Prognostic Significance of Exercise Plasma Noradrenaline Levels for Cardiac Death in Patients With Mild Heart Failure

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The present study was designed to determine whether exercise plasma noradrenaline (NA) levels could predict cardiac death in patients with mild heart failure in whom the plasma NA levels were only minimally elevated. Treadmill exercise testing with serial measurement of plasma NA and plasma adrenaline were performed in 142 patients with heart failure (New York Heart Association class I–II; age, 58 ± 12 years) and 26 age-matched normal subjects. During a median follow-up of 9.6 years, 27 cardiac deaths occurred among the patients. By univariate Cox proportional hazard analysis, left ventricular end-systolic dimension ($p < 0.001$), age ($p < 0.01$), peak exercise heart rate ($p < 0.01$), exercise plasma NA level ($p < 0.01$) and left ventricular ejection fraction ($p < 0.001$) were identified as significant prognostic markers. In a multivariate analysis, exercise plasma NA level was identified as the most powerful prognostic marker ($p < 0.001$), followed by left ventricular end-systolic dimension and peak exercise heart rate. In addition, from the Kaplan-Meier analysis, patients with a supramedian level of exercise plasma NA concentration (NA ≥ 840 pg/ml) had a significantly lower survival rate than those with an inframedian level ($p < 0.01$). Exercise plasma NA levels can provide prognostic information in patients with mild heart failure, which suggests an important role of exercise-induced activation of sympathetic nervous system activity in the prognosis of patients with mild heart failure. (*Circ J* 2002; 66: 261–266)

Key Words: Exercise test; Heart failure; Plasma norepinephrine; Prognosis; Sympathetic nervous activity

Several clinical and laboratory abnormalities are associated with the low survival rate of patients with chronic heart failure: (1) cardiac pump dysfunction expressed by left ventricular ejection fraction (LVEF);^{1–5} (2) New York Heart Association (NYHA) functional class;⁶ (3) exercise performance;^{5,7–9} and (4) the etiology of the heart disease.^{6,10} The degree of neurohormonal activation has also been implicated as an important prognostic factor and of the various neurohormonal factors, plasma noradrenaline (NA) levels are of particular importance in patients with heart failure. Cohn et al showed that an increased resting plasma NA concentration was related to high mortality in moderate to severe heart failure,¹¹ and data from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)¹² and the Vasodilator-Heart Failure Trial II (V-HeFT II)¹³ confirmed the prognostic significance of high resting plasma NA levels in a larger patient cohort with moderate to severe heart failure.

In patients with mild heart failure, on the other hand, resting plasma NA levels are not markedly elevated¹⁴ and so their significance for prognosis may be limited. Plasma NA level was a predictor of mortality in the Studies of Left

Ventricular Dysfunction (SOLVD) Trial¹⁵ but was not a prognostic factor in the Survival and Ventricular Enlargement (SAVE) Trial.¹⁶ We have previously demonstrated that the response of plasma NA level to exercise is augmented in patients with mild heart failure¹⁷ and it may be that the exercise plasma NA level provides more accurate prognostic information in these patients. However, the prognostic significance of the exercise plasma NA concentrations have not been well defined. Therefore, we conducted this study to determine whether exercise plasma NA levels can provide prognostic information in patients with mild heart failure.

Methods

Subjects

We enrolled 142 patients with heart failure (92 men, 50 women, age [mean $\pm$ SD]: 58.1 ± 11.5 years, NYHA class I–II), and 26 age-matched normal subjects (15 men, 11 women, age [mean $\pm$ SD]: 54.8 ± 7.0 years) who did not have cardiovascular disease. The etiology of the heart failure included old myocardial infarction in 71, valvular heart disease in 57, dilated cardiomyopathy in 9, and others in 5. The presence of coronary artery disease was established by coronary angiography or a history of previously documented myocardial infarction. Patients with valvular heart disease had regurgitant valvular lesions with either mitral regurgitation, aortic regurgitation, or both. Patients with effort angina, unstable angina, significant aortic stenosis, or airway diseases were excluded. Thirty-six of 142 patients had chronic atrial fibrillation; the remainder were in normal

