Heart Rate Variability Predicts ESRD and CKD-Related Hospitalization

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ABSTRACT

Autonomic imbalance, a feature of both diabetes and hypertension, may contribute to adverse cardiovascular outcomes. In animal models, sympathetic nerve activity contributes to renal damage but the extent to which autonomic dysfunction precedes the development of CKD and ESRD in humans is unknown. We measured resting heart rate and heart rate variability in 13,241 adults (45- to 64-years old) followed for a median of 16 years in the Atherosclerosis Risk in Communities (ARIC) Study. We examined heart rate parameters by quartiles, defining those in the lowest quartile (by time and frequency domain measures separately) as the risk group of interest. We identified 199 cases of incident ESRD and 541 patients with CKD-related hospitalizations; higher resting heart rate and lower heart rate variability associated with both outcomes. The fully adjusted hazard ratios for ESRD were 1.98 (95% confidence interval [CI] 1.45 to 2.70) among those in the highest heart rate quartile and 1.56 (95% CI 1.14 to 2.14) for high-frequency power. Other time and frequency domain measures were similarly and significantly associated with ESRD and CKD-related hospitalizations. These results suggest that autonomic dysfunction may be an important risk factor for ESRD and CKD-related hospitalizations and call for further studies to define the mechanisms that underlie these associations.

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Even in the absence of hypertension and diabetes mellitus, 12% of adults aged 65 years and older have chronic kidney disease (CKD), suggesting that other mechanisms of renal injury may be important in the general population.[1] An infrequently explored potential cause of renal injury is autonomic imbalance (high sympathetic tone and/or low parasympathetic tone). Histologic studies demonstrate that renal sympathetic nerve terminals are in direct contact not only with renal vasculature but also with tubules and juxtaglomerular cells.[2] In animal models, alterations in the activity of these nerves modulate renal hemodynamics, tubular transport, and renin secretion.[2–4] In animals, sympathetic denervation results in a natriuretic and diuretic response and attenuates the progression of renal failure.[2–4] In humans, several phenomena associated with autonomic imbalance, such as impaired diurnal BP variation, have been linked to chronic kidney disease and its progression, independent of mean BP and diabetes.[5–7] Whether the autonomic imbalance associated with abnormal diurnal BP

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variation is the physiologic driver of this association remains unclear.[8,9]

Although there is no gold-standard measure of autonomic balance,[9] cardiac sympathetic and parasympathetic tone can be assessed using heart rate variability (HRV) measurements—a practical way to measure autonomic balance using standard electrocardiographic monitoring. By examination of the average heart rate, and quantification of beat-to-beat variability (the SD of a patient's RR intervals, for example), HRV can be quantified. Additionally, computer algorithms that utilize Fourier (spectral) analysis have been developed to quantify cyclic changes in heart rate that occur during the course of a few seconds (high-frequency [HF] power) or during longer time periods (low-frequency [LF] and very low frequency power). For example, in most healthy young adults, resting heart rate will predictably accelerate and decelerate with the respiratory cycle (every few seconds—a high frequency). The more the heart rate varies with respiration, the higher the HRV, and in this case, the higher the "high-frequency power." A failure to exhibit this variation would be characterized as low HRV and is a marker of autonomic dysfunction. In general, lower resting heart rates and greater beat-to-beat variability in heart rate (high HRV) are associated with a healthy autonomic nervous system and good cardiovascular health. High resting heart rate and low HRV are associated with a host of adverse cardiovascular outcomes, as well as with precursors of cardiovascular disease, including features of the metabolic syndrome.[10–19]

Several small cross-sectional studies have found that patients with CKD have decreased HRV relative to those without CKD.[20–28] However, it is not known to what extent autonomic imbalance precedes the development of CKD and may contribute to its development because reverse causality—nephrosclerosis causing autonomic imbalance—may be the primary mechanism for the association. If autonomic imbalance precedes the development of chronic kidney disease, it may serve as a marker to identify patients at higher risk of developing ESRD. More important, it may serve to provide evidence that the autonomic nervous system plays a role in the pathophysiology of nephrosclerosis. Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) study, we sought to determine the relationship between low HRV and the subsequent development of adverse renal outcomes.

RESULTS

Baseline Characteristics of Patients and Ultimate Renal Outcomes

Of 13,241 patients included, 199 developed ESRD and 541 had a CKD-related hospitalization over a median of 16-year follow-up. Baseline characteristics are shown in Table 1. Baseline estimated GFR (eGFR) was moderately lower in those who ultimately developed ESRD (77 ml/min per 1.73 m^2) than in the total cohort (93 ml/min per 1.73 m^2). More than half of those who developed ESRD were black, although blacks comprised only about a quarter of the total cohort. Diabetes was present in 62% of those who developed ESRD. Systolic and diastolic BP was higher in those who went on to develop ESRD, and treatment with antihypertensives was more prevalent as well. Features of the metabolic syndrome, including obesity, high triglycerides and low HDL cholesterol were also more prevalent in those who ultimately developed renal failure.

Baseline characteristics of those with low HRV (quartile 1) *versus* those with higher HRV are shown in Table 2a (time domain measures) and Table 2b (frequency domain measures). Low HRV (quartile 1) was more prevalent in those with diabetes and hypertension, but the mean eGFR was 90 to 95 ml/min per 1.73 m^2 for all HRV categories. Higher body mass index (BMI) was modestly but significantly associated with time domain measures, but not with frequency domain measures. Triglycerides were consistently highest in those with lower HRV.

