated with worse outcomes.[24] The obtained HRV data were averaged per testing period (e.g. baseline rest, exercise, and recovery) and analyzed separately for each ANS test.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 22.0. Continuous variables are expressed as mean value ± standard deviation (SD) or median [interquartile range], depending on the normality of distribution, assessed with the Shapiro–Wilk test. Categorical variables are presented as absolute frequencies and percentages (*n*, %). Between-group comparisons for continuous variables were performed with the independent *t*-test or the Mann–Whitney test, where applicable. Categorical variables were compared with the Chi-square test. To evaluate the HRV responses during the tests of physical stress, two-way analyses of variance (ANOVAs) with repeated measures on group (HD vs PD) by time (i.e. rest, during the test) were used, followed by Tukey's post hoc test for pairwise comparisons. A P value of <0.05 was considered statistically significant for all comparisons.

Results

Baseline characteristics

Baseline characteristics of the 78 ESKD patients and 17 controls are presented in Table 1. As expected from the study design, no differences were detected between the HD and PD groups for age, sex, or dialysis vintage. Moreover, no differences were observed regarding any major comorbidity, except for the prevalence of heart failure which was marginally higher in patients undergoing HD. Serum urea, potassium, and calcium levels were higher in HD patients, while the use of renin–angiotensin blockers was more frequent in PD patients. Eight patients (11.7% of the total population) had a history of paroxysmal atrial fibrillation (4 in each HD and PD patient group), but all of them were on sinus rhythm during the examination. None of the included patients had a history of atrial flutter or had a pacemaker.

HRV indices at rest

The comparison of HRV indices at rest between HD and PD patients and controls is presented in Table 2. No differences

Table 1. Baseline characteristics of the different study groups.

	HD ($N=34$)	PD ($N=34$)	P value (HD vs PD)	Controls ($N=17$)
Age (years)	57.0 ± 15.5	57.0 ± 15.7	0.997	57.2 ± 9.7
Males (*n*, %)	18 (52.9%)	18 (52.9%)	1.000	9 (52.9%)
Dialysis vintage (months)	73.5 [77.9]	49.7 [44.6]	0.102	–
Dry weight (kg)	70.88 ± 13.91	76.07 ± 14.94	0.143	–
BMI (kg/m^2)	25.0 ± 3.7	27.3 ± 4.9	**0.035**	27.3 ± 4.0
Diabetes (*n*, %)	3 (8.8%)	6 (17.6%)	0.476	0 (0.0%)
Coronary artery disease (*n*, %)	5 (14.7%)	6 (17.6%)	0.742	0 (0.0%)
Heart failure (*n*, %)	12 (35.3%)	5 (14.7%)	0.050	0 (0.0%)
Hypertension (*n*, %)	30 (88.2%)	33 (97.1%)	0.163	3 (17.6%)
Dyslipidemia (*n*, %)	13 (38.2%)	18 (52.9%)	0.223	10 (58.8%)
Number of antihypertensives	1.44 ± 1.21	1.97 ± 1.24	0.080	0.55 ± 0.68
ACEi/ARBs (*n*, %)	10 (29.4%)	21 (61.8%)	**0.007**	4 (23.5%)
CCBs (*n*, %)	16 (47.1%)	13 (38.2%)	0.462	1 (5.8%)
Beta blocker (*n*, %)	19 (55.9%)	25 (73.5%)	0.128	0 (0.0%)
Alpha blocker (*n*, %)	3 (8.8%)	0 (0.0%)	0.239	0 (0.0%)
Diuretic (*n*, %)	11 (32.4%)	19 (55.9%)	0.051	0 (0.0%)
Central acting (*n*, %)	0 (0.0%)	3 (8.8%)	0.239	0 (0.0%)
Erythropoietin-stimulating agents (*n*, %)	27 (79.4%)	20 (58.8%)	0.066	0 (0.0%)
Hemoglobin (g/dL)	11.27 ± 1.17	11.42 ± 1.68	0.689	14.36 ± 1.22
Urea (mg/dL)	136.8 ± 38.3	112.9 ± 22.2	**0.003**	35.4 ± 8.8
Creatinine (mg/dL)	8.95 ± 2.55	8.20 ± 2.90	0.262	0.98 ± 0.21
Sodium (mmol/L)	139.4 ± 2.4	138.6 ± 3.3	0.274	139.2 ± 2.1
Potassium (mmol/L)	5.16 ± 0.63	4.54 ± 0.63	<**0.001**	4.68 ± 0.43
Calcium (mg/dL)	9.26 ± 0.70	8.84 ± 0.55	**0.008**	9.48 ± 0.62
Phosphate (mg/dL)	4.51 ± 0.88	4.77 ± 0.94	0.252	3.35 ± 0.64
Parathormone (ng/L)	268.3 [260.1]	307.6 [193.8]	0.619	–

BMI: body mass index; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CCBs: calcium-channel blockers; HD: hemodialysis; PD: peritoneal dialysis.
Bold values represent statistically significant P-values of <0.05.

