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Plasma brain natriuretic peptide level as a biochemical marker of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction

Comparison with plasma angiotensin II and endothelin-1

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Aims To evaluate the level of plasma brain natriuretic peptide as a predictor of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction.

Methods We measured plasma levels of atrial natriuretic peptide, brain natriuretic peptide, norepinephrine, angiotensin II, and endothelin-1 and monitored haemodynamic parameters in 290 consecutive patients with asymptomatic or minimally and newly symptomatic left ventricular dysfunction (functional classes I–II, mean left ventricular ejection fraction = 37%). All patients were followed up for a median period of 812 days. The Cox proportional hazards model was used to assess the association of variables with mortality and morbidity.

Results At the end of the follow-up, 24 patients had suffered cardiac death and 25 had been hospitalized for worsening heart failure during the follow-up period. Among 21 variables such as clinical characteristics, treatment, haemodynamics, and neurohumoral factors, high levels of plasma brain natriuretic peptide ($P < 0{\cdot}0001$), norepinephrine ($P = 0{\cdot}042$), left ventricular end-diastolic volume index ($P = 0{\cdot}0035$), and left ventricular end-diastolic pressure ($P = 0{\cdot}033$) were shown to be independent predictors of mortality and morbidity by stepwise multivariate analysis. Moreover, only a high level of plasma brain natriuretic peptide ($P < 0{\cdot}0001$) was shown to be an independent predictor of mortality in these patients.

Conclusions These results indicate that a high plasma brain natriuretic peptide level provides information about mortality and morbidity in patients with asymptomatic or minimally symptomatic left ventricular dysfunction.
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Key Words: Brain natriuretic peptide, asymptomatic left ventricular dysfunction, mortality, morbidity, angiotensin II.

Introduction

The importance of neurohumoral activities in the pathophysiology of congestive heart failure has been postulated. Increased levels of various vasoconstrictor neurohumoral factors have been found in patients with advanced congestive heart failure[1–5], and high plasma levels of norepinephrine, renin, and endothelin-1 have been reported to be significant prognostic indicators in patients with congestive heart failure[4,6–8]. High levels of vasodilator neurohumoral factors have also been found in patients with congestive heart failure, and a high plasma level of atrial natriuretic peptide, mainly from the atrium, has been reported to be a significant prognostic factor[6,9–11]. The level of brain natriuretic peptide, the origin of which is thought to be ventricular myocytes, is also increased in congestive heart failure patients[12–15]. Plasma levels of both plasma cardiac natriuretic peptides, atrial natriuretic peptide and brain natriuretic peptide, increased in proportion to the severity of congestive heart failure due to left ventricular systolic dysfunction, and these increases are correlated

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with haemodynamic parameters such as pulmonary capillary wedge pressure and left ventricular ejection fraction[12,14–18]. Recently, the plasma level of brain natriuretic peptide has been reported to be an important prognostic predictor in patients with acute myocardial infarction and in patients with advanced heart failure[19,20].

Since many patients suffer from heart failure, preventing progression from early-stage heart failure, such as the asymptomatic or minimally and newly symptomatic phase, to the advanced symptomatic phase is important. A few reports have discussed prognostic factors for asymptomatic or minimally symptomatic left ventricular dysfunction, and have suggested that plasma neurohumoral factors such as norepinephrine, atrial natriuretic peptide, and renin, and left ventricular remodelling are important predictors of mortality[7,21,22], but it remains unknown which neurohumoral activity is the most sensitive for predicting mortality and morbidity[7,21]. Moreover, haemodynamic parameters such as left ventricular end-diastolic pressure and left ventricular end-diastolic volume index were not measured in previous studies[7,21]. There has been no report about the prognostic role of plasma levels of brain natriuretic peptide, angiotensin II, or endothelin-1 in patients with asymptomatic or minimally symptomatic left ventricular dysfunction. On the other hand, the plasma brain natriuretic peptide level has recently been reported to be a sensitive and useful marker for early-stage heart failure[23,24]. In the present study, we examined the value of the plasma brain natriuretic peptide level and compared it to other neurohumoral factors and haemodynamic abnormalities, such as left ventricular ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume index, in assessing the morbidity and mortality of patients with asymptomatic or minimally and newly symptomatic left ventricular dysfunction.

