Plasma cardiac natriuretic peptide determination as a screening test for the detection of patients with mild left ventricular impairment

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Abstract

Objective—To determine the usefulness of measuring the cardiac natriuretic peptides, atrial natriuretic factor, N-terminal pro-atrial natriuretic factor, and brain natriuretic peptide, as screening tests for identifying patients with mild left ventricular impairment.

Design—Cross-sectional evaluation of the diagnostic accuracy of the cardiac natriuretic peptides.

Setting—Cardiac catheterisation unit, Norwegian central hospital.

Patients—A consecutive series of 254 patients undergoing diagnostic left-sided cardiac catheterisation. One hundred and twenty eight of these patients had a history of previous myocardial infarction.

Main outcome measures—The presence of normal and impaired left ventricular function, as evaluated by logistic regression analysis and estimation of the area under the receiver operating characteristic (ROC) curve (an index of overall diagnostic accuracy). Ventricular function was assessed by the measurement of left ventricular end diastolic pressure and angiographically determined left ventricular ejection fraction.

Results—Logistic regression analysis showed that plasma brain natriuretic peptide was the best predictor of increased left ventricular end diastolic pressure (≥ 15 mm Hg) ($P < 0.001$), decreased left ventricular ejection fraction ($\leq 45\%$) ($P < 0.001$), and the combination of left ventricular ejection fraction $\leq 45\%$ and left ventricular end diastolic pressure ≥ 15 mm Hg ($P < 0.001$). The areas under the ROC function for the detection of left ventricular dysfunction were 0.789 for brain natriuretic peptide, 0.665 for atrial natriuretic factor, and 0.610 for N-terminal pro-atrial natriuretic factor.

Conclusions—Plasma brain natriuretic peptide seemed to be a better indicator of left ventricular function than plasma atrial natriuretic factor or N-terminal pro-atrial natriuretic factor. However, the overall diagnostic accuracy of circulating atrial natriuretic factor, N-terminal pro-atrial natriuretic factor, and brain natriuretic peptide as indicators of normal and impaired ventricular function in an unselected group of patients with coronary heart disease and a high frequency of previous myocardial infarction was relatively modest.

(Heart 1996;76:232-237)

Keywords: chronic heart failure; left ventricular function; brain natriuretic peptide; N-terminal pro-atrial natriuretic factor

Clinical trials during the past few years have clearly shown that angiotensin converting enzyme inhibitors significantly reduce mortality and morbidity in patients with myocardial infarction and objective or clinical signs of left ventricular dysfunction^{1,2} as well as in patients with chronic asymptomatic or symptomatic left ventricular dysfunction,^{3,4} suggesting that patients with mild or asymptomatic heart failure may benefit from early pharmaceutical intervention. The prevalence of asymptomatic left ventricular dysfunction, as assessed by echocardiography in a population-based study, has recently been reported to be about 3%,⁵ indicating that this condition is a public health problem of major importance. Regrettably, clinical assessment is not a very reliable method in the diagnosis of heart failure and ventricular dysfunction.⁶ The cost of referring all patients with possible mild heart failure for objective assessment of left ventricular function is high and probably exceeds the capacity of most hospitals in terms of equipment and availability of skilled personnel.

Circulating concentrations of the cardiac natriuretic peptide family, atrial natriuretic factor,⁷⁻⁹ the N-terminal fragment of pro-atrial natriuretic factor,¹⁰ and brain natriuretic peptide^{11,12} are all higher in left ventricular dysfunction and in chronic heart failure. Significant correlations between plasma concentrations of these peptides and indices of cardiac function have been documented.¹³⁻¹⁷ It has therefore been suggested that circulating natriuretic peptides may be used as markers of asymptomatic left ventricular dysfunction in patients with suspected or known cardiac disease,^{10,18} and even be used as a criterion for treatment with angiotensin converting enzyme inhibitors in patients with mild heart failure.¹⁹ Recent data also indicate that enhanced in vitro stability of N-terminal pro-atrial natriuretic factor and brain natriuretic peptide permits less rigorous handling of blood samples compared to what is required for other peptide hormones,^{20,21} making N-terminal pro-atrial natriuretic factor and brain natriuretic peptide ideal candidates for the purpose of detecting mild left ventricular impairment in cases where complex laboratory facilities are not available.