Table 2. Resting HRV indices in the different study groups.

	HD ($N=34$)	PD ($N=34$)	P value (HD vs PD)	Controls ($N=17$)
RMSSD	57.1 ± 81.1	69.6 ± 113.4	0.792	111.5 ± 120.5*†
SD1	40.5 ± 57.5	49.4 ± 80.4	0.792	79.1 ± 85.4*†
SD2	40.3 ± 39.3	57.2 ± 84.0	0.773	89.8 ± 84.8*†
SD2/SD1	1.59 ± 0.78	1.34 ± 0.49	0.172	1.57 ± 0.73
Sample entropy	0.87 ± 0.21	0.86 ± 0.19	0.144	1.22 ± 0.56†
Approximate entropy	1.42 ± 0.55	1.54 ± 0.63	0.244	0.85 ± 0.19
DFA-α1	0.87 ± 0.40	0.70 ± 0.20	**0.047**	1.00 ± 0.33†
DFA-α2	0.44 ± 0.19	0.51 ± 0.30	0.230	0.36 ± 0.18†

RMSSD: root mean square of successive differences; SD1: standard deviation perpendicular to the line-of-identity; SD2: standard deviation along the line-of-identity; DFA: detrended fluctuation analysis; HD: hemodialysis; PD: peritoneal dialysis.
$P<0.05$ HD vs controls, †$P<0.05$ PD vs controls.
Bold values represent statistically significant P-values of <0.05.

in resting RMSSD (HD = 57.1 ± 81.1 vs PD = 69.6 ± 113.4 ms; $P=0.792$), SD1, SD2, SD2/SD1 ratio (1.59 ± 0.78 vs 1.34 ± 0.49, respectively; $P=0.172$), ApEn, SampEn, and DFA-α2 parameters were observed between the HD and PD groups; RMSSD, SD1, and SD2 were significantly lower in both ESKD groups compared to controls. DFA-α1 index was significantly higher in the HD group compared to the PD group (0.87 ± 0.40 vs 0.70 ± 0.20; $P=0.047$). Of note, DFA-α1 was significantly lower in PD than the controls.

HRV indices during the mental stress test

Table 3 presents the comparison of HRV indices during the mental-arithmetic test between HD and PD patients and controls. No significant differences in the examined linear and non-linear indices between HD and PD patients were detected (RMSSD, HD = 128.2 ± 346.0 vs PD = 87.5 ± 150.0; $P=0.893$ and SD2/SD1 = 1.45 ± 0.78 vs 1.31 ± 0.47; $P=0.659$). The SD2/SD1 ratio was marginally lower in HD and significantly lower in PD patients compared with controls. DFA-α1 was significantly lower in both HD and PD patients than controls.

HRV indices during the orthostatic test

The mean levels of HRV indices during the orthostatic test in the three study groups are presented in Supplementary Table 1. The mean levels of HRV indices after controlling for

Table 3. HRV indices during the mental-arithmetic test in the different study groups.

	HD ($N=34$)	PD ($N=34$)	P value (HD vs PD)	Controls ($N=17$)
RMSSD	128.2 ± 346.0	87.5 ± 150.0	0.893	66.9 ± 81.3
SD1	90.9 ± 245.6	62.1 ± 106.5	0.893	47.5 ± 57.7
SD2	85.0 ± 229.9	63.5 ± 100.9	0.990	60.8 ± 52.4
SD2/SD1	1.45 ± 0.78	1.31 ± 0.47	0.659	1.79 ± 0.64†
Sample entropy	0.77 ± 0.32	0.83 ± 0.26	0.548	1.45 ± 0.61
Approximate entropy	1.35 ± 0.74	1.41 ± 0.62	0.825	0.80 ± 0.21
DFA-α1	0.86 ± 0.45	0.77 ± 0.30	0.347	1.14 ± 0.29*†
DFA-α2	0.42 ± 0.19	0.38 ± 0.18	0.810	0.46 ± 0.24

RMSSD: root mean square of successive differences; SD1: standard deviation perpendicular to the line-of-identity; SD2: standard deviation along the line-of-identity; DFA: detrended fluctuation analysis; HD: hemodialysis; PD: peritoneal dialysis.
*$P<0.05$ HD vs controls, †$P<0.05$ PD vs controls.

