Determinants of Cardiac Autonomic Dysfunction in ESRD

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Background and objectives: Cardiovascular events are common in patients with ESRD. Whether sympathetic overactivity or
vagal withdrawal contribute to cardiovascular events is unclear. We determined the general prevalence and clinical correlates
of heart rate variability in patients on hemodialysis.

Design, setting, participants, & measurements: We collected baseline information on demographics, clinical conditions,
laboratory values, medications, physical performance, left ventricular mass (LVM), and 24-hour Holter monitoring on 239
subjects enrolled in the Frequent Hemodialysis Network Daily Trial.

Results: The mean R-R interval was 812 ± 217 ms. The SD of R-R intervals was 79.1 ± 40.3 ms. Spectral power analyses
showed low-frequency (sympathetic modulation of heart rate) and high-frequency power (HF; vagal modulation of heart rate)
to be 106.0 (interquartile range, 48.0 to 204 ms^2) and 42.4 ms^2 (interquartile range, 29.4 to 56.3 ms^2), respectively. LVM was
inversely correlated with log HF (−0.02 [−0.0035; −0.0043]) and the R-R interval (−1.00 [−1.96; −0.032]). Physical performance
was associated with mean R-R intervals (1.98 [0.09; 3.87]) and SD of R-R intervals (0.58 [0.049; 1.10]). After adjustment for age,
race, ESRD vintage, diabetes, and physical performance, the relationship between log HF and LVM (per 10 g) remained
significant (−0.025 [−0.042; −0.0085]).

Conclusions: Holter findings in patients on hemodialysis are characterized by sympathetic overactivity and vagal withdrawal and are associated with higher LVM and impaired physical performance. Understanding the spectrum of autonomic
heart rate modulation and its determinants could help to guide preventive and therapeutic strategies.

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C ardiovascular events in general, and sudden death in
particular, are exceptionally common in patients with
ESRD (1). Despite the potential role for autonomic
dysfunction contributing to excess cardiovascular morbidity
and mortality in uremia, few studies of cardiac autonomic
function in patients with ESRD have been performed. Measurement of heart rate variability (HRV) is a noninvasive method to
assess for autonomic modulation of sino-atrial discharge (2).
Previous studies have shown attenuated HRV to be a potent
marker of premature cardiac death in patients with high cardiovascular risk (3). Given accumulating evidence that sympathetic hyperactivity and/or vagal withdrawal may lead to left
ventricular hypertrophy and poorer physical fitness, understanding associations among these factors and potential mechanisms explaining these associations merits further study.

The Frequent Hemodialysis Network (FHN) Daily Trial aims
to examine the effects of frequent (six times per week) hemo-

dialysis *versus* conventional thrice weekly hemodialysis on left
ventricular mass (LVM) and physical function, among an array
of intermediate outcome measures (4). The study objectives and
protocol summary have been published previously (4). One of
the study's secondary goals was to describe impairments of
autonomic modulation of heart rate and to explore possible
associations with structural cardiac abnormalities and/or other
demographic, clinical, and laboratory factors or performance
measures.

We conducted the present cross-sectional study to (1) describe the magnitude of autonomic dysfunction in HRV in a
relatively large cohort of hemodialysis patients and (2) explore
the potential relations among indices of HRV and possible
clinical determinants.

Materials and Methods
Study Design
All subjects enrolled in the trial were asked to undergo 24-hour
Holter testing at baseline. A description of the array of demographic,
clinical, and laboratory factors and bioelectrical impedance analysis
conducted as part of baseline evaluation in the FHN study is available
elsewhere (4). In addition, we recorded the use of cardiovascular-
related medications including beta blockers, calcium channel blockers,
aspirin, and lipid-lowering medications. All patients received conventional hemodialysis of three sessions per week with a minimum eKt/V

of 1.1 per session and a minimum treatment time of >2.5 hours per session (5). All patients provided written informed consent. All participating sites received institutional research board/ethics board approval. The FHN Daily Trial is registered at www.clinicaltrials.gov (study number NCT00264758). Comorbidity was summarized using the modified Charlson index (6).