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Accepted for publication
13 March 1996

The major objective of the present prospective study was to evaluate the diagnostic value of circulating natriuretic peptides as indicators of cardiac function in a relevant target population. Because ischaemic heart disease is currently the most common cause of left ventricular dysfunction,^{3,4} a large, consecutive series of patients undergoing diagnostic cardiac catheterisation was enrolled in the study, based on the rationale that this population would encompass a large proportion of patients with previous myocardial infarction and varying degree of left ventricular dysfunction.

Patients and methods

PATIENTS

Patients undergoing diagnostic cardiac catheterisation for suspected coronary heart disease during a six month recruitment period were eligible for this study. Patients with a recent myocardial infarction (< 2 weeks), significant valvar heart disease, significant cardiac arrhythmia (including atrial fibrillation), ongoing cardiac ischaemia as evidenced by ST-T segment depression, and manifest renal or hepatic failure were ineligible because these conditions are known to influence significantly plasma concentrations of the natriuretic peptides. Patients with severe symptomatic chronic heart failure (New York Heart Association class III or IV) were ineligible, because these patients rarely represent a diagnostic problem and because the objective of the study was to identify patients with mild or asymptomatic cardiac impairment. Patients were enrolled consecutively during the time the primary investigator (TO) was working in the catheterisation laboratory. Before catheterisation was performed all patients had been interviewed and examined by two experienced physicians following a standardised procedure that included assessment of New York Heart Association functional class.

A total of 263 patients with suspected coronary heart disease were originally included in the study. Nine patients were excluded owing to the following causes: cardiac arrhythmia during the investigation (three patients), pronounced vasovagal reaction requiring leg elevation during the investigation (one patient), discovery of undiagnosed mitral valve prolapse (one patient), recent undiagnosed myocardial infarction (one patient) and technical errors in handling of blood samples (three patients), leaving 254 patients for data analysis. All patients gave informed, written consent to participate in the study. Approval of the study protocol had been obtained from the Regional Ethics Committee, Health Region III, Bergen, Norway, before the start of the study.

Left ventricular end diastolic pressure and left ventricular ejection fraction were prospectively defined as the two major outcome variables describing cardiac function. The predefined cutoff points were 15 mm Hg for left ventricular end diastolic pressure and 45% for left ventricular ejection fraction. In addition, the ability of the natriuretic peptides to

identify patients with (a) left ventricular dysfunction (ejection fraction $\leq$ 45% and end diastolic pressure $\geq$ 15 mm Hg) and (b) with normal left ventricular function (ejection fraction $\geq$ 55%, end diastolic pressure < 15 mm Hg, and no angiographic sign left ventricular hypokinesis) was investigated.

STUDY PROCEDURE

After at least 15 minutes' supine rest, the femoral artery and vein were cannulated and a pigtail catheter introduced into the aorta. Before contrast ventriculography, a 10 ml blood sample was drawn from the descending aorta into a prechilled plastic tube containing EDTA and aprotinin. The test tube was immediately placed on ice and centrifuged at 4°C within 15 minutes of blood collection. After blood sampling, the catheter was first placed in the ascending aorta for the registration of aortic blood pressure curves, then introduced retrogradely into the left ventricle through the aortic valve for registration of intraventricular blood pressure curves. Left ventricular end diastolic pressure was defined as a trough in the pressure pulse following the atrial contraction wave, immediately preceding the upstroke of left ventricular pressure. Left ventricular ejection fraction was ascertained by single plane contrast ventriculography in the 30° right oblique projection during held inspiration, using the area-length method.²² Haemodynamic measurements were performed by one investigator (HVM), who was blinded to the hormone data.