(Received October 31, 2001; revised manuscript received December 7, 2001; accepted December 20, 2001)

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Table 1 Baseline Characteristics of the Survivor and Cardiac Death Groups

	Survivor group (n=92)	Cardiac death group (n=27)
<i>Baseline characteristics</i>		
Age (years)	55.3±1.1	64.6±2.4*
Male sex: n (%)	56 (61%)	20 (74%)
BMI (kg/m ²)	22.1±0.3	22.3±0.5
Smokers: n (%)	45 (49%)	16 (59%)
HT: n (%)	24 (26%)	11 (41%)*
DM: n (%)	15 (16%)	6 (22%)
Atrial fibrillation: n (%)	27 (29%)	2 (7%)*
<i>Etiology of heart diseases</i>		
OMI: n (%)	48 (52%)	13 (56%)
DCM: n (%)	3 (3%)	6 (22%)*
VHD: n (%)	38 (40%)	5 (19%)
Others: n (%)	3 (3%)	1 (3%)
<i>ECG and chest X-ray</i>		
SV ₁ +RV ₅ in ECG (mV)	2.9±0.1	2.9±0.3
Cardio-thoracic ratio (%)	54.7±0.8	56.7±1.3
<i>Echocardiographic parameters</i>		
LVDd (mm)	51.2±0.9	56.6±2.4
LVDs (mm)	36.3±0.9	44.2±2.8*
LVEF (%)	61.3±1.5	52.2±3.1*
IVSth (mm)	9.9±0.2	9.7±0.3
PWth (mm)	10.2±0.2	10.2±0.3
<i>Medications</i>		
Diuretics	33 (36%)	12 (48%)
Digitalis	34 (37%)	14 (52%)
Vasodilators	49 (52%)	17 (63%)
-blockers	4 (4%)	2 (7%)
Antiarrhythmic agents	8 (9%)	9 (33%)*
Antiplatelet agents	33 (36%)	8 (30%)
Warfarin	9 (10%)	4 (15%)

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; OMI, old myocardial infarction; DCM, dilated cardiomyopathy; VHD, valvular heart disease; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; LVEF, left ventricular ejection fraction; IVSth, interventricular septal thickness; PWth, posterior wall thickness. Values are mean±SEM.

* $p < 0.05$ vs survivor group.

sinus rhythm. At the time of the entry, patients were being treated with diuretics (39%), digitalis (40%), -blockers (4%), antiarrhythmic agents (13%), antiplatelet agents (34%), warfarin (11%), and vasodilators (55%) such as angiotensin-converting enzyme inhibitors, long-acting nitrates, and calcium channel antagonists. The protocol was approved by the Ethics Committee of Tottori University and all subjects gave their informed consent to participate in the study.

Exercise Testing

A multistage treadmill exercise test was performed (CASE II, Marquette Electronics Co Milwaukee, WI, USA) using either the modified Bruce or the Sheffield protocol as previously described.¹⁷ The criteria for terminating exercise were (i) achievement of 85% of age-adjusted predicted maximal heart rate; (ii) leg fatigue or shortness of breath; (iii) significant ST segment depression (≥ 0.2 mV); (iv) frequent premature ventricular contractions; (v) abnormal blood pressure response; or (vi) finishing stage V of the modified Bruce protocol (exercise time=15 min). The number of metabolic equivalents (METs) achieved was estimated from the treadmill speed and grade based on previously reported findings.¹⁸

Plasma Catecholamine Measurements

Blood samples for measurements of plasma NA and plasma adrenaline levels were obtained after 30 min of rest in the supine position, immediately after exercise and 5 min

postexercise. Plasma NA and adrenaline concentrations were determined by high-performance liquid chromatography combined with the trihydroxyindole fluorometric procedure, as previously described.¹⁷

Baseline Data

Body mass index was calculated as body weight in kilograms divided by height in meters squared. A 12-lead ECG was obtained and SV₁+RV₅ (in mV) was calculated. The cardiothoracic ratio was calculated from chest X-ray. During the echocardiographic study, the left ventricular volume was calculated using the Teichholz modification,¹⁹ and the LVEF was calculated as [(end-diastolic volume–end-systolic volume)/end-diastolic volume]×100.