As shown in Table 3, in univariate analysis, each of the HRV metrics was strongly associated with incidence rates of ESRD and CKD-related hospitalizations. There appeared to be a threshold effect such that those in the lowest quartile (Q1) of HRV measures were at increased risk for adverse renal outcomes, but the event rates among those in the remaining three quartiles (Q2 to Q4) were comparable. This is illustrated in Figure 1 and Figure 2. There was a suggestion of a dose-response relationship: among the 745 patients who were simultaneously in the worst quartile for heart rate and LF and HF power, the unadjusted hazard ratio (HR) for ESRD was 10.15 (6.95 to 14.87) and the fully adjusted hazard ratio was 3.39 (2.12 to 5.42), compared with the 6979 patients who were not in the worst quartile for any of these three measures.

Unadjusted and adjusted hazard ratios associating low HRV with adverse renal outcomes are presented in Table 4. There was a moderately strong association between low HRV and both ESRD and CKD-related hospitalizations that remained significant after adjustment for other factors associated with adverse renal outcomes, including age, gender, race, baseline eGFR, systolic and diastolic BP, diabetes, use of antihypertensive drugs, baseline coronary disease, smoking, lipid variables, fasting insulin and glucose, BMI, and waist circumference.

Although baseline albuminuria values were not available, they were available at the time of the third follow-up visit (approximately 9 years after study inception). Using these measures, we performed sensitivity analyses that excluded all patients who ultimately developed albuminuria,[29] assuming that this would also exclude the vast majority of patients who had albuminuria at baseline. Even in this small subset, which included only 16 ESRD cases and 134 CKD-related hospitalization cases, there remained significant adjusted associations between some of the HRV measures and ultimate renal outcomes. Specifically, the fully adjusted HR for ESRD in patients with heart rates in the highest quartile was 3.17 (1.13 to 8.91) and was 4.84 (1.61 to 14.6) for those with low root mean square of successive differences in normal-to-normal RR inter-

Table 1. Baseline characteristics of the cohort of 13,241 by eventual renal outcome

Characteristic: % or Mean (SD)	Total	ESRD	CKD Hospitalization
n	13,241	199	541
Age, (years)	54 (6)	56 (5)	56 (5)
Male (%)	44.1	48.7	47.9
Black race (%)	25.7	58.8	47.3
Serum creatinine (mg/dl)	0.87 (0.41)	1.65 (2.29)	1.24 (1.69)
eGFR (ml/min per 1.73 m^2)	93 (21)	77 (37)	86 (30)
Mildly decreased (60 to 89 ml/min per 1.73 m^2) GFR (%)	49.5	39.2	44.7
Diabetes (%)	11.5	61.8	49.5
Prevalent CHD[a] (%)	4.7	11.1	11.8
Prior myocardial infarction (%)	3.9	9.6	10.5
Blood pressure category (%)			
normal	48.5	16.6	26.1
prehypertension	34.2	36.7	37.9
stage 1 hypertension	12.7	25.1	22.6
stage 2 hypertension	4.6	21.6	13.5
Systolic blood pressure (mmHg)	121 (19)	140 (25)	133 (23)
Diastolic blood pressure (mmHg)	73 (11)	78 (13)	76 (13)
Hypertensive (%) (stages 1 or 2 or on antihypertensives)	34.2	73.4	62.7
Taking antihypertensive medications (%)	24.8	56.4	49.4
Smoking status			
current (%)	26.0	27.6	29.9
former (%)	32.3	36.7	34.2
never (%)	41.7	35.7	35.9
BMI[a] (kg/m^2)	27.6 (5.3)	30.3 (6.2)	30.2 (6.4)
HDL cholesterol[a] (mg/dl)	53 (17)	47 (17)	48 (17)
LDL cholesterol[a] (mg/dl)	135 (40)	141 (53)	139 (47)
Triglycerides[a] (mg/dl)	131 (89)	188 (159)	174 (140)
Time domain measures			
mean heart rate (beats/min)	66.2 (10.0)	71.9 (13.3)	69.7 (12.5)
SDNN	37 (20)	27 (19)	30 (19)
rMSSD	5.1 (1.7)	4.3 (1.8)	4.7 (2.0)
Frequency domain measures			
HF power	18.1 (46.1)	9.3 (19.6)	13.3 (29.2)
LF power	30.9 (51.8)	15.7 (25.7)	19.1 (32.8)
ratio: LF/HF power	2.7 (2.9)	2.4 (2.9)	2.3 (2.6)

[a]Numbers of missing values (*n*): prevalent CHD (244); BMI (6); LDL (74); HDL (73); triglycerides (73); SBP (2); DBP (1); frequency domain measures (642). CHD, coronary heart disease; BMI, body mass index (weight in kg/height in m^2); SDNN, SD of all normal-to-normal RR intervals.

vals (rMSSD). The other HRV measures were not significantly associated with adverse renal outcomes in the fully adjusted models in this subset of patients.

Additional sensitivity analyses varied the baseline patients, modeling of baseline kidney function (continuous eGFR), and outcome definitions. Associations between HRV and risk of ESRD in sensitivity analyses that excluded all individuals with prevalent CKD (baseline eGFR <60 ml/min per 1.72 m^2) and modeled baseline eGFR continuously (spline, with knots at eGFR values of 60 and 90 ml/min per 1.72 m^2) were similar to the presented results. Varying the outcome to include less severe kidney dysfunction also yielded similar results. We also examined whether there was an interaction between the presence or absence of diabetes mellitus and the association between HRV measures and renal outcomes, but no significant interactions were found. When we excluded patients on antihypertensive medications at baseline, the relationship between impaired HRV and ESRD was modestly accentuated, as shown in Table 5.