Patients and methods

Between January 1992, and December 1998, we studied 290 consecutive early-stage heart failure patients with asymptomatic or minimally symptomatic left ventricular systolic dysfunction (New York Heart Association (NYHA) functional class II: slight limitation of physical activity)[25], whose symptoms had occurred within the previous 6 months, and who then underwent cardiac catheterization for clinical indications (222 men, 68 women; aged 18–82 years; mean age = 59 years, NYHA function class I–II, mean left ventricular ejection fraction = 37%). Informed consent was obtained from all patients before participation in the study, and the protocol was approved by the Human Investigations Committee of our institution. The cause of left ventricular dysfunction was ischaemic heart disease (old myocardial infarction more than 3 months after the attack) in 185 patients, and non-ischaemic heart disease in the remaining 105; dilated cardiomyopathy in 81 patients, hypertensive heart disease in 15 patients and valvular heart disease in nine patients. All patients demonstrated a left ventricular ejection fraction of <45% by left ventriculography with contrast medium. Patients who had an infection, chronic inflammatory disease, malignancy, or renal failure were excluded. Ninety-four patients were in NYHA functional class I, and 196 in class II just before the cardiac catheterization. One hundred and thirty-nine patients were clinically stable on constant doses of diuretics; 100 were treated with digoxin, 153 were treated with angiotensin converting enzyme (ACE) inhibitors, and 66 were treated with beta-blockers. Most drugs had been administered within the previous 3 months.

Right-sided cardiac catheterization was performed with a 7F Swan–Ganz catheter, and right heart pressure, including right atrial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure, were measured after at least 30 min of bed rest with the patient in a supine position. Cardiac output was measured by the thermodilution technique, and blood samples were drawn from the femoral vein for the measurement of plasma, atrial natriuretic peptide, brain natriuretic peptide, norepinephrine, angiotensin II, and endothelin-1 concentrations. Left-sided cardiac catheterization and left ventriculography were also performed with a 7F pigtail catheter, and arterial blood pressure, left ventricular end-diastolic pressure and left ventricular volume were measured.

Samples for the assay of plasma atrial natriuretic peptide, brain natriuretic peptide, and endothelin-1 concentrations were transferred to chilled disposable tubes containing aprotinin (500 kallikrein inactivator units . ml^{-1}). The blood samples were immediately placed on ice and centrifuged at 4 °C. Plasma atrial natriuretic peptide concentrations were measured with a specific immunoradiometric assay for α-human atrial natriuretic peptide using a commercial kit (Shionogi, Japan) as previously reported[20]. Plasma brain natriuretic peptide concentrations were also measured with a specific immunoradiometric assay for human brain natriuretic peptide using a commercial kit (Shionogi, Japan) as reported[20]. In 25 age-matched normal subjects, the mean plasma atrial natriuretic peptide level was $12{\cdot}7 \pm 6{\cdot}4$ pg . ml^{-1} and the mean plasma brain natriuretic peptide level $15{\cdot}2 \pm 14{\cdot}2$ pg . ml^{-1}. The plasma endothelin-1 level was determined using an antibody directed against synthetic endothelin-1 (Peninsula Laboratories, Inc., Belmont, California, U.S.A.) and ^{125}I endothelin-1 (Amersham Japan, Tokyo, Japan) as previously reported[5]. Plasma angiotensin II levels were measured by using a radioimmunoassay with a specific antibody directed against synthetic angiotensin II, as previously reported[5]. Plasma norepinephrine concentrations were measured by high-performance liquid chromatography as described[8].

Statistical analysis

All results were expressed as the mean ± SEM. The unpaired Student's t-test was used to compare mean values between the groups. Categoric data were compared against a chi-squared distribution. The predictive value of mortality and morbidity of the variables listed below were tested in a Cox proportional hazards regression analysis. Kaplan–Meier estimates of the survival functions were plotted for high and low plasma brain natriuretic peptide and angiotensin II with the median concentration of these peptides, and the differences between survival curves were analysed by a log-rank test. A value of $P<0{\cdot}05$ was considered statistically significant.