The plasma samples were stored at -70°C until analysis. Atrial natriuretic factor in plasma was determined by radioimmunoassay using kits from Amersham International (UK) after previous extraction on a C18 octadecyl silica microcolumn (Milipore). The procedure and the performance characteristics of this assay in our laboratory have been reported in detail elsewhere.²³ The analysis of N-terminal pro-atrial natriuretic factor was performed by direct radioimmunoassay without prior extraction of peptide.²⁴ The antibody was directed at the amino-acid sequence 79-98. No cross reactivity with atrial natriuretic factor was observed. The sensitivity of the assay was 40 pmol/l and the coefficients of variation within assay and between assay were < 10% and < 15%, respectively. Brain natriuretic peptide in plasma was analysed using radioimmunoassay after prior extraction with Vycor glass (Crown Corning, Liverpool, NSW, Australia). The mean recovery rate was 71%. The minimum detectable concentration was 0.45 fmol/tube. Within assay and between assay coefficients of variation were 7% and 10%, respectively. The analytical procedure has been described in detail elsewhere.²⁵ Creatinine, sodium, and potassium concentrations in serum were determined by routine laboratory methods.

STATISTICAL ANALYSIS

Haemodynamic and hormonal data are expressed as mean (SD). However, owing to a skewed distribution of hormonal data, loga-

Table 1 Characteristics of patients

Variable	Value
Demographics:	
Mean age (yr)	59 (10)
Male sex (%)	76.0
Medical history:	
Previous myocardial infarction (%)	50.4
Previous angina pectoris (%)	95.7
Coronary artery bypass grafting (%)	14.6
Percutaneous transluminal percutaneous angioplasty (%)	16.9
Hypertension (%)	32.7
Diabetes mellitus (%)	4.7
Chronic heart failure (%)	5.1
Drug treatment:	
Aspirin (%)	75.2
β Blockers (%)	73.6
Calcium channel blockers (%)	33.5
Peroral nitrates (%)	52.4
Converting enzyme inhibitors (%)	13.0
Cholesterol-lowering drugs (%)	9.4
Diuretics (%)	10.2
Catheterisation data:	
Left ventricular hypokinesia (%)	47.2
Angiographically normal coronary arteries (%)	15.4
Single vessel disease (%)	22.0
Double vessel disease (%)	25.2
Triple vessel disease (%)	37.8
Left ventricular end diastolic pressure (mm Hg)	15.3 (5.6)
Left ventricular ejection fraction (%)	64.5 (11.9)

Figure 1 Relation between plasma concentrations of atrial natriuretic factor (ANF), N-terminal pro-atrial natriuretic factor (N-ANF), and brain natriuretic peptide (BNP) and left ventricular end diastolic pressure (LVEDP) and left ventricular ejection fraction (LVEF). Horizontal lines indicate predefined decision thresholds (LVEDP 15 mm Hg; LVEF 45%).

rhythmic transformation of these values was performed. Pearson correlation and linear regression analysis were employed to assess the relation between the hormonal and haemodynamic variables. Logistic regression analysis was used to assess the ability of atrial natriuretic factor, N-terminal pro-atrial natriuretic factor, and brain natriuretic peptide to identify the prespecified subgroups of patients. Receiver operating characteristic (ROC) plots were generated to visualise the sensitivity and specificity through the complete range of plasma concentrations of the natriuretic peptides, using the software programme ROCLAB.²⁶ This computer program was also used to estimate the area under the ROC curve, which represents an index of overall test accuracy.²⁷ By convention this area ranges from 0.5 to 1.0, with a value of 0.5 meaning no apparent distributional difference between the two dichotomous classes and an area value of 1.0 meaning no distributional overlap (that is, perfect separation). So-called enhanced estimates of the area under the ROC function are reported.

Results

The demographic, clinical, and angiographic characteristics of the patients are presented in table 1. Plasma atrial natriuretic factor averaged 26.7 (15.2) pmol/l, plasma N-terminal pro-atrial natriuretic factor averaged 518 (297) pmol/l, and plasma brain natriuretic peptide averaged 16.7 (12.0) pmol/l. Figure 1 shows the relation between plasma concentrations of the cardiac natriuretic peptides and left ventricular end diastolic pressure and left ventricular ejection fraction. Logarithmically transformed plasma brain natriuretic peptide concentrations correlated significantly with both end diastolic pressure and ejection fraction, whereas logarithmically transformed plasma concentrations of atrial natriuretic factor and N-terminal pro-atrial natriuretic factor correlated significantly with end diastolic pressure but not with ejection fraction. However, the association between the natriuretic peptides and haemodynamic variables was not strong, and less than 25% of the variability in natriuretic peptide concentrations could be accounted for by the variability in ejection fraction or end diastolic pressure (table 2).