DISCUSSION

In this longitudinal study, we found that low HRV was associated with the subsequent development of renal impairment. This association remained significant after adjustment for other factors known to contribute to the development of renal failure, including diabetes, hypertension, baseline renal function, lipid variables, and parameters associated with insulin resistance and obesity. Although this does not demonstrate a cause-and-effect relationship,[8] the temporal pattern is intriguing in that abnormal HRV preceded the development of clinical renal failure by many years. Furthermore, there are plausible mechanisms by which abnormal autonomic balance may lead to kidney damage.

Sympathetic nerve terminals innervate the kidneys directly, potentially affecting tubular function by enhancing solute and fluid resorption and modifying renal microvascular function by enhancing the effects of angiotensin.[2,3,30–32] Additionally, the

Table 2a. Characteristics of the cohort by baseline HRV: time domain and heart rate measures

Characteristic: % or Mean (SD)	Time Domain and HRV Measures (Range of Values in Milliseconds)					
	Mean Resting Heart Rate (beats/min)		SDNN		rMSSD	
	Q1 (fastest) (73.9 to 127)	Q2 to Q4 (37.8 to 73.8)	Q1 (0.5 to 24.5)	Q2 to Q4 (24.6 to 394)	Q1 (0 to 4.0)	Q2 to Q4 (4.0 to 25.5)
n	3310	9931	3345	9896	3318	9923
Age, (years)	54 (6)	54 (6)	55 (6)	54 (6)[b]	56 (6)	54 (6)[b]
Male (%)	35.08	47.22[b]	38.71	46.03[b]	44.91	43.94
Black race (%)	28.40	24.84[b]	27.14	25.25	19.50[b]	27.8[b]
Serum creatinine (mg/dl)	0.86 (0.58)	0.87 (0.33)	0.88 (0.62)	0.86 (0.30)[c]	0.88 (0.54)	0.86 (0.35)[c]
eGFR (ml/min per 1.73 m^2)	95 (24)	92 (20)[b]	93 (24)	93 (20)	92 (23)	93 (20)[b]
Mildly decreased (60 to 89 ml/min per 1.73 m^2) GFR (%)	46.01	50.64[b]	47.29	50.22[c]	49.43	49.50
Diabetes (%)	18.43	9.22[b]	19.46	8.84[b]	19.35	8.91[b]
Prevalent CHD[a] (%)	4.31	4.81	6.84	3.96[b]	6.87	3.95[b]
Prior myocardial infarction (%)	3.76	3.99	5.62	3.36[b]	5.60	3.38[b]
Blood pressure category (%)						
normal	36.95	52.40[b]	40.87	51.13[b]	38.82	51.79[b]
prehypertension	38.58	32.70[b]	36.86	33.26[b]	38.94	32.57[b]
stage 1 hypertension	17.49	11.15[b]	15.78	11.70[b]	15.85	11.69[b]
stage 2 hypertension	6.98	3.75[b]	6.49	3.90[b]	6.39	3.94[b]
Systolic blood pressure (mmHg)	126 (20)	120 (18)[b]	125 (20)	120 (18)[b]	125 (20)	120 (18)[b]
Diastolic blood pressure (mmHg)	76 (11)	72 (11)[b]	75 (12)	73 (11)[b]	75 (11)	73 (11)[b]
Hypertensive (%) (stages 1 or 2 or on antihypertensives)	41.42	31.83[b]	44.75	30.67[b]	31.53	42.28[b]
Taking antihypertensive medications (%)	27.52	23.93[b]	34.18	21.66[b]	30.72	22.85[b]
Smoking status						
current (%)	25.36	26.26	26.26	25.95	23.79	26.78[b]
former (%)	29.86	33.11[b]	31.14	32.69	32.78	32.13
never (%)	44.77	40.61[b]	42.57	41.34	43.40	41.07[d]
BMI[a] (kg/m^2)	28.4 (5.9)	27 (5)[b]	28.3 (5.8)	27.4 (5.1)[b]	28.0 (5.4)	27.4 (5.3)[b]
Total cholesterol[a] (mg/dl)	218 (45)	213 (40)[b]	219 (43)	213 (41)[b]	221 (44)	213 (41)[b]
HDL cholesterol[a] (mg/dl)	53 (18)	53 (18)	53 (19)	53 (17)	52 (18)	54 (18)[b]
LDL cholesterol[a] (mg/dl)	135 (43)	124 (39)	136 (42)	134 (39)	138 (42)	134 (39)[b]
Triglycerides[a] (mg/dl)	146 (107)	126 (81)[b]	148 (109)	125 (80)[b]	153 (115)	124 (76)[b]
Time domain measures						
mean heart rate (beats/min)	81.0 (6.2)	62.4 (7.1)[b]	72.5 (11.1)	64.3 (9.0)[b]	74.4 (10.5)	63.8 (8.7)[b]
SDNN	27 (14)	41 (21)[b]	18 (5)	44 (20)[b]	21 (8)	43 (20)[b]
rMSSD	4.1 (1.3)	5.5 (1.7)[b]	3.6 (0.8)	5.6 (1.7)[b]	3.4 (0.53)	5.6 (1.6)[b]
Frequency domain measures						
HF power	16 (33)	19 (50)[b]	5.0 (5.2)	23 (53)[b]	4.3 (4.9)	23 (52)[b]
LF power	26 (42)	33 (55)[b]	8.6 (8.9)	39 (58)[b]	11.7 (13.6)	37 (58)[b]
ratio: LF/HF power	2.4 (2.5)	2.8 (3.0)[b]	2.4 (2.4)	2.8 (3.0)[b]	3.3 (3.2)	2.5 (2.7)[b]