HRV

Study staff measured continuous heart rate recordings using the KCI X5 digital Holter recorder (KCI Technology and Services). All study coordinators were trained and demonstrated competence in obtaining Holter tracings. Electrocardiographic data were stored and couriered to the core laboratory in Toronto, Canada. We analyzed the acquired data centrally in a blinded manner as previously reported (7). Only normal sinus recordings were used to assess HRV. We determined low-frequency (LF) harmonic (0.05 to 0.15 Hz; sympathetic modulation of heart rate) and high-frequency (HF) harmonic (0.15 to 0.5 Hz; parasympathetic modulation of heart rate) contributions to spectral power. LF/HF was used to denote sympathetic to parasympathetic ratio. R-R intervals and SD of R-R intervals (SDNN; a measure of beat to beat variability) were also computed.

Cardiac Magnetic Resonance Imaging

We measured left ventricular geometry and mass by cardiac magnetic resonance imaging (CMRI). As with Holter data, all CMRI images were analyzed centrally in a blinded manner. CMRI was performed on 1.5-T MRI systems (Avanto or Sonata; Siemens Medical Solutions, Erlangen, Germany, or GE Signa Systems) with eight-channel cardiac coils. We applied standard, breath-held, retrospectively electrocardiographic-gated gradient-echo sequences (steady-state free precession) in contiguous short-axis views (20 to 25 phases, 8-mm slice thickness). Using validated software (Argus; Siemens Medical Solutions), we measured volumes on end-diastolic frames by manually tracing endocardial and epicardial contours. We excluded papillary muscles from the calculation of myocardial mass. The formula of DuBois and DuBois was used to index LVM to body surface area (8).

Physical Performance

We used the Short Physical Performance Battery (SPPB) to capture the level of physical functioning. The SPPB (9) is a simple battery that can be performed at the bedside. It is based on (1) the time needed (in seconds) to walk 4 m at a normal pace; (2) the time needed to stand up and sit down five times as quickly as possible from a chair with the arms folded across the chest; and (3) a timed balance test that measures the ability to maintain balance with feet together in three positions (side by side, semitandem, and tandem). Each of the three performance measures are assigned a score ranging from 0 to 4, with 0 being the inability to complete the test and 4 indicating the highest level of performance. The total SPPB performance score ranges from 0 to 12.

Statistical Analyses

Descriptive data are presented as mean ± SD or median and interquartile range for normal and skewed population data, respectively. Potential associations among indices of HRV and various clinical determinants including LVM, SPPB, and laboratory measures were first examined graphically to determine the appropriate functional form and then tested using linear regression. Predictors that were significant at the 0.10 level on univariate testing were further examined with adjustment for age, race (black *versus* non-black), diabetes, ESRD vintage, and SPPB score.

Before performing multivariable testing, missing covariate values

(<5%) were multiply imputed while incorporating auxiliary variables reflecting factors for baseline dropout. This was done to better accommodate the assumption that missing data would be associated with variables used for imputation. SEs for the multivariable models corrected for the multiple imputation.

All statistical tests were two-tailed, with $P < 0.05$ taken to indicate significance. All analyses were conducted using SAS v9.1 (SAS Institute, Cary, NC).

Results

Our analytic cohort included 239 of the 378 (63%) enrolled subjects (Figure 1). Among the analytical cohort, 31 subjects did not qualify for randomization. Baseline characteristics of subjects who did and did not undergo randomization are summarized in Table 1. Some subjects who were excluded before randomization or otherwise voluntarily dropped from the study did not complete the Holter examination at baseline.