As shown in tables 3 and 4, all three peptides were predictive of left ventricular end diastolic pressure ≥ 15 mm Hg, whereas only brain natriuretic peptide was a significant predictor of left ventricular ejection fraction ≤ 45%. Log transformed atrial natriuretic factor and brain natriuretic peptide, but not N-terminal pro-atrial natriuretic factor, concentrations identified patients with left ventricular dysfunction, defined as end diastolic pressure ≥ 15 mm Hg and ejection fraction ≤ 45% in univariate analysis (table 3). Adjustment for patient age in a multivariate model improved somewhat the ability of the natriuretic peptides to identify these subgroups (table 4).

Table 2 Correlation between circulating cardiac natriuretic peptides (log transformed) and selected variables (n = 254)

	ln N-ANF	ln BNP	LVEDP	LVEF	Age	Creatinine
ln ANF	0.76**	0.63**	0.38**	-0.11 (NS)	0.41**	0.12 (NS)
ln N-ANF	—	0.72**	0.30**	-0.12 (NS)	0.51**	0.19*
ln BNP	—	—	0.43**	-0.39**	0.45**	0.12 (NS)
LVEDP	—	—	—	-0.23**	0.12 (NS)	0.06 (NS)
LVEF	—	—	—	—	-0.01	0.003 (NS)
Age	—	—	—	—	—	0.13*

*P < 0.05; **P < 0.001.
ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; N-ANF, N-terminal pro-atrial natriuretic factor; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; ln, natural logarithm.

Table 3 Identification of patient subgroups by cardiac natriuretic peptide determination as assessed by univariate logistic regression analysis

Natriuretic peptide	Coefficient	SE	Wald χ^2	P
Patients with LVEF $\leq$ 45% and LVEDP $\geq$ 15 mm Hg (n = 17)				
ln ANF	-1.067	0.484	4.86	0.028
ln N-ANF	-0.748	0.496	2.28	0.131
ln BNP	-1.709	0.440	15.08	< 0.001
Patients with LVEDP $\geq$ 15 mm Hg (n = 131)				
ln ANF	-1.110	0.231	23.18	< 0.001
ln N-ANF	-0.888	0.266	11.18	< 0.001
ln BNP	-1.285	0.256	25.16	< 0.001
Patients with LVEF $\leq$ 45% (n = 21)				
ln ANF	-0.793	0.414	3.66	0.056
ln N-ANF	-0.637	0.450	2.00	0.157
ln BNP	-1.382	0.388	12.69	< 0.001
Patients with LVEDP < 15 mm Hg, LVEF $\geq$ 55%, and no angiographic sign of LV hypokinesis (n = 81)				
ln ANF	0.763	0.217	12.40	< 0.001
ln N-ANF	0.808	0.278	8.45	0.004
ln BNP	1.961	0.331	35.08	< 0.001

ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; N-ANF, N-terminal pro-atrial natriuretic factor; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction.

Table 4 Identification of patient subgroups by cardiac natriuretic peptide determination as assessed by logistic regression analysis after adjustment for patient age

Natriuretic peptide	Coefficient	SE	Wald χ^2	P
Patients with LVEF $\leq$ 45% and LVEDP $\geq$ 15 mm Hg (n = 17)				
ln ANF	-1.304	0.509	6.57	0.010
ln N-ANF	-1.231	0.603	4.17	0.041
ln BNP	-2.532	0.564	20.12	< 0.001
Patients with LVEDP $\geq$ 15 mm Hg (n = 131)				
ln ANF	-1.259	0.253	24.70	< 0.001
ln N-ANF	-1.078	0.311	11.98	< 0.001
ln BNP	-1.541	0.294	27.41	< 0.001
Patients with LVEF $\leq$ 45% (n = 21)				
ln ANF	-0.975	0.438	4.96	0.026
ln N-ANF	-1.011	0.542	3.48	0.062
ln BNP	-1.964	0.476	17.01	< 0.001
Patients with LVEDP < 15 mm Hg, LVEF $\geq$ 55%, and no angiographic sign of LV hypokinesis (n = 81)				
ln ANF	1.029	0.250	16.97	< 0.001
ln N-ANF	1.237	0.334	6.30	0.012
ln BNP	2.761	0.413	44.61	< 0.001

ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; N-ANF, N-terminal pro-atrial natriuretic factor; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction.