Results

Patient characteristics of 290 consecutive patients

Forty-nine of the 290 asymptomatic or minimally symptomatic left ventricular dysfunction patients who were followed-up, died or were hospitalized for worsening congestive heart failure or recurrent myocardial infarction after 31 to 1619 days (mean 502 days). The primary end-point was morbidity and mortality due to cardiovascular causes, but no patient is known to have died of cancer. All deaths could be attributed to cardiovascular causes such as sudden death (12 patients) or progression of heart failure (10 patients) or fatal myocardial infarction (two patients). Twenty-five patients were hospitalized for worsening congestive heart failure during the study period and still survived at the end-point of the study; all hospitalizations could be attributed to cardiovascular causes, such as progression of heart failure (22 patients) or myocardial infarction (three patients). The mean follow-up period of the 241 event-free patients was 1071 days (range 31–2541 days). There was no difference between the event-positive and the event-free patients in age, gender, aetiology of heart failure, or treatment, except NYHA functional class (Table 1).

Comparison of haemodynamic and plasma neurohumoral factors in patients with cardiac events and patients without cardiac events

In the present study, cardiac events were defined as cardiac death (n = 24) or hospitalization for worsening heart failure or recurrent myocardial infarction (n = 25). The mean left ventricular ejection fraction was $37{\cdot}1 \pm 0{\cdot}5\%$ in the 290 patients with asymptomatic or minimally symptomatic left ventricular dysfunction. Among haemodynamic parameters, main pulmonary arterial pressure, left ventricular end-diastolic pressure, left ventricular end-diastolic volume index, and left ventricular end-systolic volume index were significantly higher, and mean arterial blood pressure and left ventricular ejection fraction significantly lower, in patients with cardiac events than in patients without cardiac events (Table 2). Plasma levels of cardiac natriuretic peptides are shown in Fig. 1. Plasma levels of atrial natriuretic peptide and brain natriuretic peptide were significantly higher in patients with than without cardiac events. There were no differences between the plasma levels of endothelin-1 ($2{\cdot}45 \pm 0.1$ vs $2{\cdot}53 \pm 0{\cdot}1$ pg . ml^{-1}) in patients with and without cardiac events, but the plasma levels of norepinephrine and angiotensin II levels were significantly higher in patients with than without cardiac events (Fig. 1).

Univariate and multivariate predictors of mortality and morbidity in 290 consecutive patients

Twenty-one clinical, neurohumoral and haemodynamic variables were analysed using univariate and stepwise multivariate Cox proportional hazards regression analyses (Table 3). For combined mortality and morbidity, high levels of plasma brain natriuretic peptide ($P<0{\cdot}0001$), norepinephrine ($P=0{\cdot}042$), left ventricular end-diastolic volume index ($P=0{\cdot}0035$), left ventricular end-diastolic pressure ($P=0{\cdot}033$), and no treatment with ACE inhibitors ($P=0{\cdot}013$) were significant independent predictors of cardiac events among 21 variables evaluated by stepwise multivariate analysis. The patients were stratified into two groups according to the median concentration of plasma brain natriuretic peptide (56 pg . ml^{-1}, Fig. 2) and cardiac event-free rates were constructed by Kaplan–Meier survival analysis methods. Cardiac events rate, as evaluated by Kaplan–Meier survival analysis, were also significantly higher in patients with a plasma brain natriuretic peptide concentration >56 pg . ml^{-1} ($P<0{\cdot}0001$).

By univariate analyses, neurohumoral factors such as angiotensin II, atrial natriuretic peptide, and brain natriuretic peptide, and haemodynamic variables such as left ventricular ejection fraction, main pulmonary arterial pressure, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume index were significant predictors of mortality. The patients were stratified into two groups according to the median concentration of plasma angiotensin II ($8{\cdot}5$ pg . ml^{-1}, Fig. 3) and cumulative survival curves were constructed by Kaplan–Meier survival methods. Mortality rates, as evaluated by Kaplan–Meier survival analysis, were significantly higher in patients with a plasma angiotensin II concentration >$8{\cdot}5$ pg . ml^{-1} ($P=0{\cdot}011$).

