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Prognostic value of heart rate variability in patients with renal failure on hemodialysis

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Abstract

Background: In patients with renal failure on hemodialysis cardiovascular disease is a major cause of death. It has been reported that diminished heart rate variability (HRV) relates to the unfavorable prognosis in post-infarction and/or heart failure patients. However, the prognostic value of HRV in hemodialysis patients has not been fully established.
Methods and results: Time- and frequency-domain analysis of HRV on 24-hour ambulatory electrocardiography recording was assessed prospectively in 383 chronic hemodialysis patients (220 men and 163 women, mean age 57±13 years, ejection fraction 65±12%). During 2110±903 days of follow up, 146 patients died (31 congestive heart failure, 13 fatal myocardial infarction, 13 sudden deaths, 26 stroke, and 63 non-cardiovascular deaths). A Cox univariate analysis identified the following factors as predictors of both all-cause and cardiovascular death: age, gender, ejection fraction, presence of diabetes, and HRV parameters calculated in the time- and frequency-domain. In multivariate analysis, a low standard deviation of all normal RR intervals (SDNN) value was the strongly associated with both all-cause and cardiovascular death (hazard ratios [95% confidence intervals] 0.988 [0.982–0.994] and 0.984 [0.974–0.993], respectively). From Kaplan–Meier survival curves, the incidence of all-cause and cardiovascular death was much greater in patients with a low SDNN (<75 msec), even after adjusting for the presence of diabetes ($P<0.0001$).
Conclusions: Decreased HRV on 24-hour ambulatory electrocardiography is an independent predictor of mortality in chronic hemodialysis patients.
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Keywords: Heart rate variability; Prognosis; Hemodialysis patients

1. Introduction

Patients with renal failure on hemodialysis have a poor prognosis in spite of the advances made in medical management. The 5-year mortality rate of hemodialysis patients in Japan is reported to be about 40%, and cardiovascular disease is the most common cause of death [1]. Mortality rates in patients on hemodialysis remain relatively constant over 10 years, and the cause of death also shows little variation. In hemodialysis patients, reduced heart rate variability (HRV) reflecting sympathovagal imbalance in the cardiovascular system has been observed [2,3]. Diminished 24-hour time- and frequency-domain measures of HRV are associated with an unfavorable prognosis in patients after myocardial infarction [4,5] and/or in heart failure patients [6–9]. However, the relationship between

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HRV and prognosis in patients with renal failure on hemodialysis has not been fully explored. The purpose of this multicenter study was to assess prospectively the usefulness of HRV analysis as a long-term prognostic marker in ambulatory patients with renal failure on regular hemodialysis.

2. Subjects and methods

Patients were eligible for study if they were undergoing ambulatory hemodialysis three times a week at Toyo Clinic, Iwaki Urological, and Chiba Social Insurance Hospital. Clinical stability was required for more than 1 month after induction of hemodialysis. During the period between November 1997 and May 1999, 412 consecutive patients underwent 24-hour ambulatory electrocardiographic recording, transthoracic echocardiography, and routine blood tests. Patients were excluded from the study if they had any of the following: implanted pacemaker or defibrillator, chronic or paroxysmal atrial fibrillation and/or flutter, atrioventricular or bundle-branch block, perturbation of ambulatory recordings by ectopic beats (≥10% of total beats) or excessive noise levels during the 24-hour recording. Inclusion criteria were fulfilled by 383 ambulatory patients (220 men, 163 women), whereas 29 patients did not fulfill the criteria and were excluded. Each patient gave informed consent for participation in this study in accordance with the ethics committee of the institution.

2.1. Patient characteristics

The mean age of the patients was 57±13 years (range, 18 to 91 years), and the mean duration of dialysis was 5.3± 6.0 years (range, 0.1 to 27.1 years). The mean left ventricular (LV) ejection fraction measured by echocardiography before hemodialysis was 65±12% (range, 13 to 89%). The primary etiology of renal disease in these patients was chronic glomerulonephritis in 137 patients (35.8%), diabetic nephropathy in 107 (27.9%), nephrosclerosis in 31 (8.1%), IgA nephritis in 16 (4.2%), polycystic renal disease in 12 (3.1%), and other diseases in 80 (20.9%). There were 120 patients (31.3%) with diabetes mellitus at the time of study registration. At baseline medical therapy included calcium antagonists in 203 patients (53.0%), angiotensin-converting enzyme inhibitors and/or angiotensin-II receptor blockers in 68 (17.8%), nitrates in 63 (16.4%), digoxin in 19 (5.0%), and beta blockers in 18 (4.7%) in varying combinations. Antiarrhythmic agents were being administered to 25 patients (6.5%) because of non-sustained ventricular tachycardia (disopyramide in 11, mexiletine in 8, procainamide in 5, and amiodarone in 1).