The ROC plots shown in fig 2 illustrate the sensitivity and specificity of atrial natriuretic factor, N-terminal pro-atrial natriuretic factor, and brain natriuretic peptide measurements with regard to the correct identification of patients with combined raised left ventricular end diastolic pressure and reduced left ventricular ejection fraction throughout the range of peptide concentrations. Table 5 presents the area under the ROC functions for the identification of the previously defined patient subgroups; this provides an index of overall diagnostic accuracy for the cardiac natriuretic peptides. The diagnostic accuracy of brain natriuretic peptide was greater than those of N-terminal pro-atrial natriuretic factor and atrial natriuretic factor for all predefined patient subgroups. According to the ROC area estimation, a randomly selected individual from the subgroup with end diastolic pressure $\geq$ 15 mm Hg and ejection fraction $\leq$ 45% will have a higher plasma brain natriuretic peptide value than a randomly selected individual from the remaining group of patients 79% of the time, but a higher N-terminal pro-atrial natriuretic factor value only 61% of the time.

Discussion

Important lessons can be learned from the present investigation. First, although plasma concentrations of the cardiac natriuretic peptides show significant associations with indices of left ventricular function, their ability to discriminate between normal and impaired ventricular function, as documented by ROC analyses, is relatively modest. Secondly, plasma brain natriuretic peptide seems to be a better indicator of left ventricular function, and in particular of left ventricular ejection fraction, than atrial natriuretic factor and N-terminal pro-atrial natriuretic factor. Nevertheless, the ability of brain natriuretic peptide determination to discriminate between patients with normal and those with abnormal left ventricular ejection fraction is not very impressive in this series of patients, even after adjustment for patient age. Given the relatively poor diagnostic accuracy of the cardiac natriuretic peptides as indicators of increased left ventricular filling pressures and systolic performance, the clinical usefulness of such

Figure 2 ROC plot of (A) atrial natriuretic factor, (B) N-terminal pro-atrial natriuretic factor, and (C) brain natriuretic peptide for distinguishing between patients with left ventricular dysfunction (subjects with left ventricular ejection fraction $\leq$ 45% and left ventricular end diastolic pressure $\geq$ 15 mm Hg) and the remaining group of patients.

Table 5 Diagnostic accuracy of the cardiac natriuretic peptides as evaluated by area under the ROC curve estimates

Natriuretic peptide	Area
Patients with LVEF ≤ 45% and LVEDP ≥ 15 mm Hg	
ANF	0.665
N-ANF	0.610
BNP	0.789
Patients with LVEDP ≥ 15 mm Hg	
ANF	0.680
N-ANF	0.619
BNP	0.698
Patients with LVEF < 45%	
ANF	0.625
N-ANF	0.595
BNP	0.738
Patients with LVEDP < 15 mm Hg, LVEF > 55%, and no angiographic sign of LV hypokinesis (n = 81)	
ANF	0.651
N-ANF	0.606
BNP	0.761

ANF, atrial natriuretic factor; BNP, brain natriuretic peptide; N-ANF, N-terminal pro-atrial natriuretic factor; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction.

measurements as a screening measure in the diagnosis of mild cardiac dysfunction seems to be limited.