According to stepwise multivariate analyses, only a high level of plasma brain natriuretic peptide ($P<0{\cdot}0001$) was shown to be a significant independent predictor of mortality (Table 4). In the present study, the relative risk ratio of brain natriuretic peptide was $1{\cdot}004$

Table 1 Patient characteristics of 290 consecutive patients with asymptomatic or minimally symptomatic left ventricular dysfunction

	All patients (n=290)	Events (−) (n=241)	Events (+) (n=49)
Age (year)	59·0 ± 0·7	60·2 ± 1·9	58·8 ± 0·8
Sex (male/female)	222/68	188/53	34/15
Aetiology of left ventricular dysfunction			
Ischaemic cardiomyopathy	185	160	25
Non-ischaemic cardiomyopathy	105	81	24
NYHA functional class*			
I	94	85	9
II	196	156	40
Treatment			
Diuretics	139	112	27
ACE inhibitors	153	122	31
Digitalis	100	80	20
Beta-blockers	66	52	14

*$P<0·05$.

Table 2 Haemodynamic parameters in 290 consecutive patients with asymptomatic or minimally symptomatic left ventricular dysfunction according to cardiac events

	All patients (n=290)	Events (−) (n=241)	Events (+) (n=49)
Heart rate (beats . min^{-1})	71·1 ± 0·9	70·7 ± 0·9	72·6 ± 2·4
Mean arterial blood pressure (mmHg)	92·0 ± 0·9	93 ± 0·19	87·4 ± 2·4*
Right atrial pressure (mmHg)	2·9 ± 0·1	2·7 ± 0·1	3·4 ± 0·4
Mean pulmonary arterial pressure (mmHg)	14 ± 0·3	13·3 ± 0·3	18 ± 1·3#
Left ventricular end-diastolic pressure (mmHg)	11·2 ± 0·3	10·5 ± 0·3	14·4 ± 0·9#
Cardiac index (l . min^{-1} . m^{-2})	2·74 ± 0·04	2·8 ± 0·04	2·6 ± 0·09
Left ventricular end-diastolic volume index (ml . m^{-2})	124 ± 2·4	118 ± 2·0	151 ± 19·3#
Left ventricular end-systolic volume index (ml . m^{-2})	79·7 ± 2·1	74 ± 1·6	109 ± 8·8#
Left ventricular ejection fraction (%)	37·1 ± 0·5	38·3 ± 0·5	30·9 ± 1·5#

*$P<0·05$; #$P<0·0001$ vs events (−).

(95% confidence interval, 1·003–1·006). The patients were stratified into two groups according to the median concentration of plasma brain natriuretic peptide (56 pg . ml^{-1}, Fig. 4) and cumulative survival curves were constructed by Kaplan–Meier survival methods. Mortality rates, as evaluated by Kaplan–Meier survival analysis, were significantly higher in patients with a plasma brain natriuretic peptide concentration >56 pg . ml^{-1} ($P<0·0001$).

Discussion

Various circulating neurohumoral factors are increased in patients with heart failure, and these parameters are thought to play important roles in the pathogenesis of heart failure[1–11]. High levels of neurohumoral factors such as atrial natriuretic peptide, norepinephrine, plasma renin activity, and endothelin-1 are associated with increased mortality rates in patients with advanced congestive heart failure[2,6,8,9]. Since many patients suffer from heart failure, preventing the progression of congestive heart failure from early-stage heart failure, such as the asymptomatic or minimally and newly symptomatic phase, to the advanced symptomatic phase is important. However, few reports have discussed prognostic factors for asymptomatic or minimally symptomatic left ventricular dysfunction. Rouleau *et al.*[7] reported that among neurohumoral factors such as atrial natriuretic peptide, norepinephrine, plasma renin activity, and aldosterone, only plasma renin activity and atrial natriuretic peptide were independently predictive of mortality in 534 patients in the SAVE (Survival And Ventricular Enlargement) study. Benedict *et al.*[21] reported that among atrial natriuretic peptide, plasma renin activity, and norepinephrine in a subgroup analysis of SOLVD (Studies of Left Ventricular Dysfunction), only a high plasma norepinephrine level was a significant marker for prognosis in patients with asymptomatic left ventricular dysfunction. Therefore, it is unclear which neurohumoral activation is most sensitive for predicting mortality in patients with early-stage heart failure. Moreover, haemodynamic parameters, such as left ventricular end-diastolic pressure and left ventricular end-diastolic volume index, which