The mean LVM of the analytic cohort was 144 ± 56 g, and the mean SPPB score was 8.4 ± 2.7 (Table 2). The distribution of these outcome measures are shown in Figure 2. The mean R-R interval was 812 ± 217 ms, with the SDNN being 79.1 ± 40.3 ms. Spectral analysis showed that the median LF and HF harmonics were 106 (48.0; 204) and 42.4 (29.4; 56.3) ms², respectively. LF/HF was 2.37 (1.43; 3.93). Diabetes, ESRD vintage, Charlson comorbidity index, left ventricular end-diastolic volume, plasma parathyroid hormone, phosphate, albumin, calcium, BP, and interdialytic weight gain were not associated with measures of heart rate variability. There were significant univariate associations between the mean R-R interval and age, race, LVM, hemoglobin concentration, SPPB, and the use of calcium channel blockers. Among the various indices of HRV,
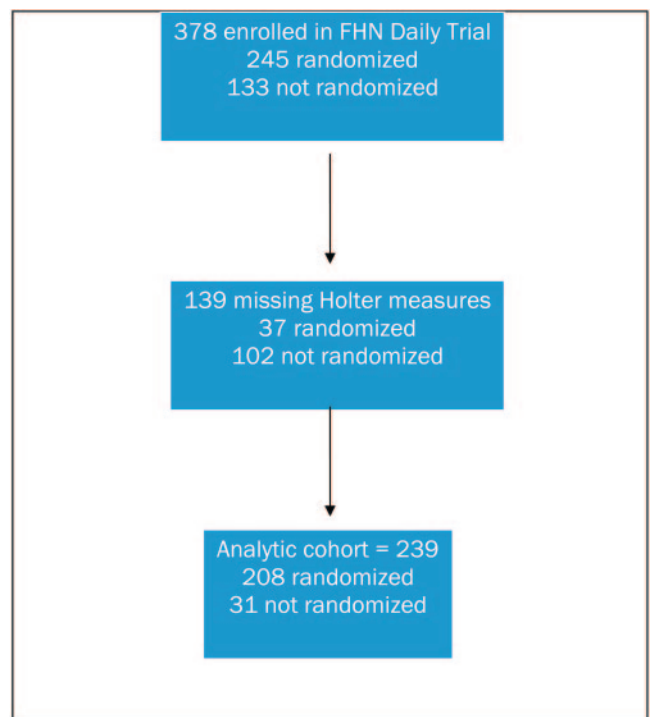

Figure 1. Derivation of the analytic cohort.

Table 1. Baseline characteristics

Variable	Analytical Cohort (*n* = 239)	Randomized Patients (*n* = 208)	Patients Who Did Not Complete Baseline (*n* = 31)
Age (years)	50.1 ± 13.6	50.1 ± 13.4	49.8 ± 15.0
Female	97 (41%)	84 (40%)	13 (42%)
Black race	100 (42%)	91 (44%)	9 (29%)
ESRD vintage (years)	3.16 (1.33; 6.48)	3.63 (1.60; 6.93)	1.68 (1.07; 2.54)
Diabetes[a]	97 (42%)	87 (42%)	10 (40%)
Congestive heart failure[a]	48 (21%)	41 (20%)	7 (28%)
COPD[a]	13 (6%)	10 (5%)	3 (12%)
Past myocardial infarction[a]	30 (13%)	25 (12%)	5 (20%)
Peripheral vascular disease[a]	26 (11%)	22 (11%)	4 (16%)
Charlson comorbidity index[a]			
0	93 (40%)	83 (40%)	10 (40%)
1	40 (17%)	37 (18%)	3 (12%)
2	40 (17%)	38 (18%)	2 (8%)
3–4	42 (18%)	36 (17%)	6 (24%)
5–6	14 (6%)	12 (6%)	2 (8%)
7–12	4 (2%)	2 (1%)	2 (8%)
Beta blocker[a]	139 (60%)	126 (61%)	13 (50%)
Calcium channel blocker[a]	120 (51%)	110 (53%)	10 (38%)
Aspirin[a]	89 (38%)	78 (38%)	11 (42%)
Statins and/or other lipid lowering medications[a]	83 (35%)	76 (37%)	7 (27%)

Descriptive data are presented as mean ± SD or median and quartiles for normal and skewed population data, respectively. COPD, chronic obstructive pulmonary disease.

[a]Missing data in five to six patients among the analytical cohort.

univariate associations were shown between log HF and LVM, log LF and the use of calcium channel blockers, SDNN and physical performance, and SDNN and age (Table 3). After adjusting for age, race, ESRD vintage, diabetes, and physical performance, the relation between LVM (per 10 g) and log HF remained statistically significant (-0.025 [-0.042; -0.0085]; $P = 0.003$; Figure 3). Similarly, after adjusting for the same base variables, the use of calcium channel blockers remained inversely related to log HF (-0.36 [-0.55; -0.18]; $P = 0.001$) and to log LF (-0.36 [-0.62, -0.11]; $P = 0.0056$).