Endpoint

Follow-up data were obtained from routine hospital visits, a telephone interview with the patient or family members, and a questionnaire sent to the patients. The endpoint of the study was cardiac death, which included heart failure death and sudden death. Cardiac deaths within 24 h of acute symptoms heralded by an abrupt loss of consciousness were considered ‘sudden’, whereas those resulting from deterioration of congestive symptoms were classified as ‘progressive heart failure’. For patients who died during the follow-up period, additional information was obtained from the attending physicians, hospital charts, or by phone contact of the patient’s relatives. All events were determined by reviewers who were blind to the

results of exercise testing.

Statistical Analysis

Data are presented as the mean $\pm$ SEM for continuous variables and as percentage for categorical variables. Differences between the 2 groups (survivor group and cardiac death group) were tested for significance by Mann-Whitney U test. The chi-square test was used for comparing categorical variables. Repeated measures analysis of variance (ANOVA) was used to examine the difference in heart rate, systolic blood pressure, and plasma NA and adrenaline response to exercise. To determine the independent predictors for cardiac death, univariate and multivariate analyses were performed using the Cox proportional-hazards regression model. Survival curves were traced using the Kaplan-Meier method and compared using a log-rank test. All analyses were performed with a StatView statistical program (Version 5.0, SAS Institute Inc Cary, NC, USA). The differences were considered significant when *p* values were less than 0.05.

Results

Follow-up Data

During a median follow-up period of 9.6 years (range, 0.5–12.2 years), 27 cardiac deaths (15 progressive heart failure deaths and 12 sudden deaths) and 23 non-cardiac deaths (6 stroke deaths, 5 cancer deaths, and 12 deaths from other reasons) occurred among the 142 patients with heart failure. No cardiac deaths occurred among the 26 normal subjects. Because the endpoint of the present study was cardiac death, we excluded subjects with non-cardiac death from further analysis. Therefore, the final study population consisted of 119 patients with heart failure and 26 normal subjects.

Baseline Characteristics and Exercise Tolerance

Compared with the survivors, patients in the cardiac death group were older (Table 1) and the group included more patients with hypertension and dilated cardiomyopathy. In the patients who died, the left ventricular end-systolic dimension was larger and the LVEF was lower. Drug regimens at the time of the entry were similar between the 2 groups, except for the more frequent use of antiarrhythmic agents in patients who eventually died of cardiac death. No difference was detectable between the 2 groups in the male to female ratio, body mass index, number of smokers, coexisting diabetes mellitus, or degree of left ventricular hypertrophy. The serum creatinine level, lipid profiles, and liver function were not significantly different between the 2 groups (data not shown).

There was no significant difference in exercise tolerance between the 2 groups (survivors vs cardiac death: 7.1 ± 0.3 vs 6.2 ± 0.5 METs, NS). The reasons for exercise termination were symptoms (46% vs 48%), achievement of target heart rate (36% vs 37%), ECG abnormalities (13% vs 11%), and others (2% vs 4%), and these values did not differ significantly between the 2 groups.

Heart Rate, Blood Pressure, and Plasma NA Response to Exercise

The response of heart rate, systolic blood pressure, and plasma catecholamine to exercise are shown in Fig 1. The peak exercise heart rate (135 ± 2 vs 117 ± 5 beats/min, $p<0.01$) was significantly lower in the cardiac death group, as was the peak systolic blood pressure (168 ± 4 vs 155 ± 6 mmHg, $p<0.01$). The plasma NA levels at rest were not significantly different between the 2 groups (195 ± 12 vs 217 ± 18 pg/ml, NS), but those at peak exercise (894 ± 51 vs $1,203\pm183$ pg/ml, $p<0.01$), and 5 min postexercise (334 ± 22 vs 493 ± 104 pg/ml, $p<0.01$) were significantly higher in patients in the cardiac death group. The plasma adrenaline response to exercise was not significantly different between the 2 groups (ANOVA, $p=0.18$).

