Nephrol Dial Transplant (2003) 18: 318–325

Nephrology Dialysis Transplantation

Original Article

Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis

Hidekatsu Fukuta, Junichiro Hayano, Shinji Ishihara, Seiichiro Sakata, Seiji Mukai, Nobuyuki Ohte, Kazuhito Ojika[1], Keiko Yagi[1], Hiroko Matsumoto[1], Sinken Sohmiya[1] and Genjiro Kimura

Third Department of Internal Medicine, Nagoya City University Medical School, Nagoya and [1]Division of Hemodialysis Treatment, Clinic Tsushima, Tsushima, Japan

Abstract

Background. Although decreased heart rate variability (HRV) is an independent predictor of death in various populations, its prognostic value in patients with end-stage renal disease on chronic haemodialysis is unknown.

Methods. We prospectively studied 120 chronic haemodialysis patients (age 61 ± 11 years; males 51%; diabetics 38%; duration of haemodialysis therapy 50 ± 114 months) who underwent 24 h electrocardiography at baseline for analysis of time- and frequency-domain HRV.

Results. All HRV measures in the patients were significantly reduced compared with those obtained from 62 age-matched healthy subjects. During a follow-up period of 26 ± 10 months, 21 patients died (17.5%); 10 from cardiac causes and 11 from non-cardiac causes (seven fatal strokes and four other causes). A Cox proportional hazards model revealed that, of the HRV measures, decreases in the triangular index (TI), very-low-frequency (0.0033–0.04 Hz) power, ultra-low-frequency (<0.0033 Hz) power (ULF) and the ratio of low-frequency (0.04–0.15 Hz) power to high-frequency (0.15–0.4 Hz) power had significant predictive value for cardiac death. None of the HRV measures, however, had predictive value for non-cardiac death, including stroke death. Even after adjustment for other univariate predictors including age, diabetes, serum albumin and coronary artery disease, the predictive value of decreased TI and ULF remained significant—adjusted relative risk (95% confidence interval) per 1 SD decrement of TI and ULF, 3.28 (1.08–9.95) and 1.92 (1.01–3.67), respectively.

Conclusions. Decreases in some HRV measures, particularly those reflecting long-term variability, are independent predictors of cardiac death in chronic haemodialysis patients.

Keywords: ambulatory 24 h electrocardiogram; autonomic nervous system; haemodialysis; heart rate variability; prognosis

Introduction

Despite recent progress in haemodialysis, mortality is still high in patients with end-stage renal disease on chronic haemodialysis. Recent studies have reported that this is due to an increasing prevalence of cardiac complications in this population [1,2]. Identification of high-risk individuals, particularly those susceptible to cardiac death, is of clinical importance.

In various populations, decreased heart rate variability (HRV) identifies patients at an increased risk of death, particularly that of cardiac death [3–8]. HRV refers to a measure of the beat-to-beat variations of heartbeat interval. For the purpose of survival/risk prediction, HRV is analysed using 24 h ambulatory Holter recordings of electrocardiogram (ECG), and it is expressed as two different kinds of measures; those reflecting statistical or geometric range of the variations within certain periods of time (time-domain measures) and those reflecting magnitude (power) of cyclic components of variations within specific ranges of frequency (frequency-domain measures). Recently, we reported that decreased HRV predicts an increased risk of death in a small cohort of chronic haemodialysis patients with angiographically proven coronary artery disease [9]. It is unknown, however, whether this finding can be extended to general populations of chronic haemodialysis patients. In this study, we examined the independent prognostic value of analysing HRV in patients with end-stage renal disease on chronic haemodialysis.

Correspondence and offprint requests to: Junichiro Hayano, MD, Third Department of Internal Medicine, Nagoya City University Medical School, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya, 467-8601, Japan. Email: hayano@med.nagoya-cu.ac.jp

Subjects and methods

Patients

We studied outpatients with end-stage renal disease who were on regular chronic haemodialysis therapy for at least >3 months (a 4 h session, three times a week) at the Hemodialysis Center of Clinic Tsushima between 1997 and 1999. Patients were eligible if they were between 20 and 80 years of age. Patients were excluded from this study if they had a history of any of the followings at baseline: myocardial infarction, stroke, a major surgical procedure within the previous 2 months, haemodynamically significant valvular or congenital heart disease, atrial fibrillation or flutter, high grade heart block or a permanent pacemaker, chronic obstructive lung disease, severe hepatic disease, malignant neoplasms, or other physical or mental problems that limited their normal daily activities.