Discussion

Left ventricular hypertrophy (LVH), poor physical performance, and sympathetic overactivity are known attributes of uremia (10–13). Our study adds to the literature by showing a potential mechanistic link among these three independent adverse clinical risk factors leading to excess cardiac morbidity and mortality in ESRD. In addition, our observations highlight that loss of vagal modulation of heart rate is an independent correlate of LVM after controlling for the effects of age, race, diabetes, ESRD vintage, and physical performance.

Sympathetic activation and vagal withdrawal have been associated with poor cardiovascular prognosis in patients with ESRD (14). Increased muscle sympathetic nerve activity has also been shown (15). Because patients undergoing hemodialysis have significantly higher sympathetic burst fre-

quency than patients with bilateral nephrectomy, this finding has been attributed to an afferent signal arising from the failing kidney. There is now an emerging body of literature showing the independent contribution of elevated sympathetic activity and/or vagal withdrawal on LVH in ESRD (16). Norepinephrine is known to cause cardiomyocyte hypertrophy *in vitro* (17). Using an observational design, Zoccali *et al.* (10) examined the association between plasma norepinephrine and LVH in patients with ESRD. These investigators showed that 91 of 197 (46%) of their patients had plasma norepinephrine concentrations above the upper limit of the normal range. In addition, patients with the highest tertile in plasma norepinephrine concentrations were 3.8-fold more likely to have concentric LVH. Similarly, using Holter electrocardiography, Nishimura *et al.* (18) documented in a cohort of 154 patients with diabetes undergoing hemodialysis an inverse association between echocardiographically derived LVM index and HF harmonic ($r^2 = 0.08$). These authors suggested that parasympathetic withdrawal in ESRD may be a complication of diabetic neuropathy leading to higher LVM. Zoccali *et al.* (19) also examined the clinical influence of parasympathetic control of the heart by studying respiratory sinus arrhythmia in 50 patients with ESRD. Once again, abnormal parasympathetic function was independently linked to concentric LVH as assessed by two-dimensional echocardiography. Our observations are consistent with the notion that cardiac autonomic dysfunction is asso-
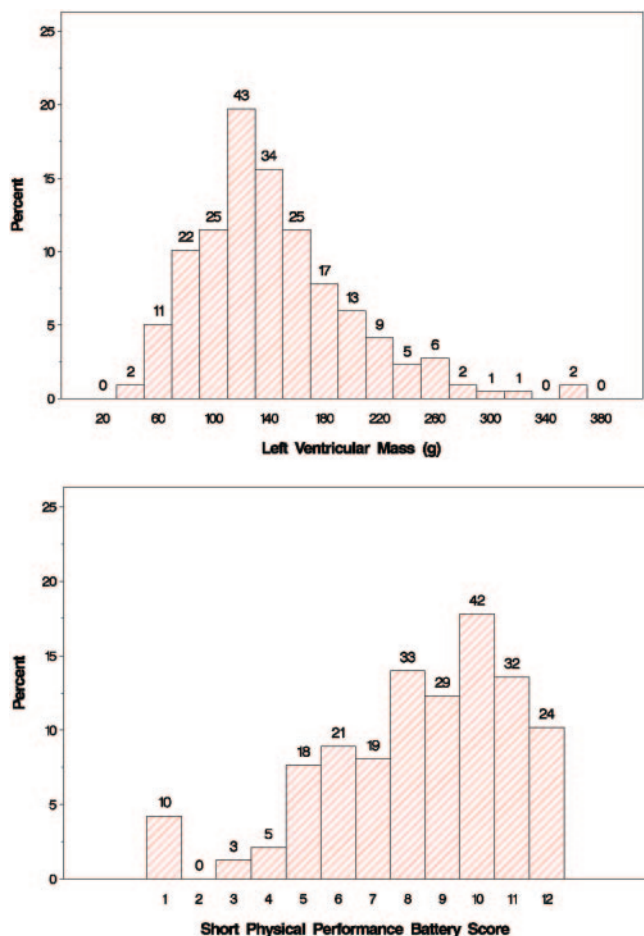
Figure 2. Distributions of LVM and SPPB score.

ciated with LVH in ESRD. In addition, given that CMRI was used to determine our cohort's LVM, it is reasonable to assume that our assessment of LVM was less likely to be confounded by various measurement errors such as excess extracellular fluid volume, a problem known to plague echocardiogram-derived estimates of LVM.