Fig 1. Serial changes in heart rate, systolic blood pressure and plasma noradrenaline and adrenaline levels in response to exercise in patients in the cardiac death group (closed circles) and survivors (open circles). Peak, peak exercise; Rec 5, 5 min postexercise. Values are mean $\pm$ SEM. * $p<0.05$ vs survivors.

Table 2 Univariate and Multivariate Predictors of Cardiac Death in Patients With Mild Heart Failure

Variable	Univariate		Multivariate	
	chi-square	<i>p</i> value	chi-square	<i>p</i> value
LV end-systolic dimension	14.54	0.0001	18.27	<0.0001
Age	13.65	0.0019	2.15	0.4705
Peak exercise HR	13.37	0.0003	13.97	0.0002
Exercise plasma NA level	8.71	0.0032	21.13	<0.0001
LV ejection fraction	8.58	0.0002	0.82	0.5166
Peak exercise SBP	3.04	0.0813	0.91	0.3388
Resting plasma NA level	1.23	0.2662	0.64	0.4205

LV, left ventricular; HR, heart rate; NA, noradrenaline; SBP, systolic blood pressure.

Fig 2. Kaplan-Meier analysis of the cumulative rates of survival in patients with heart failure stratified into 2 groups on the basis of a median concentration (840 pg/ml) of peak exercise plasma noradrenaline (NA). The prognosis of patients with peak exercise plasma NA levels ≥ 840 pg/ml differed significantly from those with lower peak exercise plasma NA levels (< 840 pg/ml).

In the 26 normal subjects, resting and peak exercise heart rates were 65 ± 2 and 142 ± 2 beats/min, respectively. The peak exercise heart rate in patients in the cardiac death group was significantly lower than that of normal subjects. In normal subjects, the resting and peak exercise plasma NA levels were 137 ± 10 and 677 ± 91 pg/ml, respectively. The resting plasma NA concentration in both survivors (195 ± 12 pg/ml) and those who died from cardiac death (217 ± 18 pg/ml) was slightly, but significantly higher than that of normal subjects. The peak exercise plasma NA level in patients in the cardiac death group ($1,203 \pm 183$ pg/ml) was significantly higher than that of normal subjects.

Prognostic Analysis and Kaplan-Meier Survival Curve

To detect independent predictors for cardiac death, the following 7 variables were analyzed using Cox regression analyses: (1) age; (2) LVEF; (3) left ventricular end-systolic dimension; (4) peak exercise heart rate; (5) peak exercise systolic blood pressure; (6) resting plasma NA level; and (7) peak exercise plasma NA level (Table 2). By univariate analysis, left ventricular end-systolic dimension, age, peak exercise heart rate, exercise plasma NA level, and LVEF were significant predictors for cardiac death. According to stepwise multivariate analyses, exercise plasma NA level, left ventricular end-systolic dimension, and peak exercise heart rate were significant predictors and of these exercise plasma NA level was identified as the most powerful prognostic marker. Kaplan-Meier survival curves were plotted for the 2 groups of patients on the basis of a median concentration (840 pg/ml) of exercise plasma NA (Fig 2). Survival rate was significantly lower in patients with peak exercise plasma NA level ≥ 840 pg/ml than for those with an exercise plasma NA level below this cut-off point (log-rank $p=0.028$).

Discussion

The novel finding in this study was that in patients with mild heart failure, whose resting plasma NA levels is only mildly elevated, exercise plasma NA concentrations can provide prognostic information for cardiac death.

Exercise Plasma NA Level as a Prognostic Factor

Compared with the age-matched normal subjects, the

patients with mild heart failure had slightly higher plasma NA levels, which was consistent with previous reports.¹⁴⁻¹⁶ When the resting plasma NA levels were compared between the cardiac death patients and the survivors, no significant differences were found. However, the peak plasma NA levels immediately after exercise were significantly higher in patients in the cardiac death group compared with survivors. Multivariate analysis revealed that exercise plasma NA level was the most powerful prognostic marker for cardiac mortality. Furthermore, patients with an exercise plasma NA concentration equal to or above a median level (NA ≥ 840 pg/ml) had a significantly worse prognosis than those with a lower exercise plasma NA levels. Therefore, the exercise plasma NA level can provide important prognostic information for cardiac mortality in patients with mild heart failure.