The modest association observed between cardiac natriuretic peptide concentrations and haemodynamic indices does not accord with the results of several previous small-scale studies of a limited number of patients with a wide range of cardiac function and peptide concentrations.^{12-14 16 17} These studies, however, were not designed to evaluate the diagnostic accuracy of the cardiac natriuretic peptides in the identification of patients with asymptomatic or mildly symptomatic ventricular dysfunction. In a population-based study, plasma concentrations of atrial natriuretic factor correlated weakly with non-invasive indices of heart failure, the association being entirely due to increased concentrations in subjects with severe dyspnoea.²⁸ Another study, which did not assess cardiac function objectively, found increased plasma concentrations of atrial natriuretic factor and N-terminal pro-atrial natriuretic factor in subjects with congestive heart failure and ischaemic heart disease, but did not report any data on diagnostic accuracy.²⁹ To our knowledge, the only previous large-scale investigation which has attempted to assess the sensitivity and specificity of atrial peptides as indicators of cardiac function is the study by Lerman *et al*, encompassing an unselected population of patients referred to the Mayo Clinic for radionuclide ventriculography.¹⁰ The impressive results of the study showed that N-terminal pro-atrial natriuretic factor identified patients with asymptomatic left ventricular dysfunction with a sensitivity and specificity > 90%. The main reason for the discrepancy between the results of Lerman *et al* and the present data seems to be related to the low plasma N-terminal pro-atrial natriuretic factor values (28 (13) pmol/l) observed in their control group of 25 subjects. Our laboratory's reference values for N-terminal pro-atrial natriuretic factor obtained from a sample of 386 presumably healthy men show a much wider distribution (384 (179) pmol/l) than

that of the control group in Lerman *et al*'s study. The normal values for N-terminal pro-atrial natriuretic factor reported by Hall *et al* (588 (231) pmol/l) in a group of 134 healthy individuals with an average age of 60 (6) years also show a distribution pattern similar to the reference values of our laboratory.³⁰ Although reference values may vary considerably among laboratories, the wide scatter of values in healthy individuals and in patients with normal left ventricular function investigated in this study strongly indicates that a pronounced diversity in plasma concentrations is a physiological phenomenon characteristic of the cardiac natriuretic peptides. Our results suggest that a high proportion of false positive classifications—that is, subjects with raised circulating concentrations despite normal cardiac function—is a major limitation in the use of cardiac natriuretic peptides as indicators of mild left ventricular impairment. In addition, many patients with impaired left ventricular function seem to have relatively low circulating concentrations, further contributing to the overlap between patients with reduced and normal ventricular function.

Rather than calculating the sensitivity and specificity at an upper reference value, the present study assessed the overall diagnostic accuracy by estimating the area under the ROC function. Whereas reporting only one specific value for sensitivity and specificity provides a possibly misleading oversimplification of diagnostic accuracy, ROC analysis provides a comprehensive reflection of the ability of the test to make the diagnostic distinction throughout the range of decision thresholds.²⁷ To our knowledge, no previous study has evaluated the diagnostic accuracy of cardiac natriuretic peptides for the detection of mild left ventricular impairment by ROC analysis. Blood for cardiac natriuretic peptide measurements was sampled from aorta in the present study. It has previously been convincingly demonstrated that peripheral venous and left ventricular concentrations of atrial natriuretic factor and brain natriuretic peptide correlate closely ($r = 0.94$ and $r = 0.99$, respectively).¹⁷ Consequently, it is unlikely that our results would have differed had the blood samples been obtained from a peripheral vein.

The relatively poor diagnostic accuracy of circulating cardiac natriuretic peptides does not necessarily imply that measurements of these peptides are unsuitable as criteria for therapeutic intervention. The ability of neuro-humoral markers to predict outcome³⁰⁻³⁴ may be more important than their ability to correlate with other surrogates for outcome. Future use of cardiac natriuretic peptide measurement as a criterion for treatment with angiotensin converting enzyme inhibitor should, however, only be considered after its value has been proven in prospective trials in relevant patient populations.

We thank Professor Eric Espiner and Dr Tim Yandle, Department of Endocrinology, Christchurch Hospital, Christchurch, New Zealand for performing the brain natriuretic peptide analyses and Dr Olli Vuolteenaho, Department of Physiology, University of Oulu, Oulu, Finland, for performing the N-terminal pro-atrial natriuretic factor

analyses. Dr James M DeLeo, Division of Computer Research and Technology, National Institutes of Health, Bethesda, Maryland, USA, generously provided the software programme ROCLAB. We also thank Dr Tor Melberg and Dr Ståle Barvik for performing the physical examinations of the patients and for their contribution in the catheterisation laboratory.

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