BMI, body mass index (weight in kg/height in m^2); CHD, coronary heart disease.
[a]Numbers of missing values (*n*): prevalent CHD (244); BMI (6); LDL (74); HDL (73); triglycerides (73); systolic blood pressure (2); diastolic blood pressure (1); frequency domain measures (642).
[b]$P < 0.001$ between Q1 and (Q2 to Q4).
[c]$P < 0.01$ between Q1 and (Q2 to Q4).
[d]$P < 0.05$ between Q1 and (Q2 to Q4).

global health of the vasculature is affected by the autonomic nervous system's role in regulating hemodynamics, vascular tone, metabolism, and inflammation.[9,33–37] This is relevant because the glomerulus is adversely affected by the same pathophysiological factors that lead to atherosclerosis, including hypertension, endothelial dysfunction, dyslipidemia (particularly high triglycerides and low HDL cholesterol), insulin resistance, inflammation, and oxidative stress.[4,38–42] Given that these risk factors for cardiovascular disease are also associated with high sympathetic and low parasympathetic tone,[19,43–45] it is not surprising that HRV and other measures of autonomic tone are related to the progression of renal dysfunction.

Our study has several limitations. First, baseline urinary albumin excretion was not measured. Therefore, it is difficult to exclude the possibility of reverse causality—early renal disease leading to dysregulated autonomic tone—because some

Table 2b. Characteristics of the cohort by baseline heart rate variability: frequency domain measures

Characteristic: % or Mean (SD)	Frequency Domain Measures [Range of Values in (beats/min)^2 for HF and LF]					
	HF Power		LF Power		Ratio: LF/HF Power	
	Q1 [0.01 to 3.5]	Q2 to Q4 [3.5 to 1700]	Q1 [0.003 to 6.3]	Q2 to Q4 [6.3 to 1440]	Q1 [0.02 to 1.0]	Q2 to Q4 [1.0 to 70.6]
n	3152	9447	3153	9446	3155	9444
Age, (years)	56 (6)	53 (6)[b]	56 (6)	54 (6)[b]	54 (6)	54 (6)
Male (%)	51.14	40.89[b]	39.87	44.65[b]	29.54	48.10[b]
Black race (%)	19.80	27.29[b]	28.99	24.22[b]	39.94	20.56[b]
Serum creatinine (mg/dl)	0.90 (0.54)	0.85 (0.34)[b]	0.89 (0.59)	0.86 (0.31)[b]	0.85 (0.48)	0.87 (0.37)[d]
eGFR (ml/min per 1.73 m^2)	91 (21)	94 (21)[b]	92 (23)	93 (20)[c]	95 (23)	92 (20)[b]
Mildly decreased (60 to 89 ml/min per 1.73 m^2) GFR (%)	51.21	49.13[d]	47.38	50.40[c]	43.87	51.58[b]
Diabetes (%)	16.59	9.75[b]	17.60	9.41[b]	13.72	10.71[b]
Prevalent CHD[a] (%)	7.76	3.48[b]	7.39	3.60[b]	4.83	4.46
Prior myocardial infarction (%)	6.45	2.96[b]	6.13	3.06[b]	4.08	3.75
Blood pressure category (%)						
normal	43.97	50.05[b]	43.07	50.35[b]	45.93	49.40[b]
prehypertension	36.45	33.50[c]	35.30	33.89	33.00	34.66
stage 1 hypertension	13.99	12.20[c]	14.72	11.96[b]	14.64	11.99[b]
stage 2 hypertension	5.55	4.24[c]	6.88	3.80[b]	6.43	3.95[b]
Systolic blood pressure (mmHg)	123 (20)	120 (19)[b]	124 (21)	120 (18)[b]	123 (21)	121 (18)[b]
Diastolic blood pressure (mmHg)	74 (11)	73 (11)[d]	74 (12)	73 (11)[b]	74 (12)	73 (11)[b]
Hypertensive (%) (stages 1 or 2 or on antihypertensives)	39.21	32.39[b]	43.77	30.8 [b]	42.16	31.41[b]
Taking antihypertensive medications (%)	29.28	23.15[b]	33.75	21.66[b]	32.10	22.21[b]
Smoking status						
current (%)	26.50	25.69	28.90	24.89[b]	30.56	24.34[b]
former (%)	33.99	31.51[c]	31.03	32.50	28.92	33.20[b]
never (%)	39.50	42.78[b]	40.06	42.59[d]	40.51	42.44
BMI[a] (kg/m^2)	27.9 (5.4)	27.5 (5.3)[b]	28.3 (5.8)	27.3 (5.1)[b]	28.2 (5.8)	27.3 (5.1)[b]
Total cholesterol[a] (mg/dl)	217 (43)	214 (41)[c]	215 (43)	214 (41)	213 (42)	215 (41)[c]
HDL cholesterol[a] (mg/dl)	51 (18)	54 (18)[b]	52 (18)	54 (18)[c]	55 (18)	53 (18)[b]
LDL cholesterol[a] (mg/dl)	136 (41)	134 (40)	134 (41)	135 (39)	132 (40)	135 (40)[b]
Triglycerides[a] (mg/dl)	146 (104)	126 (83)[b]	143 (103)	127 (84)[b]	126 (81)	133 (92)[b]
Time domain measures						
mean heart rate (beats/min)	68.3 (10.7)	65.6 (9.7)[b]	68.4 (11.2)	65.6 (9.6)[b]	66.0 (11.0)	66.4 (9.7)
SDNN	27 (14)	40 (20)[b]	26 (14)	41 (20)[b]	37 (24)	37 (18)
rMSSD	4.0 (1.1)	5.5 (1.7)[b]	4.3 (1.4)	5.4 (1.7)[b]	5.8 (2.1)	4.9 (1.4)[b]
Frequency domain measures						
HF power	1.7 (1.0)	23.6 (52.1)[b]	3.7 (5.0)	22.9 (52.3)[b]	31.5 (80.7)	13.7 (24.1)[b]
LF power	6.2 (7.9)	39.1 (57.3)[b]	3.0 (1.8)	40.2 (56.8)[b]	16.4 (37.8)	35.7 (54.9)[b]
ratio: LF/HF power	3.7 (4.1)	2.4 (2.3)[b]	1.7 (1.9)	3.0 (3.1)[b]	0.60 (0.24)	3.4 (3.0)[b]