Protocols

No more than 1 month before the index 24 h Holter ECG for this study, blood chemistry, 12-lead ECG, chest roentgenogram and variables related to haemodialysis were obtained for assessing baseline clinical features, then each patient underwent a 24 h Holter ECG with a portable ECG recorder (RAC-1202, Nihon Koden, Tokyo, Japan) between haemodialysis sessions while following their usual daily activities. The patients were subsequently followed up as part of their regular haemodialysis at the Hemodialysis Center of Clinic Tsushima.

Control subjects

To compare HRV between chronic haemodialysis patients and healthy individuals, we recruited age-matched healthy controls. The control subjects were selected after undergoing a thorough medical evaluation for latent disorders. The evaluations included medical history, physical examination, blood cell count, blood biochemistry and 12-lead ECG. Elderly subjects (65 years or older) were also screened for occult cardiovascular disease by exercise tolerance testing. The healthy controls underwent a 24 h Holter ECG while following their usual daily activities, but they were not subjected to follow-up studies.

All the patients and healthy subjects gave informed consents to participate in the study, and the study protocols were approved by Institutional Review Board of Nagoya City University Medical School.

Data analysis

Cut-off points for the clinical variables in haemodialysis patients were determined according to the earlier study [10] that reported predictors of the risk of death among chronic haemodialysis patients in Japan. Kt/V (an index of fractional urea clearance) and protein catabolic rates were determined by Shinzato's method [10]. Diabetes was defined as any of the followings: presence of diabetic nephropathy, use of insulin or oral hypoglycaemic agents or random plasma blood glucose >200 mg/dl. Hypertension was defined as regular use of anti-hypertensive drugs. Abnormal ECG was defined as one that had at least one of the following: (i) ST-segment depression or T-wave inversion (>0.1 mV), (ii) high voltage (R in V_5 or V_6 plus S in V_1 >3.5 mV) accompanied by either flat (<10% of R) or biphasic T-wave, (iii) left bundle branch block, (iv) abnormal Q-wave (>0.03 s in duration) except for that in ${}_aV_R$. Coronary artery disease was defined as angiographically demonstrated coronary artery disease (major epicardial artery with 75% or more stenosis on angiogram) or a history of myocardial infarction that was confirmed by enzymatic and/or electrocardiographic changes. Cerebrovascular disease was defined as clinical signs of stroke that was confirmed by computed tomography.

The endpoint of the follow-up study was death, which was classified into cardiac death (acute myocardial infarction, progression of cardiac failure and sudden cardiac death) and non-cardiac death. Sudden cardiac death was defined as unexpected death within 1 h after the onset of a new symptom, or unexpected, unobserved death.

Analysis of HRV

In both haemodialysis patients and controls, recorded Holter ECGs were analysed with a Holter ECG scanner (DSC-3100, Nihon Koden, Tokyo, Japan), which detected and labeled QRS complexes automatically. Results of the automatic analysis were reviewed, and any errors in R-wave detection and in QRS labelling were edited manually. Only recordings with a total analysable length for $\geqslant$23.5 h were used. According to the results of QRS labelling, those who had frequent ectopic beats, which were defined as ventricular and supra-ventricular ectopic beats >10% of total recorded beats, were excluded from the study.

Normal-to-normal R-R interval data obtained from the edited time sequence of R-wave and QRS labelling were transferred to a computer workstation (S-7/7000U, Fujitsu). For time-domain HRV measures, the mean normal-to-normal R-R intervals (NN) and the standard deviation of normal-to-normal R-R intervals during 24 h (SDNN) were calculated. Triangular index (TI), a time-domain geometric measure, was also computed as described in a previous report [5].

For analysing frequency-domain HRV measures, spectral power was quantified by fast Fourier transformation for the following frequency bands: 0.15–0.4 Hz (high frequency), 0.04–0.15 Hz (low frequency), 0.0033–0.04 Hz (very-low frequency) and <0.0033 Hz (ultra-low frequency) [11]. These values were transformed into natural logarithmic values to obtain a normal distribution.

Statistical analysis

We used a SAS program package (SAS Institute, Cary, NC) for all statistical analysis. Differences in quantitative and categorical data at baseline between the study groups were compared, respectively, by the Student's *t*-test and the Fisher exact probability test. Relative risks of various HRV measures for cardiac and non-cardiac death were determined by a Cox proportional hazards regression model. To assess the independent predictive value of HRV measures for death, Cox hazards analysis was performed including the baseline clinical variables that showed significant univariate predictive value. To obtain the best predictive model for death, multivariate Cox hazards analysis with step-wise model building was performed by including all clinical variables (listed in Table 1) and HRV measures as candidates. Survival curves of patient groups stratified by HRV measures were calculated by the Kaplan–Meier method with log-rank test. Data is presented as the mean ± SD [median (range)]. Risk of death is presented as relative risk (RR) with its 95% confidence interval (CI). For all statistical analysis, $P<0.05$ was considered significant.