HR in HD and PD patients are depicted in Supplementary Table 2. HRV indices at rest and during the orthostatic test in HD and PD patients are depicted in Figure 1. No significant differences between the dialysis groups in any of the examined HRV indices were observed. Within each individual study group, the RMSSD, SD1, SD2, SD2/SD1, ApEn, and DFA-α1 indices did not show significant alterations during the orthostatic test compared to the resting period. SampEn was significantly decreased during the test in both study groups ($P<0.05$ vs rest), while DFA-α2 presented a significant rise during the orthostatic test only in HD patients ($P<0.05$ vs rest).

HRV indices during the recovery of the sit-to-stand test

The mean levels of HRV indices during the recovery of the sit-to-stand test in the three study groups are presented in Supplementary Table 1. Figure 2 presents HRV indices at rest and during the recovery of the sit-to-stand test in patients on HD and on PD. Again, none of the studied HRV parameters was different during sit-to-stand recovery between the study groups. However, the RMSSD, SD1, SD2, and the DFA-α2 indices presented a different course in this period; these indices remained significantly higher during the sit-to-stand recovery compared to rest in HD individuals, while they returned to baseline in PD patients (RMSSD: HD = 57.1 ± 81.1 vs 126.7 ± 185.7 ms; $P=0.028$; PD = 69.6 ± 113.4 vs 115.3 ± 139.4 ms; $P=0.148$ and SD2: HD = 40.3 ± 39.3 vs 102.4 ± 143.0; $P=0.026$; PD = 57.2 ± 84.0 vs 102.7 ms; $P=0.104$; rest vs recovery period, respectively). The SD2/SD1, ApEn, and DFA-α1 parameters returned to baseline levels during the sit-to-stand recovery period in both HD and PD patients. The SampEn index significantly declined following the sit-to-stand test in both groups ($P<0.05$).

HRV indices during handgrip test and recovery

The mean levels of HRV indices during the handgrip test and the 3-min recovery period in the three study groups are presented in Supplementary Table 1. The mean levels of HRV indices after controlling for HR in HD and PD patients are presented in Supplementary Table 2. HRV indices at rest, during the handgrip test, and the recovery period are presented in Supplementary Figure 1. No significant between-group differences were detected for all studied indices during handgrip and handgrip recovery periods. Within each patient group, all HRV parameters (except for DFA-a2) remained relatively unaltered during the handgrip test and recovery in both HD and PD patients. The DFA-α2 index significantly decreased during the recovery period ($P<0.05$ vs handgrip) only in PD patients.

Discussion

This is the first study comparing linear and non-linear HRV indices between HD and PD patients both at rest, as well as during mental and physical stress tests. Although both HD and PD patients displayed significantly impaired resting HRV indices, these parameters were not different between the two ESKD groups, with the exception of DFA-α1 index that was higher in HD. During the mental-arithmetic test and the physical stress tests, HRV indices were similar between the HD and PD patients. Moreover, both dialysis groups presented similar patterns of HRV responses to orthostatic and handgrip exercise tests; however, after the sit-to-stand test, RMSSD, SD1, SD2, and DFA-α2 indices remained elevated only in the HD group, indicating an impaired ability to return to baseline following a stress-induced stimulation of the sympathetic nervous system (SNS). These data suggest that patients undergoing HD exhibit a greater difficulty in recovering normal ANS function after a submaximal test compared to patients on PD.