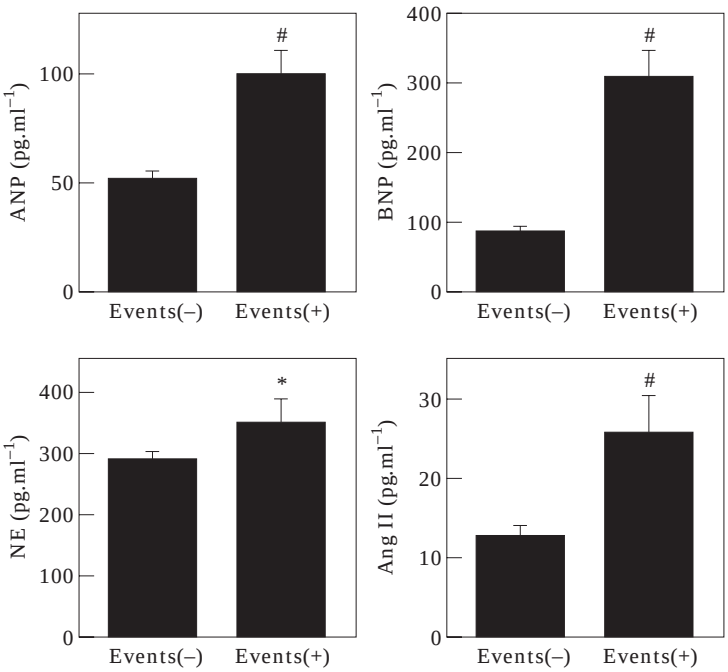

Figure 1. **Comparison of plasma neurohumoral factors in patients with cardiac events and patients without cardiac events. Events (+) = cardiac death or hospitalization for worsening heart failure or recurrent myocardial infarction. *$P < 0{\cdot}05$, #$P < 0{\cdot}0001$ vs the value of patients without cardiac events. ANP = atrial natriuretic peptide, BNP = brain natriuretic peptide, NE = norepinephrine, AngII = angiotensin II.**

Table 3 Univariate and multivariate predictors of morbidity and mortality of 290 consecutive patients with asymptomatic or minimally symptomatic left ventricular dysfunction

Variable	Univariate chi-square	*P* value	Multivariate chi-square	*P* value
Age (year)	0·49	ns	0·857	0·354
Gender (male)	0·907	ns	0·006	0·936
Functional class	6·99	0·008	0·059	0·807
Aetiology (ICM = 1, non ICM = 0)	2·906	ns	0·112	0·738
Heart rate (beats . min^{-1})	0·391	ns	1·353	0·244
Mean arterial blood pressure (mmHg)	5·27	0·0216	3·43	0·057
Cardiac index (l . min^{-1} . m^{-2})	0·878	ns	0·216	0·642
Left ventricular ejection fraction (%)	28·9	<0·0001	0·640	0·423
Right atrial pressure (mmHg)	3·23	ns	0·026	0·872
Mean pulmonary arterial pressure (mmHg)	32·8	<0·0001	0·018	0·893
Left ventricular end-diastolic pressure (mmHg)	22·8	<0·0001	4·532	0·033
Left ventricular end-diastolic volume index (ml . m^{-2})	28·4	<0·0001	8·544	0·0035
Norepinephrine (pg . ml^{-1})	8·28	0·004	4·117	0·0424
Endothelin-1 (pg . ml^{-1})	0·004	ns	0·025	0·875
Angiotensin II (pg . ml^{-1})	13·63	0·0002	0·005	0·942
Atrial natriuretic peptide (pg . ml^{-1})	33·3	<0·0001	0·094	0·759
Brain natriuretic peptide (pg . ml^{-1})	90·5	<0·0001	23·83	<0·0001
Treatments				
Diuretics (treatment = 1, no treatment = 0)	0·235	ns	0·394	0·530
Digitalis (treatment = 1, no treatment = 0)	0·613	ns	1·307	0·253
ACEI (treatment = 1, no treatment = 0)	3·89	0·048	6·158	0·013
Beta-blockers (treatment = 1, no treatment = 0)	3·26	ns	0·023	0·879

ICM = ischaemic cardiomyopathy; ACEI = angiotensin converting enzyme inhibitors.