Results

We evaluated 137 haemodialysis patients, of whom 17 were excluded due to either atrial fibrillation or frequent ectopic beats. The remaining 120 patients, aged 61 ± 11 years [61 (21–79)], were enrolled in our study. During a follow-up period of 26 ± 10 [28 (3–39)] months, 21 died (17.5%)—10 from cardiac causes (four acute myocardial infarctions, four progression of cardiac failure and two sudden cardiac death) and 11 from non-cardiac causes (seven fatal strokes, two malignant neoplasms and two haemorrhagic shock). The non-survivors lived 27 ± 9 [31 (3–36)] months after being enrolled in the study. No patient underwent renal transplantation during the follow-up period.

Baseline characteristics

Baseline characteristics of patients grouped by survival status are shown in Table 1. Compared with the patients who survived during follow-up, those who died of cardiac causes were older and had lower levels of serum albumin. There was no significant difference between the patients who died of non-cardiac causes and those who survived during follow-up.

Table 1. Clinical features of patients grouped by survival status

	Survivor ($n=99$)	Cardiac death ($n=10$)	Non-cardiac death ($n=11$)
Baseline			
Age, years	61 ± 11	70 ± 8[a]	61 ± 12
Male, *n* (%)	51 (52)	5 (50)	5 (45)
Duration of haemodialysis, months	52 ± 129	50 ± 58	31 ± 22
Diabetes mellitus, *n* (%)	36 (36)	5 (50)	4 (36)
Coronary artery disease, *n* (%)	5 (5)	2 (20)	0 (0)
Cerebrovascular disease, *n* (%)	9 (9)	2 (20)	3 (24)
Current smoking, *n* (%)	41 (41)	7 (70)	4 (36)
Total cholesterol (mg/dl)	169 ± 37	163 ± 43	184 ± 41
Hypertension, *n* (%)	54 (55)	4 (40)	6 (55)
Abnormal ECG, *n* (%)	17 (17)	3 (30)	4 (36)
Ventricular ectopic beats >30/h, *n* (%)	19 (19)	2 (20)	0 (0)
Haematocrit (%)	30.6 ± 3.7	31.5 ± 5.5	28.5 ± 2.9
Serum albumin (g/dl)	3.70 ± 0.26	3.49 ± 0.30[a]	3.65 ± 0.24
Cardio-thoracic ratio >50%, *n* (%)	32 (32)	5 (50)	6 (55)
% Body weight increase across weekend >8%, *n* (%)	4 (4)	0 (0)	0 (0)
% Body weight increase across weekend <2%, *n* (%)	8 (8)	1 (10)	0 (0)
Kt/V	1.37 ± 0.23	1.42 ± 0.19	1.44 ± 0.16
Protein catabolic rate <0.9, *n* (%)	25 (25)	4 (40)	4 (36)
Medication			
Calcium channel antagonists, *n* (%)	54 (55)	4 (40)	6 (55)
Angiotensin-converting enzyme inhibitors, *n* (%)	10 (10)	0 (0)	1 (9)
Beta-blockers, *n* (%)	2 (2)	0 (0)	0 (0)

Data represent mean ± SD or *n* (%).
[a] $P<0.05$ *vs* survivor.

Table 2. Heart rate variability measures in patients grouped by survival status and in healthy control subjects

	Survivor ($n=99$)	Cardiac death ($n=10$)	Non-cardiac death ($n=11$)	Healthy control ($n=62$)
Time-domain measures				
Mean NN during 24 h (ms)	748 ± 98	718 ± 120	750 ± 57	839 ± 101[b]
Day time (ms)	663 ± 99	659 ± 131	654 ± 82	708 ± 95[b]
Night time (ms)	832 ± 115	778 ± 123	846 ± 98	970 ± 132[b]
Day–night difference (ms)	169 ± 89	119 ± 82	192 ± 141	263 ± 110[b]
SDNN (ms)	96.8 ± 32.3	77.5 ± 35.0	104.7 ± 48.1	144.4 ± 40.3[b]
TI	25.4 ± 8.9	17.9 ± 6.2[a]	30.2 ± 13.8	38.2 ± 9.4[b]
Frequency-domain measures				
HF power [ln(ms^2)]	4.39 ± 1.11	4.50 ± 1.23	4.57 ± 1.06	5.07 ± 0.88[b]
LF power [ln(ms^2)]	4.73 ± 1.28	4.04 ± 1.68	4.67 ± 1.39	5.90 ± 0.84[b]
VLF power [ln(ms^2)]	6.22 ± 1.17	5.34 ± 1.58[a]	6.15 ± 1.02	7.30 ± 0.64[b]
ULF power [ln(ms^2)]	8.99 ± 0.92	8.23 ± 0.85[a]	9.15 ± 1.07	9.70 ± 0.74[b]
LF/HF	1.82 ± 1.34	0.77 ± 0.44[a]	1.60 ± 1.81	2.85 ± 2.21[b]

Data represent mean ± SD. ln, logarithmic transformation of power spectral measures.
[a] $P<0.05$ *vs* survivor.
[b] $P<0.05$ *vs* all three patient groups by survival status.