The pathophysiology of autonomic dysfunction in ESKD is multifactorial. Factors including uremic milieu, ESKD-related fluid, and electrolyte imbalances and, for patients on HD, the intermittent nature of therapy can provoke significant alterations in the endoneurial space, resulting in damage of nerve fibers in the peripheral and central nervous system and prompting baroreceptor dysfunction.[25] Furthermore, vascular remodeling and increased arterial stiffness are also related with defective baroreceptor control, whereas cardiac hypertrophy blunts cardiopulmonary reflex and chemosensitive receptors control; these phenomena may play a major role in ANS dysfunction.[26] Additional mechanisms including renin–angiotensin system hyperactivation, endothelial dysfunction, inflammation, metabolic acidosis, anemia, and insulin resistance may also lead to an imbalance between

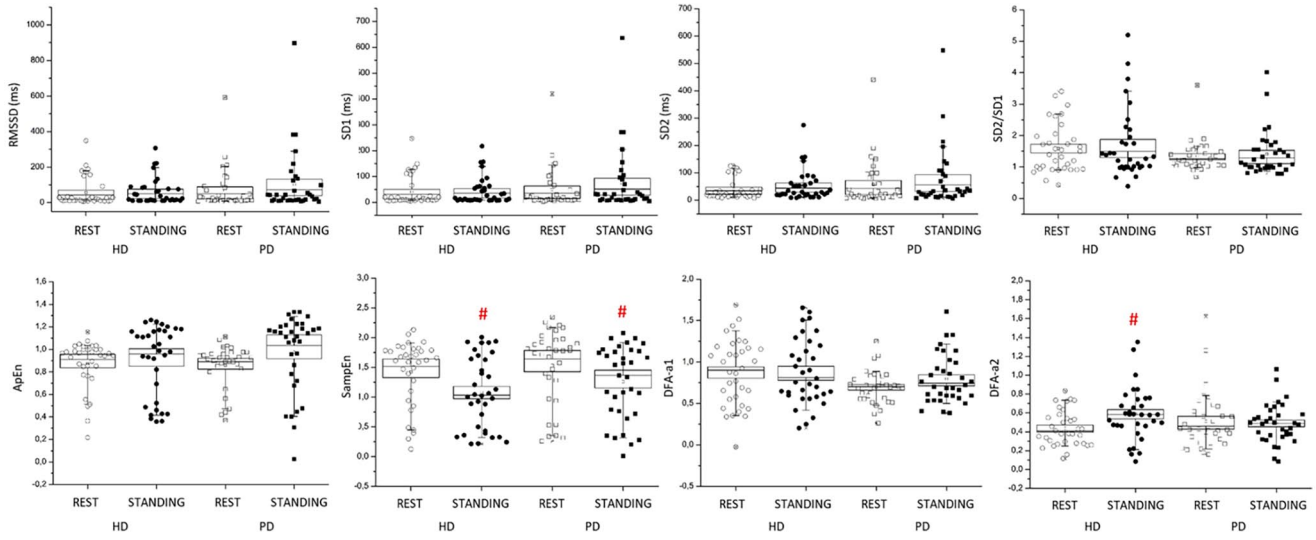

Figure 1. HRV indices at rest and during the orthostatic test in hemodialysis and peritoneal dialysis patients.
HD: hemodialysis; PD: peritoneal dialysis.
Box represents the mean value ± SD; whiskers represent the 10–90% interval.
#$P < 0.05$ vs rest (within-group).