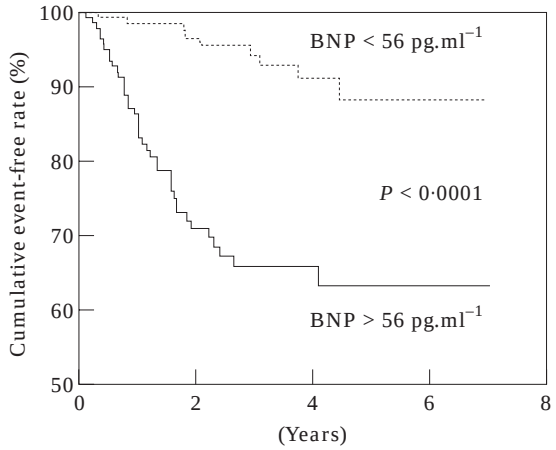

Figure 2. **Kaplan–Meier cardiac event-free rate for 290 consecutive early-stage heart failure patients with asymptomatic or minimally symptomatic left ventricular dysfunction subdivided into two groups according to the median concentration of brain natriuretic peptide (BNP) II (56 pg . ml^{-1}).**

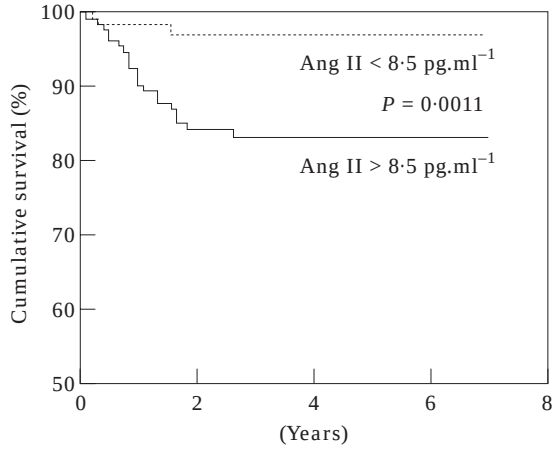

Figure 3. **Kaplan–Meier survival plots for 290 consecutive early-stage heart failure patients with asymptomatic or minimally symptomatic left ventricular dysfunction subdivided into two groups according to the median concentration of angiotensin II (Ang II) (8·5 pg . ml^{-1}).**

are markers of left ventricular remodelling, were not measured in the previous studies[7,21]. Although plasma brain natriuretic peptide has recently been shown to be a more sensitive biochemical marker than atrial natriuretic peptide for left ventricular dysfunction and prognosis of patients with acute myocardial infarction and advanced congestive heart failure[19,20,23,24], there have been no studies on plasma brain natriuretic peptide as a prognostic predictor in patients with early-stage heart failure.

In the present study, we demonstrated for the first time that a high plasma level of brain natriuretic peptide, which is secreted mainly from the ventricle, is a more important predictor of morbidity and mortality than the plasma level of atrial natriuretic peptide, which is secreted mainly from the atrium, or other neurohumoral factors such as norepinephrine, angiotensin II, or endothelin-1, which were previously shown to be markers of prognosis in advanced congestive heart failure[2,6,8,9]. We also showed that a high plasma brain natriuretic peptide level is a significant independent factor, if used with haemodynamic parameters such as left ventricular ejection fraction, left ventricular end-diastolic pressure, left ventricular end-diastolic volume index, with which to assess mortality in early-stage heart failure patients with asymptomatic or minimally and newly symptomatic left ventricular dysfunction. These findings suggest that the plasma brain natriuretic peptide concentration is a useful marker of left ventricular dysfunction or injury in patients with asymptomatic or minimally symptomatic left ventricular dysfunction, since brain natriuretic peptide is ventricular in origin[13,15]. Our findings in the 'latent phase' of the development of heart failure may support the hypothesis that excessive neurohumoral activation is ultimately a maladaptive response to myocardial injury, eventually contributing to the development of overt heart failure.