HRV measures

Time- and frequency-domain HRV measures in haemodialysis patients grouped by survival status and in healthy control subjects are shown in Table 2. Data on the healthy controls were obtained from 62 subjects aged 60 ± 13 [61 (21–80)] years. In all three groups of patients, all time- and frequency-domain HRV measures, including low-frequency power and ratio of low-frequency power to high-frequency power (LF/HF), were reduced compared with those in healthy controls. Within patient groups, compared with the patients who survived during the follow-up, those who died of cardiac causes had lower TI, very-low-frequency power (VLF), ultra-low-frequency power (ULF) and LF/HF. There was no significant difference between the patients who died of non-cardiac causes and those who survived during the follow-up. Trendgrams, histograms and power spectra of NN during 24 h are shown for representative patients in Figure 1.

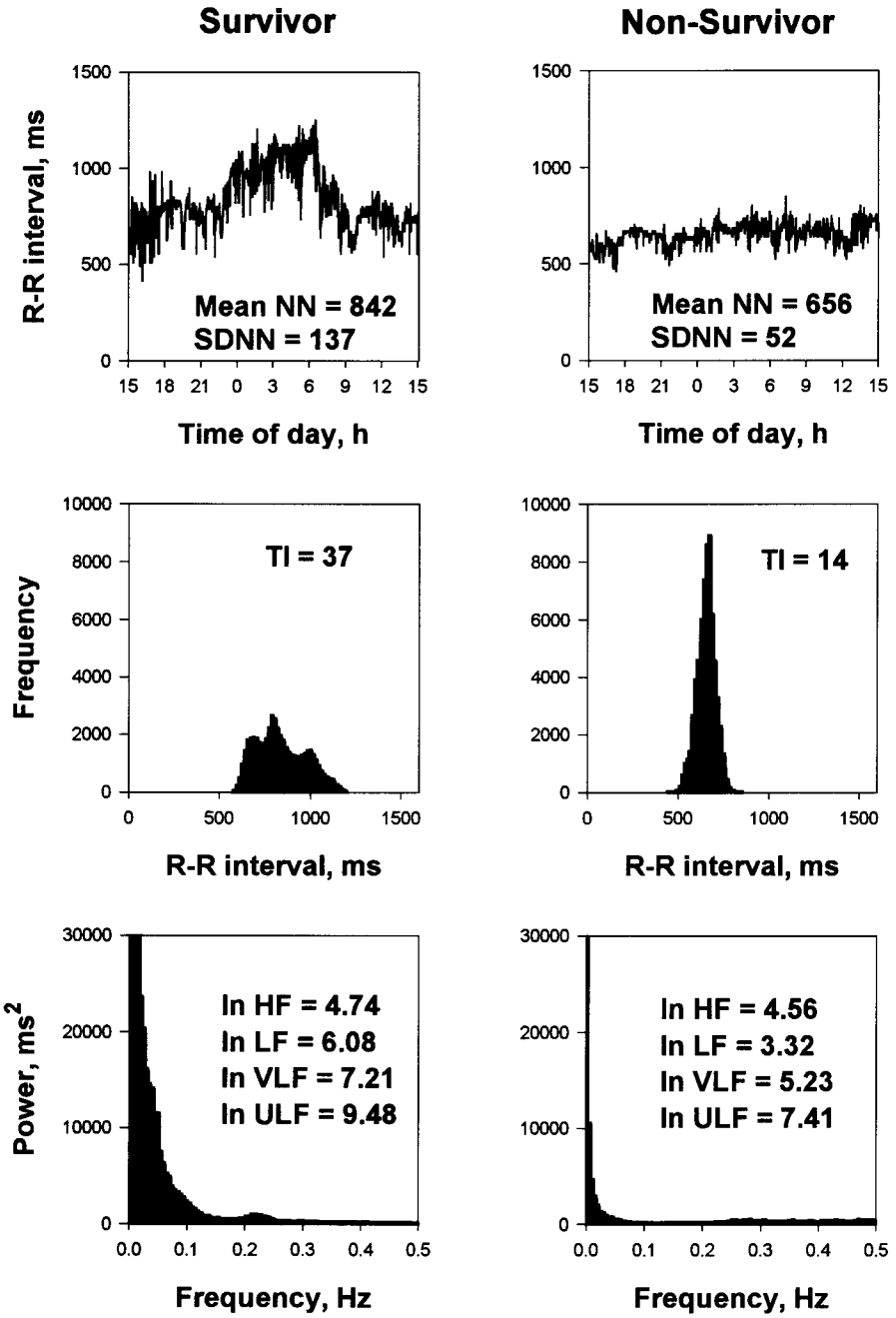

Fig. 1. Trendgrams, histograms and power spectra of 24 h normal-to-normal R-R intervals for a male patient who survived during a follow-up of 34 months (left) and a male patient who died from progression of cardiac failure 23 months after this measurement (right).

Table 3. Univariate and adjusted relative risk (RR) of heart rate variability measures by Cox proportional hazards regression analysis

	Cardiac death		Non-cardiac death	
	Univariate	Adjusted[a]	Univariate	Adjusted[b]
Mean NN during 24 h	1.41 (0.71–2.80)	1.13 (0.52–2.44)	1.05 (0.57–1.96)	1.07 (0.54–2.13)
During day	1.04 (0.56–1.92)	0.90 (0.43–1.89)	1.04 (0.56–1.94)	0.95 (0.50–1.80)
During night	1.77 (0.86–3.64)	1.36 (0.62–3.00)	1.05 (0.57–1.93)	1.14 (0.62–2.12)
Day–night difference	2.03 (0.92–4.48)	1.69 (0.72–3.97)	1.02 (0.56–1.83)	1.14 (0.70–1.87)
SDNN	2.11 (0.96–4.66)	1.68 (0.69–4.08)	0.98 (0.55–1.75)	1.18 (0.67–2.06)
TI	4.32 (1.36–13.7)[c]	3.28 (1.08–9.95)[c]	0.72 (0.41–1.29)	1.06 (0.80–2.26)
ln HF	0.93 (0.51–1.70)	0.91 (0.48–1.72)	0.87 (0.45–1.51)	1.06 (0.58–1.94)
ln LF	1.65 (0.89–3.05)	1.32 (0.68–2.55)	1.06 (0.58–1.96)	1.20 (0.62–2.33)
ln VLF	1.87 (1.09–3.20)[c]	1.54 (0.80–2.96)	1.09 (0.59–2.02)	1.13 (0.57–2.24)