BMI, body mass index (weight in kg/height in m^2); CHD, coronary heart disease; SDNN, SD of all normal-to-normal RR intervals.
[a]Numbers of missing values (*n*): prevalent CHD (244); BMI (6); LDL (74); HDL (73); triglycerides (73); systolic blood pressure (2); diastolic blood pressure (1); frequency domain measures (642).
[b]$P < 0.001$ between Q1 and (Q2 to Q4).
[c]$P < 0.01$ between Q1 and (Q2 to Q4).
[d]$P < 0.05$ between Q1 and (Q2 to Q4).

patients may have had albuminuria at baseline despite having preserved eGFR. However, our sensitivity analyses suggested that even among those with normal eGFR at baseline and those who did not have albuminuria midway through follow-up, there was still a relationship between HRV and the development of clinical renal complications. We lacked serum creatinine measurements during the 3-year follow-up visits, which impaired our ability to assess CKD progression. Additionally, about 2000 patients enrolled in ARIC did not have baseline HRV measurements, and the HRV measurements themselves were limited by the absence of postural stimulation and longer recording intervals. Although continuous hospitalization surveillance was used to define incident ESRD and vital data, only events occurring in acute care hospitals were investigated, and events occurring in other institutions, such as nursing homes, might be missed. In addition, there is a

Table 3. Events and incidence rates of ESRD and CKD hospitalization events by quartiles of HRV measures

	Quartiles of Measures				*P*[a]
	Q1	Q2	Q3	Q4	
Time Domain Measures					
Mean Heart Rate					
ESRD events/*n*	101/3310	36/3310	30/3313	32/3308	
ESRD incidence/1000 person-years	2.10	0.72	0.59	0.63	<0.001
CKD hospitalization events/*n*	221/3310	110/3310	102/3313	108/3308	
CKD hospitalization incidence/1000 person-years	4.63	2.20	2.02	2.15	<0.001
SDNN					
ESRD events/*n*	110/3345	34/3269	27/3331	28/3296	
ESRD incidence/1000 person-years	2.29	0.68	0.53	0.55	<0.001
CKD hospitalization events/*n*	253/3345	102/3269	98/3331	88/3296	
CKD hospitalization incidence/1000 person-years	5.31	2.06	1.93	1.74	<0.001
rMSSD					
ESRD events/*n*	108/3318	24/3332	36/3258	31/3333	
ESRD incidence/1000 person-years	2.26	0.47	0.72	0.61	<0.001
CKD hospitalization events/*n*	228/3318	95/3332	98/3258	120/3333	
CKD hospitalization incidence/1000 person-years	4.80	1.87	1.98	2.36	<0.001
Frequency Domain Measures					
HF Power					
ESRD events/*n*	92/3152	36/3149	40/3141	21/3157	
ESRD incidence/1000 person-years	2.02	0.76	0.83	0.43	<0.001
CKD hospitalization events/*n*	210/3152	104/3149	111/3141	87/3157	
CKD hospitalization incidence/1000 person-years	4.64	2.19	2.31	1.79	<0.001
LF Power					
ESRD events/*n*	95/3153	42/3165	29/3134	23/3147	
ESRD incidence/1000 person-years	2.11	0.87	0.60	0.47	<0.001
CKD hospitalization events/*n*	222/3153	123/3165	93/3134	74/3147	
CKD hospitalization incidence/1000 person-years	4.97	2.57	1.94	1.53	<0.001
Ratio of LF/HF Power					
ESRD events/*n*	68/3155	47/3133	31/3166	43/3145	
ESRD incidence/1000 person-years	1.46	0.99	0.65	0.89	0.001
CKD hospitalization events/*n*	173/3155	129/3133	108/3166	102/3145	
CKD hospitalization incidence/1000 person-years	3.73	2.74	2.27	2.13	<0.001

SDNN, SD of all normal-to-normal RR intervals.
[a]For difference in incidence rates between Q1 and (Q2 to Q4).

possibility that hospitalizations occurred outside of the study area. We cannot exclude the possibility of residual confounding, particularly given that adjustment for other cardiovascular risk factors attenuated the relationship between HRV and renal outcomes; variables that we did not measure and analyze include markers of baseline inflammation, nutrition, and physical fitness. Finally, we acknowledge that heart rate and heart rate variability are affected by factors other than endogenous autonomic tone (such as medications that affect heart rate) and that there are other ways to examine autonomic tone (such as direct measurement of circulating norepinephrine levels, heart rate recovery after exercise, and direct measurement of sympathetic nerve electrical output).[9] We hope that other researchers will use different cohorts to determine whether non-HRV markers of autonomic dysfunction predict subsequent renal dysfunction.