To our knowledge, there have been no reports about the prognostic value of plasma levels of angiotensin II and endothelin-1 in early-stage heart failure patients. Swedberg *et al.*[26] reported that plasma angiotensin II levels were significantly higher in non-survivors than in survivors in patients with advanced congestive heart failure and that the effect of enalapril on mortality was related to the reduction of plasma angiotensin II. In the present study, plasma angiotensin II levels were significantly higher in non-surviving than in surviving patients with early-stage heart failure, including patients who were treated with ACE inhibitors, and high plasma angiotensin II was a prognostic predictor by univariate analysis, suggesting that the plasma angiotensin II level is not constantly suppressed during long-term treatment with ACE inhibitors[27]. Our findings may suggest that high doses of ACE inhibitors and/or angiotensin II receptor antagonists would be useful for the treatment of patients whose plasma angiotensin II level is still high in spite of the administration of ACE inhibitors.

In the present study, a high plasma norepinephrine level was an independent predictor of morbidity and mortality, which is consistent with the results of a previous study[7,27]. Regarding the plasma endothelin-1 level, we previously reported the usefulness of endothelin-1 as a prognostic indicator in patients with advanced heart failure[5]. In the present study, there was no difference in plasma endothelin-1 between the surviving and non-surviving patients, suggesting a limitation of plasma endothelin-1 as a predictor of morbidity and mortality in early-stage heart failure, probably due to the fact that endothelin-1 is a local factor.

A prognostic role for atrial natriuretic peptide, which is mainly secreted from the atrium, has been well established in patients with advanced congestive heart failure[6,9]. In the case of myocardial infarction, the plasma level of atrial natriuretic peptide is a more useful indicator of prognosis than various other neurohumoral

Table 4 Univariate and multivariate predictors of mortality of 290 consecutive patients with asymptomatic or minimally symptomatic left ventricular dysfunction

Variable	Univariate chi-square	*P* value	Multivariate chi-square	*P* value
Age (year)	0·699	ns	1·079	0·298
Gender (male)	0·390	ns	0·723	0·395
Functional class	2·714	ns	0·201	0·653
Aetiology (ICM = 1, non ICM = 0)	0·685	ns	0·141	0·707
Heart rate (beats . min^{-1})	0·244	ns	0·552	0·457
Mean arterial blood pressure (mmHg)	1·434	ns	3·34	0·067
Cardiac index ($l . min^{-1} . m^{-2}$)	0·126	ns	0·005	0·945
Left ventricular ejection fraction (%)	7·805	0·0052	0·141	0·699
Right atrial pressure (mmHg)	2·52	ns	0·140	0·707
Mean pulmonary arterial pressure (mmHg)	24·10	<0·0001	0·321	0·570
Left ventricular end-diastolic pressure (mmHg)	20·33	<0·0001	2·075	0·149
Left ventricular end-diastolic volume index ($ml . m^{-2}$)	7·83	0·0051	0·085	0·773
Norepinephrine ($pg . ml^{-1}$)	0·062	ns	0·006	0·937
Endothelin-1 ($pg . ml^{-1}$)	0·064	ns	0·031	0·860
Angiotensin II ($pg . ml^{-1}$)	9·687	0·0019	0·284	0·594
Atrial natriuretic peptide ($pg . ml^{-1}$)	19·3	<0·0001	2·909	0·088
Brain natriuretic peptide ($pg . ml^{-1}$)	100·5	<0·0001	59·21	<0·0001
Treatment				
Diuretics (treatment = 1, no treatment = 0)	0·025	ns	0·082	0·774
Digitalis (treatment = 1, no treatment = 0)	0·301	ns	3·066	0·080
ACEI (treatment = 1, no treatment = 0)	0·287	ns	0·517	0·471
Beta-blockers (treatment = 1, no treatment = 0)	1·630	ns	1·638	0·200

ICM = ischaemic cardiomyopathy; ACEI = angiotensin converting enzyme inhibitors.