ln ULF	2.21 (1.20–4.07)[c]	1.92 (1.01–3.67)[c]	1.04 (0.56–1.90)	1.06 (0.60–1.88)
LF/HF	6.47 (1.29–32.4)[c]	3.68 (0.73–18.5)	1.22 (0.61–2.44)	1.08 (0.57–2.01)

Data represent RR (95% CI) corresponding to 1 SD decrement in each HRV measure. ln, logarithmic transformation of power spectral measures.
[a]Adjusted for age, serum albumin and coronary artery disease.
[b]Adjusted for haematocrit and cerebrovascular disease.
[c]$P < 0.05$.

Survival analysis

Cox proportional hazards regression analysis showed that among time- and frequency-domain HRV measures, decreased TI, VLF, ULF and LF/HF were significant predictors of cardiac death. None of these HRV measures, however, predicted non-cardiac death (Table 3).

Cox proportional hazards regression analysis showed that, among clinical variables age [RR (95% CI), 1.11 (1.03–1.21)], serum albumin [2.40 (1.25–4.61) per 1 SD decrement] and coronary artery disease [5.95 (1.26–28.1)] were significant predictors of cardiac death and haematocrit [1.19 (1.01–1.39) per 1% decrement] and cerebrovascular disease [4.73 (1.22–18.3)] were significant predictors of non-cardiac death. Even after adjustment for these clinical variables with significant univariate predictive value, the predictive value of decreased TI and ULF for cardiac death remained significant [adjusted RR (95% CI) of 1 SD decrement of TI and ULF for cardiac death, 3.28 (1.08–9.95) and 1.92 (1.01–3.67), respectively; Table 3]. Multivariate Cox regression analysis with step-wise model building including as candidates all clinical variables listed in Table 1 and HRV measures revealed that the risk of cardiac death was best predicted by serum albumin [2.38 (1.23–5.49) per 1 SD decrement] and TI [4.29 (1.41–13.0) per 1 SD decrement] and that of non-cardiac death was best predicted by cerebrovascular disease [4.73 (1.22–18.3)]. Additionally, considering the reported adverse prognostic influence of diabetes, we added the presence of diabetes into the Cox regression model. The predictive value of decreased TI for cardiac death remained significant [4.24 (1.37–13.1)] even after adjustment for diabetes.