The clinical implications of our findings are uncertain. Although there is clarity that reducing BP by any number of means can retard the progression to renal failure,[46,47] drugs that block the renin-angiotensin-aldosterone system remain the mainstay for preventing the progression to nephropathy in patients with diabetes or early renal damage.[48] Some of the renoprotective effects of these agents may be mediated in part by cross-talk between the sympathetic nervous system and the renin-angiotensin-aldosterone system.[49] Although animal models indicate that sympathetic denervation of the kidneys can provide renoprotective effects,[50] there is little evidence that centrally or peripherally acting sympatholytics have unique renoprotective effects in humans.[51] Rather than suggesting a change in clinical practice, we hope our findings will encourage further research to better define the putative role of the autonomic nervous system in precipitating and exacerbating renal disease in humans; this, in turn, may ultimately lead to novel therapeutic approaches once the mechanisms for our findings are better characterized.

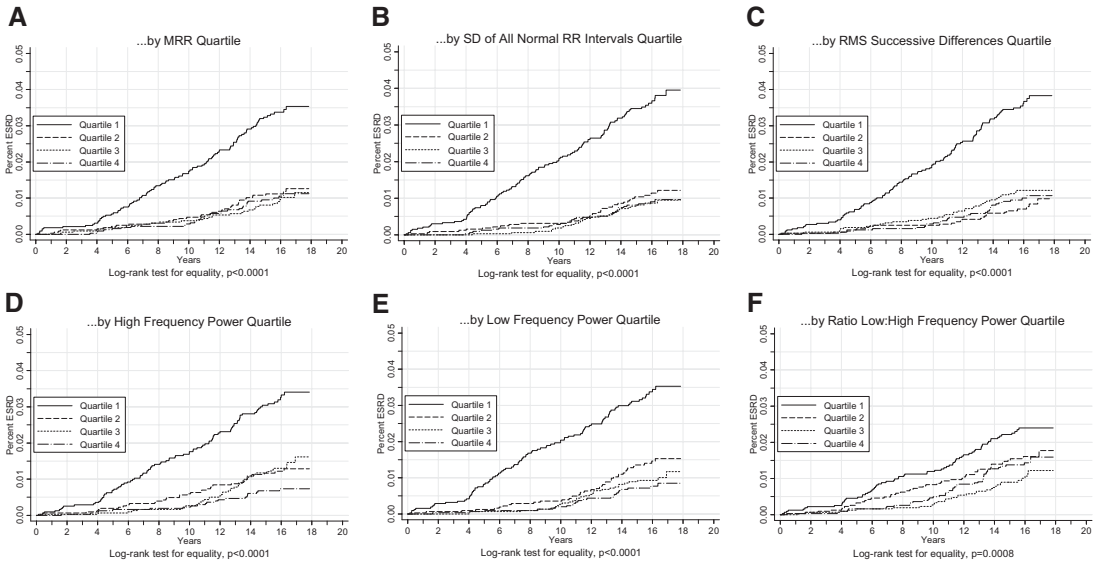

Figure 1. Those in the lowest HRV quartile are at increased risk of renal failure. Time to ESRD (Kaplan-Meier estimates) by quartiles of heart rate measures. Time to ESRD by quartiles of HRV measures: (A through C) time domain measures; (D through F) frequency domain measures. RMS, root-mean squared.

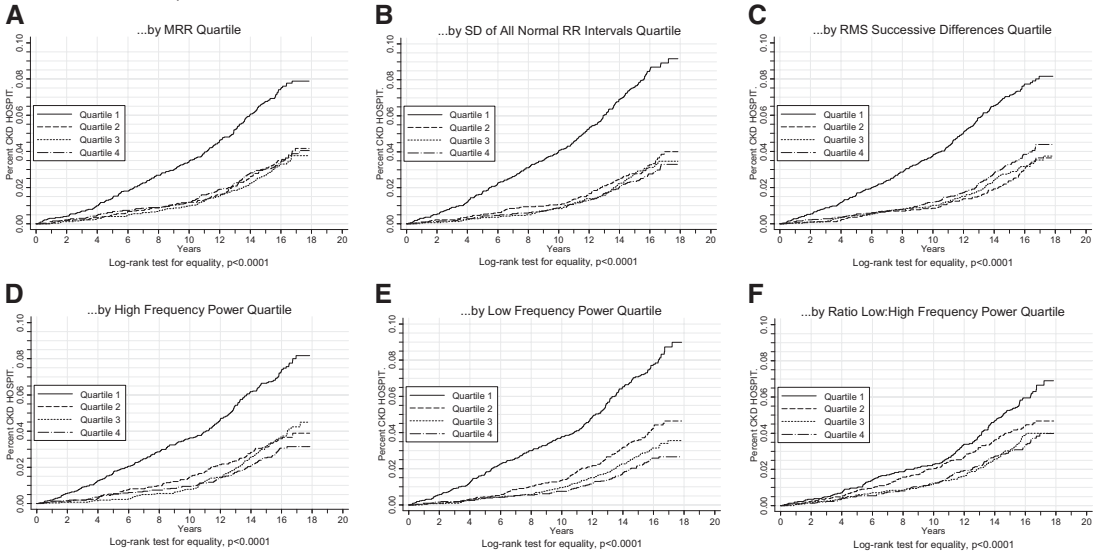

Figure 2. Those in the lowest HRV quartile are at increased risk of hospitalization. Time to kidney-related hospitalization (Kaplan-Meier estimates) by quartiles of heart rate measures. Time to kidney-related hospitalization by quartiles of HRV measures: (A through C) time domain measures; (D through F) frequency domain measures.