2.2. Ambulatory electrocardiogram recording and heart rate variability analysis

Ambulatory electrocardiogram leads were attached to patients 1 h before hemodialysis, and recordings carried out for 24 h using two-channel recorders (SM-28, SM-30, SM-60, Fukuda Denshi Co. Ltd, Tokyo, Japan). QRS complexes and arrhythmias were labeled and edited manually using the Marquette 8000 Laser Holter System. Only tapes with analysable QRS labeling for a duration exceeding 23 h were used. As noted, tapes with ectopic beats ≥10% of total recorded beats were excluded from this study. Qualifying tapes were subsequently analyzed to measure HRV using a validated Marquette HRV software program (version 002A, Marquette

Table 1
Clinical characteristics and heart rate variability measures in relation to survival

	Survivors (n=237)	Non-survivors (n=146)	p value
Age (years)	52±13	64±11	<0.001
Gender (man/woman) (n)	148/89	72/74	0.014
Duration of hemodialysis (years)	5.6±6.2	4.7±5.5	0.474 [a]
Diabetes mellitus (n)	49 (20.7%)	71 (48.6%)	<0.001
Hematocrit (%)	28.3±5.4	30.1±22.6	0.462 [a]
LVEF (%)	67±10	62±14	<0.001 [a]
Etiology of renal failure			
Glomerulonephritis (n)	107 (45.1%)	30 (20.5%)	
Diabetic nephropathy (n)	41 (17.3%)	66 (45.2%)	
Nephrosclerosis (n)	15 (6.3%)	16 (11.0%)	<0.001
IgA nephritis (n)	14 (5.9%)	2 (1.4%)	
Polycystic renal disease (n)	8 (3.4%)	4 (2.7%)	
Other (n)	52 (21.9%)	28 (19.1%)	
Medication			
Calcium antagonists (n)	122 (51.5%)	81 (55.4%)	0.462
ACE inhibitors or ARB (n)	46 (19.4%)	22 (15.1%)	0.336
Nitrates (n)	18 (7.6%)	45 (30.8%)	<0.001
Digoxin (n)	10 (4.2%)	9 (6.2%)	0.469
Beta blockers (n)	14 (5.9%)	4 (2.7%)	0.215
Antiarrhythmic agents (n)	13 (5.4%)	12 (8.2%)	0.296
Time domain measures			
mean NN (ms)	777±97	775±107	0.876
SDNN (ms)	111±33	85±34	<0.001
SDANN (ms)	103±32	80±32	<0.001
RMSSD (ms)	19±11	17±9	0.001 [a]
pNN50 (%)	3.16±5.96	2.19±4.86	0.009 [a]
Frequency domain measures			
Ln TP (ln ms^2)	5.95±0.88	5.20±0.94	<0.001
Ln LF (ln ms^2)	4.78±1.11	3.74±1.20	<0.001
Ln HF (ln ms^2)	3.65±0.89	3.24±0.94	<0.001
LF/HF ratio	1.33±0.25	1.17±0.29	<0.001

Data are expressed as mean±SD or number (%) of patients; p values give the comparison between survivors and nonsurvivors.

Abbreviations: LVEF = left ventricular ejection fruction; ACE inhibitors = angiotensin converting enzyme inhibitors; ARB = angiotensin II receptor blockers; mean NN = mean normal to normal RR intervals; SDNN = standard deviation of all NN intervals; SDANN = standard deviation of 5-minute mean NN intervals; RMSSD = square root of the mean square successive difference of NN intervals; pNN50 = percentage of adjacent NN intervals >50 ms different; Ln = natural logarithm; TP = total power (0 to 1.0 Hz); LF = power within low-frequency band (0.04 to 0.15 Hz); HF = power within high-frequency band (0.15 to 0.40 Hz).

[a] Data are compared by the Mann–Whitney's U-test.

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