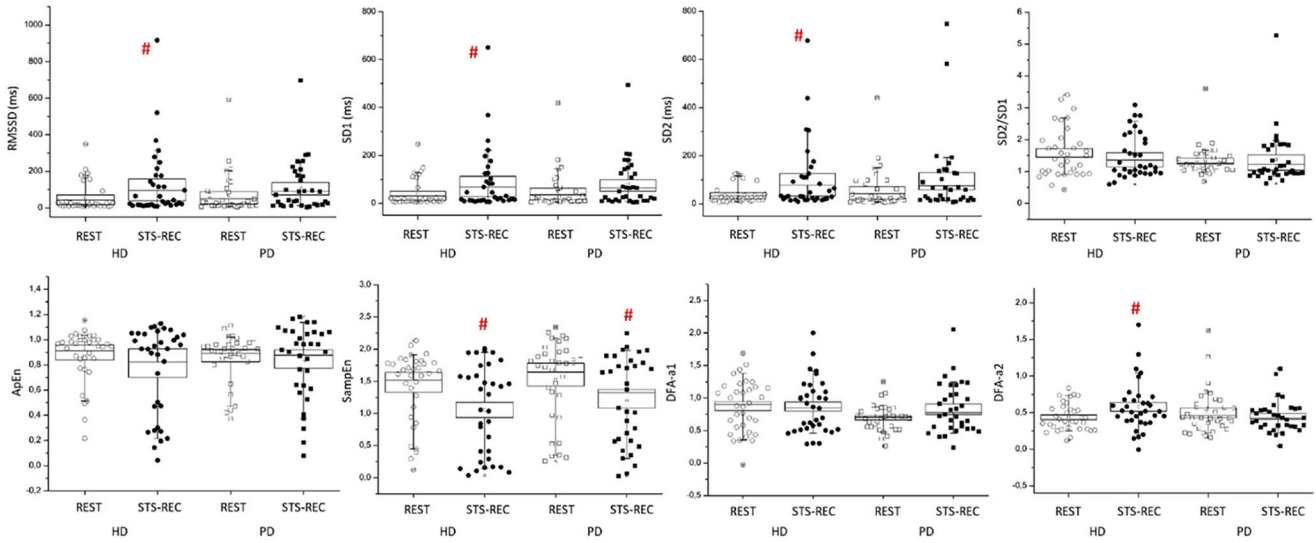

Figure 2. HRV indices at rest and at the recovery of the sit-to-stand test in hemodialysis and peritoneal dialysis patients.
HD: hemodialysis; PD: peritoneal dialysis.
Box represents the mean value ± SD; whiskers represent the 10–90% interval.
#$P < 0.05$ vs rest (within-group).

sympathetic and parasympathetic responses affecting the proper ANS function.[25,26]

In this study, we found that resting HRV indices are significantly impaired in ESKD individuals compared to controls, and this is in agreement with the existing literature. Previous studies suggested that HD patients exhibit abnormal HRV responses that can be further blunted from the HD procedure itself.[16–18,27] In 44 patients, Kurata et al.[28] found the time-domain indices of HRV being significantly blunted in the HD group versus controls. A small study measured frequency-domain HRV indices in 14 HD patients and 14 matched controls and showed that low-frequency (LF) power and high-frequency (HF) power of HRV at rest were significantly impaired in the former.[29] Longitudinal data suggest that these abnormal HRV responses are independently associated with adverse cardiovascular outcomes.[12,13] Relevant studies in PD patients are scarce. Resting time-domain parameters of HRV, notably RMSSD, were impaired in 21 PD patients compared to 25 healthy controls.[30] Similarly, a study in 65 PD and 72 controls showed that non-linear indices of HRV were significantly blunted in the former.[31] Again, these abnormal HRV responses have been showed to be independent predictors of mortality in these patients.[14] With regard to HRV indices during mental stress, we showed for the first time that the SD2/SD1 ratio was significantly lower in PD patients and DFA-a1 was significantly lower in both ESKD

groups compared to controls. This finding suggests possible impairment of ANS response in both HD and PD patients during mental stress. Future works are needed in order to expand our knowledge in this topic and identify the underlying mechanisms.

To the best of our knowledge, this study is the first to compare HRV in patients undergoing HD and PD. Given that the HD procedure is a major factor predisposing to ANS imbalance,[16–18] we hypothesized that patients undergoing PD would have less impaired ANS function, due to the different nature of the modality. However, we observed that HRV indices were similar between the two groups both at rest and after stimulation with mental and physical stress tests. These findings could be, at least partially, explained by the fact that several mechanisms involved in the pathophysiology of ANS dysfunction[26] may be similarly impaired in patients receiving these two dialysis modalities. Factors like total small solute clearance, volume overload, blood pressure (BP) control, subclinical inflammation, anemia prevalence, and others were commonly found to be no different between HD and PD patients.[19,32–35] Elegant studies examining vascular function also suggest that these parameters were similar between HD and PD. In a recent study of our group, including 38 HD patients, 38 PD patients, and 38 controls, endothelial postocclusive forearm skin vasodilatory response assessed with laser speckle contrast imaging (an index of endothelial dysfunction) did not differ between HD and PD patients but was significantly impaired in both ESKD groups compared with controls.[36] Moreover, other studies showed similar levels of office and ambulatory pulse wave velocity between the two dialysis modalities,[37,38] suggesting no differences in arterial stiffness. Finally, as cardiac hypertrophy is considered to impact the cardiopulmonary reflex and chemosensitive receptors control, the largely similar cardiac geometry, systolic and diastolic function indices between HD and PD,[35] could also explain – at least in part – our findings. As such, our findings are in general agreement with previous works that have evaluated other parameters related to sympathetic versus parasympathetic balance. Two studies examining cardiac and skin SNS response showed no differences between the two dialysis modalities.[39,40] Short-term blood pressure variability (BPV), a parameter closely related with ANS function and sympathetic versus parasympathetic drive,[41,42] was also not different between HD and PD patients in a recent study.[34]