CONCISE METHODS

Study Cohort

The ARIC Study is a prospective observational cohort of 15,792 individuals aged 45 to 64 years, drawn from four U.S. communities. Examinations included a baseline visit between 1987 and 1989, follow-up examinations approximately every 3 years, and annual telephone interviews. Hospitalization events were ascertained through December 31, 2004. Further details of the ARIC cohort have been previously published.[52]

For this study, we excluded participants lacking baseline serum creatinine values ($n = 149$), reported a race other than white or black ($n = 49$), and excluded blacks from the Minnesota and Washington County study centers ($n = 55$) based on low numbers of blacks at these sites. We also excluded participants missing important exposure and covariate information ($n = 2196$ missing baseline HRV measures and 102 missing baseline hypertension or diabetes information). Analyses were based on the remaining 13,241 study participants.

Data Collection

Demographic data, medical history, and measurements of height, weight, and BP were obtained during each clinical examination. Laboratory measures were performed as described previously.[52] Diabetes mellitus was defined as a fasting glucose of ≥126 mg/dl, nonfasting

Table 4. HR associated with lowest quartiles of time and frequency domain measures[a]

	Time Domain Measures			Frequency Domain Measures		
	Mean Heart Rate Q1	SDNN Q1	rMSSD Q1	HF Power Q1	LF Power Q1	Ratio: LF/HF Power Q1
Outcome: ESRD						
Unadjusted HR (95% CI)	3.28 (2.49 to 4.34)	3.96 (2.99 to 5.24)	3.81 (2.89 to 5.04)	3.04 (2.29 to 4.05)	3.31 (2.49 to 4.41)	1.74 (1.29 to 2.34)
Adjusted 1[b] HR (95% CI)	2.24 (1.65 to 3.04)	1.90 (1.40 to 2.58)	2.30 (1.69 to 3.14)	1.65 (1.21 to 2.27)	1.42 (1.04 to 1.95)	1.11 (0.81 to 1.53)
Adjusted 2[c] HR (95% CI)	1.99 (1.46 to 2.71)	1.85 (1.36 to 2.51)	2.07 (1.52 to 2.84)	1.57 (1.14 to 2.15)	1.41 (1.03 to 1.94)	1.20 (0.88 to 1.65)
Adjusted 3[d] HR (95% CI)	1.98 (1.45 to 2.70)	1.83 (1.35 to 2.50)	2.08 (1.52 to 2.84)	1.56 (1.14 to 2.14)	1.40 (1.02 to 1.93)	1.20 (0.88 to 1.65)
Outcome: CKD Hospitalizations						
Unadjusted HR (95% CI)	2.22 (1.87 to 2.63)	2.85 (2.40 to 3.37)	2.36 (1.99 to 2.80)	2.25 (1.89 to 2.69)	2.54 (2.13 to 3.02)	1.58 (1.32 to 1.90)
Adjusted 1[b] HR (95% CI)	1.71 (1.42 to 2.05)	1.81 (1.51 to 2.18)	1.58 (1.31 to 1.90)	1.58 (1.30 to 1.90)	1.49 (1.23 to 1.80)	1.20 (0.99 to 1.46)
Adjusted 2[c] HR (95% CI)	1.53 (1.27 to 1.85)	1.73 (1.44 to 2.08)	1.46 (1.31 to 1.90)	1.50 (1.24 to 1.81)	1.43 (1.18 to 1.73)	1.23 (1.02 to 1.50)
Adjusted 3[d] HR (95% CI)	1.51 (1.25 to 1.82)	1.70 (1.41 to 2.04)	1.47 (1.22 to 1.77)	1.48 (1.22 to 1.79)	1.40 (1.16 to 1.70)	1.23 (1.01 to 1.49)

SDNN, SD of all normal-to-normal RR intervals.
[a]Where Q2 to Q4 is the reference group, HR = 1.00.
[b]Adjusted for age, gender, race/study center combined variable, baseline eGFR category, systolic blood pressure, diastolic blood pressure, use of antihypertensive agents, prevalent coronary heart disease, previous myocardial infarction, smoking status, diabetes status, total cholesterol, HDL cholesterol, and ln(triglycerides).
[c]Adjusted for above in addition to fasting plasma glucose and insulin.
[d]Adjusted for above in addition to fasting plasma glucose, insulin, and BMI.

Table 5. HR for ESRD associated with HRV measures among those patients NOT on antihypertensive medications at baseline (n = 9947)[a]

	Time Domain Measures			Frequency Domain Measures		
	Mean Heart Rate Q1	SDNN Q1	rMSSD Q1	HF Power Q1	LF Power Q1	Ratio: LF/HF Power Q1
Unadjusted HR (95% CI)	4.37 (2.85 to 6.70)	4.10 (2.69 to 6.26)	4.04 (2.65 to 6.17)	2.40 (1.54 to 3.74)	2.94 (1.89 to 4.57)	2.00 (1.27 to 3.15)
Adjusted 1[b] HR (95% CI)	2.57 (1.59 to 4.13)	2.05 (1.27 to 3.30)	2.39 (1.47 to 3.89)	1.58 (0.96 to 2.58)	1.66 (1.02 to 2.71)	1.29 (0.79 to 2.10)
Adjusted 2[c] HR (95% CI)	2.35 (1.43 to 3.85)	2.01 (1.24 to 3.25)	2.26 (1.38 to 3.69)	1.56 (0.95 to 2.56)	1.63 (0.99 to 2.68)	1.36 (0.82 to 2.25)
Adjusted 3[d] HR (95% CI)	2.32 (1.41 to 3.82)	1.95 (1.20 to 3.17)	2.21 (1.36 to 3.62)	1.52 (0.92 to 2.50)	1.62 (0.98 to 2.66)	1.39 (0.84 to 2.31)

SDNN, SD of all normal-to-normal RR intervals.
[a]Where Q2 to Q4 is the reference group, HR = 1.00.
[b]Adjusted for age, gender, race/study center combined variable, baseline eGFR category, systolic blood pressure, diastolic blood pressure, prevalent coronary heart disease, previous myocardial infarction, smoking status, diabetes status, total cholesterol, HDL cholesterol, and ln(triglycerides).
[c]Adjusted for above in addition to fasting plasma glucose and insulin.
[d]Adjusted for above in addition to fasting plasma glucose, insulin, and BMI.

glucose of ≥200 mg/dl, self-reported physician diagnosis of diabetes, or use of diabetic medications.