When the patients were dichotomized by the median values of TI and ULF, cardiac mortality rates during the follow-up in the high TI and ULF groups were 3.3 and 3.3%, respectively, and those for low TI and ULF groups were 13.3 and 13.3%, respectively. Survival curves of those two patient groups are shown in Figure 2.

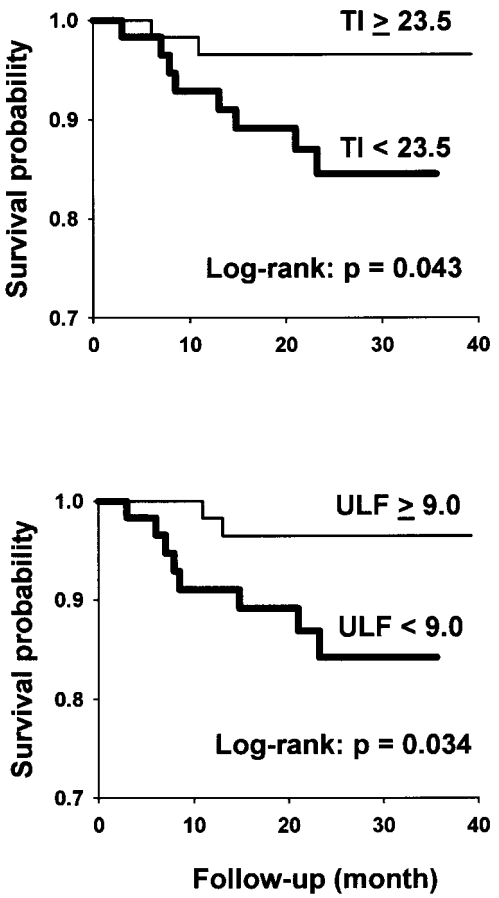

Fig. 2. Kaplan–Meier survival curves for cardiac death in patients dichotomized by the median values of triangular index (TI) and ultra-low-frequency power (ULF).

Discussion

Major findings

In this study, we examined the prognostic value of time- and frequency-domain HRV measures in 120 patients with end-stage renal disease on chronic haemodialysis, who were followed for 26 ± 10 months. We observed that decreases in TI (a time-domain geometric measure) and ULF (a frequency-domain measure) are significant predictors of cardiac death and that their predictive value is independent of both established cardiovascular risks and other known risks for death among chronic haemodialysis patients. We also observed that none of the HRV measures has predictive value for non-cardiac death, including stroke. These results indicate that decreased HRV assessed as TI and ULF poses an increased risk for cardiac death during long-term follow-up in chronic haemodialysis patients.

HRV of haemodialysis patients

HRV is reduced substantially in chronic haemodialysis patients compared with healthy individuals. Recent studies have reported that SDNN [12] and TI [13], analysed from 24 h ECG recordings, are reduced significantly in chronic haemodialysis patients compared with age-matched healthy subjects. Our study confirms and extends those findings, demonstrating that both time-domain and frequency-domain HRV measures are decreased substantially in haemodialysis patients compared with age-matched healthy individuals.

Although decreased HRV has prognostic value in various populations [3–8], to our knowledge this is the first study to show its value in a general population of chronic haemodialysis patients. In our previous study [9], we showed that decreased TI is a significant predictor of death in chronic haemodialysis patients with angiographically proven coronary artery disease, and that the predictive value is independent of established cardiovascular risks, including angiographic findings and other known risks for death in chronic haemodialysis patients. The present study is significant in demonstrating the prognostic value of decreased TI in general populations of chronic haemodialysis patients.

Our observations indicate that the predictive value of decreased HRV is independent of diabetes in chronic haemodialysis patients. Diabetes is a possible cause of decreased HRV in chronic haemodialysis patients [12]. Diabetes also is an established risk factor for death in chronic haemodialysis patients [10]. In this study, however, we observed that the predictive value of decreased TI for cardiac death remained substantially unchanged even after adjustment for diabetes. This suggests that, in this population, a substantial part of the prognostic association of decreased HRV may not be mediated by diabetes, and that each may adversely affect prognosis in additional ways.