Studies of HRV and ESRD have consistently shown a decrement in HRV (2,20,21). Reduced HRV has been established as an independent risk factor in patients with high cardiac risk profile (22), which was exemplified by The Autonomic Tone and Reflexes After Myocardial Infarction (3) trial. This study enrolled 1284 patients with a recent (<28 day) myocardial infarction. Sympathetic overactivity was assessed by SDNN. During 21 months of follow-up, patients with SDNN <70 ms experienced a 3.2-fold increase in cardiac mortality. Consistent with this observation, other investigators examined the prognostic value of impaired HRV in ESRD patients. Oikawa *et al.* (23) found that SDNN of <75 ms was associated with a 3.64-fold increase in cardiovascular death among 383 patients on chronic hemodialysis. Nishimura *et al.* (24) found that 5-year survival was 98.1% in patients with LF/HF <1.9, whereas sudden cardiac death free survival rate was only 29% in patients with LF/HF >1.9.

Normal engagement of the sympathetic nervous system op-

Table 2. Baseline clinical and laboratory values

Variable	N Missing	Analytical Cohort (n = 239)	N Missing	Randomized Patients (n = 208)	N Missing	Patients Who Did Not Complete Baseline (n = 31)
Hemoglobin (g/dl)	20	12.0 ± 1.3	9	12.0 ± 1.2	11	12.3 ± 1.7
Plasma parathyroid hormone (pg/ml)	14	316 (193; 562)	3	313 (193; 565)	11	359 (189; 559)
Plasma calcium (mEq/L)	3	2.49 ± 0.25		2.50 ± 0.26	3	2.48 ± 0.09
Plasma phosphate (mg/dl)	3	5.76 ± 1.62		5.79 ± 1.58	3	5.58 ± 1.88
Interdialytic weight gain (kg)	7	3.41 ± 1.73		3.40 ± 1.66	7	3.49 ± 2.29
Albumin (g/dl)	3	3.96 ± 0.41		3.96 ± 0.41	3	3.96 ± 0.35
Systolic BP (mmHg)	3	148 ± 21		147 ± 21	3	152 ± 24
Diastolic BP (mmHg)	3	80 ± 13		80 ± 13	3	79 ± 13
Left ventricular mass (g)	21	144 ± 56		142 ± 55	21	175 ± 71
Left ventricular end diastolic volume (g)	24	179 ± 61		178 ± 61	21	201 61
Short physical performance battery score	3	8.4 ± 2.7		8.4 ± 2.7	3	8.4 ± 3.0

Descriptive data are presented as mean ± SD or median and quartiles for normal and skewed population data, respectively.

Table 3. Results of univariate associations

A. Time domain analyses

Variables	Mean RR interval (ms) Estimate (95% Confidence Interval)	P	SDNN (ms) Estimate (95% Confidence Interval)	P
Age (per decade)	3.62 (−0.15, 7.38)	0.059	−2.05 (−3.07, −1.03)	0.0001
Black race (vs. non-black race)	−11.2 (−21.5, −0.85)	0.034	2.29 (−0.6, 5.18)	0.12
Left ventricular mass (per 10 g)	−1.00 (−1.96, −0.032)	0.043	0.09 (−0.18, 0.36)	0.51
Hemoglobin (g/dl)	4.13 (0.059, 8.2)	0.047	−0.95 (−2.13, 0.23)	0.11
SPPB (per unit)	1.98 (0.09, 3.87)	0.041	0.58 (0.049, 1.10)	0.032
Calcium channel blocker	−12.9 (−23.2, −2.5)	0.015	1.54 (−1.38, 4.45)	0.30