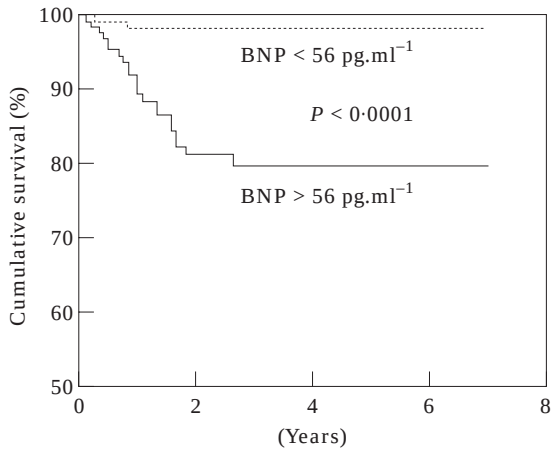

Figure 4. **Kaplan–Meier survival plots for 290 consecutive early-stage heart failure patients with asymptomatic or minimally symptomatic left ventricular dysfunction subdivided into two groups according to the median concentration of brain natriuretic peptide (BNP) in plasma (56 pg . ml^{-1}).**

factors, including norepinephrine and the renin–angiotensin–aldosterone system. However, in both the SAVE and CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) II trials[7,28], plasma atrial natriuretic peptide was also significantly associated with the severity of left ventricular dysfunction, and the independent predictive value of plasma atrial natriuretic peptide levels was markedly reduced or eliminated in multivariate analyses that included left ventricular ejection fraction, which is firmly established as a powerful determinant of prognosis after myocardial infarction. Brain natriuretic peptide is secreted predominantly from the ventricle in response to ventricular damage or dilatation, although smaller amounts are also released from atrial myocytes. Circulating levels of brain natriuretic peptide increase in patients with myocardial infarction in proportion to the severity of the disease, and brain natriuretic peptide may be a sensitive marker of left ventricular remodelling[13,14]. In the present study, the plasma brain natriuretic peptide level was an independent predictor of morbidity and mortality in multivariate analysis that included haemodynamic parameters such as left ventricular ejection fraction, left ventricular end-diastolic pressure and left ventricular end-diastolic volume index in 290 patients with asymptomatic left ventricular dysfunction or minimally and newly symptomatic left ventricular dysfunction, including 185 patients with old myocardial infarction. Our findings indicate that knowledge of brain natriuretic peptide levels in the chronic phase of the disease would help in evaluating the severity of the disease and predicting the morbidity and mortality of patients with myocardial infarction with left ventricular dysfunction, whether assessment of haemodynamic parameters such as left ventricular ejection fraction, left ventricular end-diastolic pressure and left ventricular end-diastolic volume index is possible or not. The assessment of plasma brain natriuretic peptide is a simple, cost-effective, and useful addition to the standard clinical assessment of patients with asymptomatic or minimally symptomatic left ventricular dysfunction due to ischaemic heart disease.

Study limitations

Treatments, such as those using ACE inhibitors and beta-blockers, were not randomized on entry to the present study; therefore, it may be difficult to evaluate the effects of the drugs on morbidity and mortality. The limitation of the effects of the drugs in the present study shows that no treatment with ACE inhibitors was an independent risk for morbidity and mortality. This suggests that ACE inhibitors are useful in early stage congestive heart failure, which is consistent with the results of previous studies. Although the small number of deaths is a limitation, comparisons of the multiple parameters measured in the same patients can provide important information for evaluation of morbidity and mortality in patients with asymptomatic or minimally symptomatic left ventricular dysfunction.

Conclusions

High plasma levels of brain natriuretic peptide, which is mainly derived from the ventricle, can be an important predictor of mortality and morbidity in patients with asymptomatic or minimally and newly symptomatic left ventricular dysfunction. Moreover, we demonstrated that the plasma level of brain natriuretic peptide is a more useful predictor than levels of other neurohumoral factors, and indicated that the plasma brain natriuretic peptide level provides important information independent of haemodynamic parameters such as left ventricular ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume index for predicting morbidity and mortality. These findings suggest that the plasma brain natriuretic peptide concentration is a useful biochemical marker of left ventricular damage or dysfunction, since brain natriuretic peptide is ventricular in origin. The assessment of plasma brain natriuretic peptide is simple and cost-effective, and can be repeated, and thus may be a useful addition to the standard clinical investigation of patients with asymptomatic or minimally symptomatic left ventricular dysfunction.

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