Possible mechanisms

The prognostic information in decreased HRV seems to reside in reductions of long-term fluctuations caused by many factors. Consistent with earlier studies on the prognostic value of HRV in other populations [4,5], we observed larger predictive values in HRV measures reflecting long-term or global fluctuations (TI and ULF). The frequency range covered by these measures is wide—specifically, ULF ranges from 0.00001 to 0.003 Hz (period from 5 min to 24 h). Circadian variation of heart rate could be a major factor and, in fact, ULF power generally correlates with day–night difference in NN (for our data, correlation coefficient between square root of ULF and day–night difference in NN, 0.80, $P = 0.0001$). We observed, however, that the day–night difference in NN itself has no significant predictive value. The foregoing suggest that many sources of fluctuation may be involved in determining the prognostic value of HRV; they may include: circadian and ultradian rhythms, neurohumoral and temperature regulatory activities, physical and mental activities—including postural changes, food intake, exercise, social stimuli and wake–sleep cycles.

Although autonomic dysfunction has been reported to be a potential mechanism underling the relationship between decreased HRV and adverse prognosis, the results of our study are unlikely to provide evidence for this hypothesis. Experimental studies have indicated the importance of vagal functions in protecting the heart from serious ventricular arrhythmias, particularly in the presence of exaggerated sympathetic activity [14]. In this study, however, neither the HF component of HRV, an index of cardiac vagal function, nor LF/HF, a putative marker of sympathetic predominance [11], had significant predictive value. The latter was particularly reduced in the cardiac death patients compared with the survivors and, even, the healthy controls. The foregoing may be attributable to the fact that in contrast to its measurements under laboratory conditions, HRV obtained by ambulatory ECG is not an appropriate measure of autonomic function because of many confounding variables, such as daily activities, environment, circadian changes and medications used [11].

Clinical implications

This study shows the potential value of decreased HRV in predicting death in patients on chronic haemodialysis. Despite progress in haemodialysis, the mortality rate of patients on chronic haemodialysis has not changed substantially during the last decade because of an increasing prevalence of cardiac complications [1,2]. Establishing new clinical tools for identifying high-risk patients, particularly those with an increased risk for cardiac death, is important. Decreased HRV may provide unique and clinically useful information for identifying in this population

high-risk patients with an adverse prognosis, particularly those with an increased risk of cardiac death. Additionally, its prognostic value may be independent of the presence of diabetes.

Analysis of HRV may identify the patients who require further and more precise evaluations of cardiac status and careful haemodialysis treatment. Decreased HRV has been recognized to precipitate serious ventricular arrhythmias by modulating arrhythmogenic substrates such as myocardial infarction and cardiomyopathy, particularly under ischaemia [14]. Patients with decreased HRV should be examined for the presence of these cardiac problems and patients with such conditions should be treated to prevent myocardial ischaemia. It is important to note that haemodialysis sessions themselves aggravate myocardial ischaemia—hypotension induced by haemodialysis decreases myocardial perfusion pressure and alterations in haemoglobin–oxygen affinity reduce myocardial oxygen supply [15]. To prevent haemodialysis-related myocardial ischaemia, prolonged dialysis sessions with low ultrafiltration rates, careful titration of target weight and administration of oxygen during dialysis are recommended. A recent study reported that isolated high-rate ultrafiltration decreases HRV, whereas diffusive haemodialysis with a low ultrafiltration rate increases HRV during haemodialysis session [16]. The study suggested that low interdialytic weight gain and a low ultrafiltration rate together with adequate haemodialysis should be the preferred strategy in patients with reduced HRV. Additionally, beta-blockers tend to be seldom prescribed to haemodialysis patients in Japan. In fact, only two patients among the survivors and none of cardiac death patients were on beta-blockers at baseline in our study. Increased use of beta-blockers seems an important therapeutic option in high-risk patients.

It is plausible, also, that therapeutic interventions that normalize HRV could improve the prognosis of chronic haemodialysis patients. Recent studies report that HRV can be improved in chronic haemodialysis patients by some interventions, such as exercise training [13] and renal transplantation [17, 18]. Further studies are necessary, however, not only to establish effective therapeutic interventions for modulating HRV, but also to determine whether the improvement of HRV by such interventions improves the prognosis in this population.