B. Frequency domain analyses

Variables	LogHF (95% Confidence Interval)	P	Log LF (95% Confidence Interval)	P	LF/HF (95% Confidence Interval)	P
Left ventricular mass (per 10 g)	−0.018 (−0.0035, −0.0043)	0.045	−0.017 (−0.041, 0.0067)	0.16	0.00047 (−0.040, 0.041)	0.98
Calcium channel blocker	−0.35 (−0.53, −0.17)	0.0002	−0.37 (−0.62, −0.11)	0.005	0.02 (−0.42, 0.46)	0.93

SPPB, short physical performance battery score; SDNN, SD of RR intervals; HF, high-frequency harmonic.
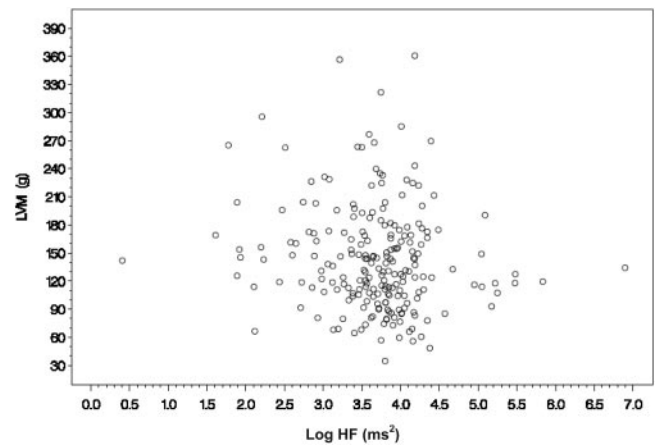

Figure 3. Scatterplot of LVM *versus* logHF.

timizes physical fitness and exercise performance. In health, the sympathetic nervous system is responsible for the increases in heart rate, stroke volume, and optimal distribution of blood flow to the working muscle (25–27). It is interesting to note that we showed a direct association between SDNN and physical performance in our analytical cohort, implying that patients who do not have a sustained increase in sympathetic modulation of heart rate have better physical performance scores. A tonic increase in cardiac sympathetic activity may lead to end-organ unresponsiveness. Indeed, previous investigators examined ß$_2$-adrenoceptor densities and responsiveness in circulating lymphoctes among normotensive and hypotensive hemodialysis patients (28). As expected, these authors noted that there was an elevation in plasma norepinephrine concentrations in all patients with ESRD and in particular hypotensive patients on hemodialysis. However, the densities and responsiveness of adrenceptors were most reduced in those patients with the highest plasma norepinephrine concentrations. The authors suggested that a sustained increase in sympathetic activity may lead to downregulation of adrenceptors contributing to hemodynamic instability during hemodialysis. In this cohort, it is tempting to hypothesize that sustained elevation in cardiac sympathetic activity may lead to cardiac unresponsiveness, which may be associated with poor physical performance in ESRD.

This study has several important limitations. Although we hypothesized an association between structural cardiac abnormalities (by CMRI) and HRV, as well as other clinical factors with HRV, we tested multiple hypotheses because of the exploratory nature of the study. Therefore, it is possible that one or more of the significant associations we described may be "false positives." We did not perform maneuvers other than Holter testing to assess for autonomic dysfunction. Although our sample was large relative to previous studies of HRV in ESRD, we had limited statistical power to detect associations, which are modest in magnitude, especially after multivariable adjustment. Because these analyses were cross-sectional, we could not determine whether the associations we found were causal. Longitudinal analyses of HRV in the FHN study sub-

jects may provide additional insight into the factors associated with cardiac autonomic dysfunction and the extent to which HRV may be modifiable.

In summary, derived from a relatively large cohort of patients on hemodialysis, we showed associations among vagal modulation of heart rate, LVM, and physical performance. After controlling for various confounders, higher LVM remained significantly associated with the loss of vagal modulation of heart rate, as was impaired physical performance. Understanding the spectrum of autonomic heart rate modulation and its determinants may help to guide preventive and therapeutic strategies to reduce the burden of cardiovascular disease in this population.

Acknowledgments

Disclosures

None.

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