An exception to our aforementioned findings is the different response in some HRV indices during the recovery period following the sit-to stand test between the HD and PD groups. The sit-to stand test is a functional mobility test, commonly used in clinical research and practice[43] that requires a repeated stimulation of baroreceptors to adjust to the hemodynamic changes due to changes in body posture. It is considered to be more reflective of daily life activities, especially in older individuals, and thus, it can be sensitive for the detection of small dysregulations in cardiac autonomic responses.[43] In this analysis, we showed that during the recovery period from the sit-to-stand test, RMSSD, SD1, SD2, and DFA-α2 indices remained higher than baseline only in HD patients, suggesting that after a stress-induced stimulation of the SNS, HD individuals exhibited a greater difficulty in recovering normal ANS function compared to patients on PD. Future studies are warranted in order to examine whether these differences in stress-induced ANS dysregulation between HD and PD patients affect adverse outcomes, including the incidence of arrhythmias in these populations.

This study has several strengths. It is the first to investigate the effects of different kidney replacement therapies in ANS dysfunction. We used a careful age-, sex- and dialysis-vintage matching and an elaborate protocol to measure several linear and non-linear HRV indices utilizing state-of-art devices. We also included a group of controls without CKD that underwent the same measurements. In addition, we measured HRV not only at rest but also in response to mental and physical stimulation maneuvers, allowing the recording of even small – otherwise undetectable – ANS dysregulations. With regard to limitations, our study included a relatively small sample size; however, this is a common limitation of relevant studies in the field. The study did not exclude patients receiving β-blockers even though the use of β-blockers could affect ANS function and consequently, HRV measurements; this was, however, an intentional choice taking into consideration that over half of dialysis patients are prescribed β-blockers for several comorbidities,[44] and thus, conducting a study in β-blocker-naïve patients would not be representative of the population. Furthermore, it cannot be excluded that the slight between-group imbalance observed in use of RAAS blockers and levels of some electrolytes may have impacted the different responses to sit-to-stand tests. However, RAAS blockers exhibit different effects on HRV, with angiotensin-converting enzyme inhibitor (ACEi) and mineralocorticoid receptor antagonists (MRAs) increasing and angiotensin-receptor blockers (ARBs) decreasing HRV in human studies, so no uniform effect seems to be present.[45] In addition, there is no evidence that small differences in electrolyte levels influence HRV in ESKD; in a single study in 75 HD patients, changes in electrolyte levels before and after dialysis session did not influence HRV indices.[46] Finally, a small proportion of patients (4 HD and 4 PD patients) had a history of atrial fibrillation but all of them were on sinus rhythm during the HRV examination. Relevant studies including patients with atrial fibrillation not on sinus rhythm during the examination showed that the correlation between HRV and HR was similar to that reported in patients with sinus rhythm.[47] As such, atrial fibrillation history is rather unlikely to have affected our findings.

In conclusion, our study demonstrated that there were no significant differences between HD and PD patients in linear and non-linear HRV indices, neither at rest nor after stimulation via mental and physical stress tests. These results suggest that ANS function is rather not affected by the type of dialysis therapy received and that patients from both dialysis modalities are prone to the development of ANS-modulated arrhythmogenic background. However, the impaired ability of the ANS to return to baseline after stimulation with functional tests, as shown by the delayed HRV responses after the sit-to-stand test, suggests a possible further impairment of the HD patients in recovering normal ANS function after

a physical stress test compared to patients on PD. In future, more detailed studies may shed more light in these complex phenomena.

AUTHORS' CONTRIBUTIONS

PS and KD contributed to research idea and study design. DF, MPT, AK, AZ, AT, CD, and PP contributed to data acquisition. DF, KD, MPT, and PS contributed to data analysis/interpretation. KD, MPT, and AZ contributed to statistical analysis. DF, KD, MPT, and PS contributed to manuscript drafting. MJ, AP, and PS contributed to supervision or mentorship.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ETHICAL APPROVAL

The study protocol (NCT05278702) was approved by the Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki (approval no. 2433) and the Institutional Review Board of Hippokration Hospital, Thessaloniki, Greece (approval no. 444). All procedures were performed according to the Declaration of Helsinki (2013 Amendment), and all participants provided informed written consent prior to study enrollment.

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SUPPLEMENTAL MATERIAL

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