To our knowledge, only one earlier study has investigated the prognostic value of the plasma NA level during exercise,²⁰ but that study did not find it to be of prognostic value. There are important differences between the 2 studies. First, Madsen et al included patients with more advanced heart failure and lower mean LVEF. Second, their patients were older than the present patients. Third, they used an upright ergometer exercise test, whereas we used a treadmill exercise test. These differences may explain, at least in part, the inconsistent results.

Left Ventricular End-Systolic Dimension and Chronotropic Incompetence as Prognostic Factors

Our study confirmed previously reported findings that the left ventricular end-systolic dimension is a significant prognostic marker for cardiac death.²¹ Many previous studies have demonstrated that the LVEF is a strong prognostic marker for mortality in patients with heart failure,¹⁻⁵ but although univariate analysis in the present study confirmed the relationship between LVEF and cardiac mortality, LVEF did not provide additional prognostic information after the introduction of peak exercise plasma NA levels and left ventricular end-systolic dimension as covariates in the multivariate model. We speculate that the relatively well-preserved systolic function in the present patients made the prognostic value of the LVEF inferior compared with the other variables.

In the patients in the cardiac death group, the increase in heart rate during exercise was blunted despite the exaggerated activation of sympathetic nervous system activity, and the smaller peak in heart rate was a prognostic marker. These results are consistent with recent reports that demonstrated chronotropic incompetence is an important prognostic marker.^{22,23} Although the precise mechanism has not been clarified, abnormalities in the α -adrenergic receptor pathway may be involved.²⁴

Clinical Implications

Neurohormonal activation with increased plasma levels of noradrenaline, natriuretic peptides, endothelin-1, and angiotensin II is a hallmark of congestive heart failure and recent reports have emphasized the importance of plasma brain natriuretic peptide²⁵ and endothelin-1²⁶ concentrations. However, the value of exercise neurohormones in predicting morbidity and mortality is relatively unknown.

A high plasma NA level in moderate to severe heart failure is an important prognostic marker, but its prognostic value for patients with mild heart failure is limited. Dynamic exercise increases the plasma NA level and a subgroup of

patients exhibits an exaggerated response to exercise. Our data suggest that such patients are at high risk for cardiac death, and this test can be used as a prognostic marker for mild heart failure patients in whom resting plasma NA levels are only minimally elevated.

An excessive increase in sympathetic nervous system activity appears to be deleterious for patients with heart failure. Although the direct association between augmented plasma NA during exercise and increased cardiac mortality is not clear, the persistent exposure to high plasma NA levels at the time of exercise stress may be harmful in patients who already have organic heart disease. A growing body of evidence indicates that β -blockers improve prognosis in patients with heart failure²⁷ but because the present study began in late 1980, many of the patients were not on this treatment. We speculate that drug regimens with β -blockers would lead to a better prognosis in those patients with heart failure who show the augmented plasma NA response during exercise, although it was not within the scope of our current investigation.

Study Limitations

We acknowledge that there are several limitations to this study. First, because of the inclusion of patients with valvular heart disease, the mean LVEF was relatively high and thus, our conclusions cannot readily be extended to those with a depressed LVEF. Second, we did not measure oxygen uptake and blood lactate levels and the exercise workload of the heart failure patients could be more precisely evaluated with these measurements. Third, the reproducibility of exercise plasma NA levels was not determined. Fourth, we did not assess the effects of various medications and exercise and these factors may have influenced the prognosis.^{28,29} Finally, there is a limitation in using plasma NA level as an index of sympathetic nervous system activity, because plasma NA concentration is regulated by multiple factors.³⁰ However, a good correlation between muscle sympathetic nerve activity and plasma NA level has been reported in patients with heart failure,³¹ suggesting the clinical usefulness of the plasma NA level as an overall sympathetic outflow.

Conclusions

The present study showed that the exercise plasma NA level can provide prognostic information in patients with mild heart failure in whom the resting plasma NA levels are minimally elevated. These results suggest an important role of exercise-induced activation of sympathetic nervous system activity in the prognosis of patients with mild heart failure.

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