Seated BP measurements were taken after 5 minutes of rest. Standard methods were used to determine lipid levels.[53] Cigarette smoking was determined by self-report (current, former, or never). Coronary heart disease was defined as physician-diagnosed myocardial infarction, evidence of prior myocardial infarction by electrocardiogram, or prior coronary revascularization. eGFR was calculated using the four-variable Modification of Diet in Renal Disease (MDRD) Study equation.[54] Urinary albumin was measured from a spot urine sample at visit 4 (1996 through 1998) as the ratio of albumin to creatinine (ACR). Albuminuria was defined as ACR ≥30 mg/g.

HRV was measured from 2-minute beat-to-beat heart rate recordings taken in a supine position at baseline. Heart rate data were analyzed by time domain analysis and frequency domain analysis as described previously.[55] Time domain and heart rate measures included mean normal-to-normal RR interval length (which we converted to heart rate in beats per minute for ease of interpretation), the SD of all normal-to-normal RR intervals, and the rMSSD. For frequency domain measures, a fast Fourier transform algorithm was used.[19] Spectral analysis was used to calculate power (area under the power spectral density curve), although it was not technically feasible to do so for 642 patients. Given the relatively short duration of these recordings, we report only HF and LF power (or their ratio) and do not report very low frequency power. HF power was defined as the total area between 0.15 and 0.4 Hz (cycles between 2.5 and 6.7 seconds), which is thought to correspond to the heart rate variation that results with normal respiration, mediated predominantly by the vagus nerve.[56] LF power was defined as the total area between 0.04 and 0.15 Hz, which is thought to relate to changes in sympathetic neural output.[56] Reproducibility of each of these measures has been shown to be high.[57]

Outcome Assessment—Hospitalization and ESRD

Deaths and hospitalizations through 2004 were identified via annual participant interviews, local hospital discharge lists, and county death certificates and included all those coded (International Classification of Diseases, Ninth Revision [ICD-9]) for chronic renal disease (581 to 583.91, 585 to 588.91), hypertensive renal disease (403 to 403.91), hypertensive heart and renal disease (404 to 404.93), unspecified disorder of kidney and ureter (593.9), diabetes with renal manifestations (250.40 to 250.43), kidney transplant, renal dialysis or adjustment/fitting of catheter (V42.0, V45.1, or V56), or either hemodialysis (39.95) or peritoneal dialysis (54.98) without simultaneous acute renal failure (584, 586, 788.9, and 958.5). Also included as cases were participants with acute renal failure (ARF) as a cause of death, if they had an earlier diagnosis of CKD.[58,59] Excluded were individuals that had a transplant or dialysis code on the same date as another ARF code (586, 584, 788.9) without previous CKD and those with an ARF code of 958.5 (traumatic anuria). Corresponding ICD-10 codes were used for deaths after ICD-10 implementation.

Cases of ESRD were assessed through continuous surveillance of hospitalizations through December 31, 2004, and included ICD codes specified for kidney transplant, dialysis, or a procedural code indicating dialysis. Participants with an underlying cause of death of ARF, conditional upon having an earlier diagnosis of CKD (as defined by the ICD-9 codes above), and excluding individuals that have had a transplant or dialysis code on the same date as another ARF code (586, 584, 788.9) without previous CKD (and excluding anyone with an ARF code of 958.5) were defined as ESRD cases.

Statistical Analysis

Baseline characteristics of the cohort were compared across ESRD status, CKD hospitalization status, and HRV quartiles using χ^2 and t tests. Follow-up time was calculated from baseline to the earliest date of ESRD (or CKD hospitalization); participants were censored at the earliest of the following: time of death, withdrawal, or December 31, 2004. Crude incidence rates and their 95% confidence intervals for the time to development of ESRD, or hospitalization, were computed using Poisson regression models.

On the basis of a prospectively defined analysis, HRV measures were divided into two groups with one group at or below the 25th percentile and the other group above the 25th percentile.[17] Because we converted the RR interval to heart rate for ease of interpretation, the corresponding first quartile for the RR interval corresponds to the highest quartile of heart rate. We conducted Cox proportional hazards regression to examine the relationship between the lowest quartile of HRV and incident ESRD or CKD hospitalization. Multivariable models included age, gender, a race/study center combined variable, baseline eGFR category (defined as eGFR <45, 45 to 60, 60 to 75, 75 to 90, 90 to 120, or >120 ml/min per 1.73 m^2), systolic BP, diastolic BP, use of antihypertensive agents, prevalent coronary heart disease, smoking, diabetes, total cholesterol, HDL cholesterol, and triglyceride concentrations. Additional models included fasting insulin and glucose, BMI, and waist circumference. Models including LDL cholesterol in place of total cholesterol were examined, but did not substantially change results so were dropped from final models. Sensitivity analyses, which included eGFR as a continuous variable, were performed.

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DISCLOSURES

None.

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