Limitations

We have to point out several limitations in this study. First, this is an observational study performed in the setting of general outpatient chronic haemodialysis therapy for end-stage renal disease. Only a part of our subjects underwent precise evaluations of their cardiac status by coronary and left ventricular angiography. Thus, in the present study, we were unable to examine the prognostic value of decreased HRV in relation to specific cardiac conditions in the patients. However, we have reported previously that the predictive value of decreased HRV in chronic haemodialysis patients with coronary artery disease is independent of angiographic findings such as left ventricular ejection fraction and the number of diseased coronary arteries [9]. Secondly, although this study was performed on a relatively large number of patients, the occurrence of cardiac death was low (8.3%). Thus, the predictive value of decreased HRV (13.3%) was not high enough to predict cardiac outcome. Also, the low event rate did not allow us to evaluate the association of decreased HRV with specific causes of cardiac death. Thirdly, it is unclear whether HRV is a stable measure in haemodialysis patients, because HRV may be affected by the haemodialysis session itself. Earlier studies have reported that HRV analysed from short-term ECG recordings improves immediately after a single haemodialysis session, due to an improvement of hypervolaemia [19] and a removal of uraemic toxins [20]. However, in this study, we measured HRV from 24 h Holter ECGs performed between haemodialysis sessions. Finally, we cannot exclude the possibility that abnormal electrolytes triggered fatal arrhythmia and caused sudden cardiac death. However, routine laboratory data obtained from the patients who died of sudden cardiac death showed no evidence of abnormal electrolytes.

Conclusion

We conclude that decreases in some HRV measures, particularly those reflecting long-term variability, are independent predictors of cardiac death during long-term follow-up in patients with end-stage renal disease on chronic haemodialysis.

Acknowledgements. This work was supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture, Tokyo, Japan (11670698 to J.H.), a Grant-in-Aid for Research in Nagoya City University, Nagoya, Japan (1999 to J.H.) and a Research Grant from Pfizer Health Research Foundation, Tokyo, Japan (99A052 to J.H.).

References

1. Tomita J, Kimura G, Inoue T *et al.* Role of systolic blood pressure in determining prognosis of hemodialyzed patients. *Am J Kidney Dis* 1995; 25: 405–412
2. Kimura G, Tomita J, Nakamura S, Uzu T, Inenaga T. Interaction between hypertension and other cardiovascular risk factors in survival of hemodialyzed patients. *Am J Hypertens* 1996; 9: 1006–1012
3. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59: 256–262
4. Bigger JT Jr, Fleiss JL, Steinman RC *et al.* Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation* 1992; 85: 164–171
5. Farrell TG, Bashir Y, Cripps T *et al.* Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. *J Am Coll Cardiol* 1991; 18: 687–697

6. Tsuji H, Venditti FJ Jr, Manders ES *et al*. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994; 90: 878–883
7. Fauchier L, Babuty D, Cosnay P, Autret ML, Fauchier JP. Heart rate variability in idiopathic dilated cardiomyopathy: characteristics and prognostic value. *J Am Coll Cardiol* 1997; 30: 1009–1014
8. La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. *Lancet* 1998; 351: 478–484
9. Hayano J, Takahashi H, Toriyama T *et al*. Prognostic value of heart rate variability during long-term follow-up in chronic haemodialysis patients with end-stage renal disease. *Nephrol Dial Transplant* 1999; 14: 1480–1488
10. Shinzato T, Nakai S, Akiba T *et al*. Survival in long-term haemodialysis patients: results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant* 1997; 12: 884–888
11. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93: 1043–1065
12. Tamura K, Tsuji H, Nishiue T *et al*. Determinants of heart rate variability in chronic hemodialysis patients. *Am J Kidney Dis* 1998; 31: 602–606
13. Deligiannis A, Kouidi E, Tourkantonis A. Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol* 1999; 84: 197–202
14. Schwartz PJ, La Rovere MT, Vanoli E. Autonomic nervous system and sudden cardiac death. Experimental basis and clinical observations for post-myocardial infarction risk stratification. *Circulation* 1992; 85: I77–I91
15. Wizemann V. Coronary artery disease in dialysis patients. *Nephron* 1996; 74: 642–651
16. Galetta F, Cupisti A, Franzoni F *et al*. Changes in heart rate variability in chronic uremic patients during ultrafiltration and hemodialysis. *Blood Purif* 2001; 19: 395–400
17. Rubinger D, Sapoznikov D, Pollak A, Popovtzer MM, Luria MH. Heart rate variability during chronic hemodialysis and after renal transplantation: studies in patients without and with systemic amyloidosis. *J Am Soc Nephrol* 1999; 10: 1972–1981
18. Yildiz A, Sever MS, Demirel S *et al*. Improvement of uremic autonomic dysfunction after renal transplantation: a heart rate variability study. *Nephron* 1998; 80: 57–60
19. Weise F, London GM, Pannier BM, Guerin AP, Elghozi JL. Effect of hemodialysis on cardiovascular rhythms in end-stage renal failure. *Kidney Int* 1995; 47: 1443–1452
20. Forsström J, Forsström J, Heinonen E, Välimäki I, Antila K. Effects of haemodialysis on heart rate variability in chronic renal failure. *Scand J Clin Lab Invest* 1986; 46: 665–670

Received for publication: 24.1.02
Accepted in revised form: 20.8.02