Cohort study of plasma natriuretic peptides for identifying left ventricular systolic dysfunction in primary care

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Abstract

Objectives: To determine whether blood natriuretic peptide concentrations are helpful in identifying or excluding left ventricular systolic dysfunction in stable survivors of acute myocardial infarction.
Design: Comparison of blood natriuretic peptide concentrations with echocardiographic assessment of left ventricular systolic function in a general practice population.
Setting: Practices in Western District of Glasgow audit group.
Subjects: 134 long term survivors of myocardial infarction recalled for echocardiography as part of a primary care secondary prevention audit.
Main outcome measures: Area under the receiver operating curve for brain natriuretic peptide and *N*-terminal atrial natriuretic peptide.
Results: Brain natriuretic peptide was of some diagnostic utility in identifying the minority of subjects with severe left ventricular dysfunction (area under curve = 0.73) but was unable to discriminate between patients with moderately severe dysfunction and those with preserved left ventricular function (area under curve for moderate or severe dysfunction = 0.54). The corresponding values for *N*-terminal atrial natriuretic peptide for severe and moderate or severe dysfunction were 0.55 and 0.56 respectively.
Conclusions: Blood natriuretic peptide concentrations are not useful in identifying important left ventricular systolic dysfunction in stable survivors of myocardial infarction.

Introduction

Many studies have shown that the prognosis of patients with heart failure due to left ventricular systolic dysfunction can be improved by treatment with an angiotensin converting enzyme inhibitor.[1] Clinical outcome in patients with asymptomatic left ventricular dysfunction can also be improved by these drugs.[2] The identification of these patients on clinical grounds is, however, unreliable. Three studies in symptomatic patients with a diagnosis of heart failure showed that only 25-40% of subjects actually had left ventricular systolic dysfunction.[3–5] Clinical identification of asymptomatic left ventricular systolic dysfunction is even more difficult.

As a result, it has been suggested that all patients with clinically suspected heart failure or at risk of asymptomatic left ventricular systolic dysfunction should be investigated to confirm the diagnosis.[6] Echocardiography has become the standard investigation for this purpose, but provision remains limited.[6] Twelve lead electrocardiography may help target echocardiography at those most likely to have left ventricular systolic dysfunction.[7–9]

Measurement of plasma concentrations of atrial and brain natriuretic peptides has also been advocated as a means of identifying patients with left ventricular systolic dysfunction.[10 11] These peptides are secreted in increased quantities by the failing heart, are stable in whole blood for up to three days at room temperature, and can be measured with a relatively simple, rapid, and inexpensive assay.[12 13] Small clinical studies and epidemiological surveys have suggested that these peptides may be useful in identifying left ventricular systolic dysfunction in selected groups of patients.[11 14–17] The true test of such an approach, however, is to use it in ordinary clinical practice and where it is likely to be most valuable—that is, primary care. We report a study carried out in general practice in the United Kingdom among survivors of myocardial infarction with a high prevalence of other illnesses.

Subjects and methods

The West Glasgow general practitioner audit group decided that, as part of good clinical practice, all patients with a history of myocardial infarction should be reviewed with respect to the use of secondary prevention measures such as aspirin, β blockers, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, and angiotensin converting enzyme inhibitors. As part of this review patients were recalled for echocardiography to determine whether left ventricular systolic dysfunction was present. We decided to evaluate the use of natriuretic peptides in identifying left ventricular systolic dysfunction in these patients. Referred patients were seen by a doctor (SJMcC), who took a standard medical and drug history and carried out a clinical examination. A 12 lead electrocardiogram was then recorded and 10 ml of blood taken

from a forearm vein for measurement of brain natriuretic peptide and *N*-terminal atrial natriuretic peptide. All samples were taken into chilled potassium-EDTA tubes and placed on ice. Plasma was separated in a refrigerated centrifuge and stored at −20°C until assay. Both natriuretic peptides were measured as previously reported.[13 18] The peptides were measured in a single batch by an investigator without knowledge of the clinical or echocardiographic findings.

A standard echocardiographic examination was carried out by an experienced cardiac technician (LC). Two dimensional, M-mode, and colour flow and pulsed wave Doppler recordings were obtained with the patient in the left lateral decubitus position.

Echocardiographic measurements

Echocardiograms were recorded using an Acuson 128 x p/10c ultrasound machine. Left ventricular wall thickness was measured. Valvular function was quantified using Doppler (including colour flow) echocardiography. Left ventricular end diastolic and end systolic dimensions were used to derive fractional shortening.

A semiquantitative assessment of overall left ventricular systolic function (preserved function or mild, moderate, and severe impairment) was also made. As a rough estimate, mild impairment was equated to a left ventricular ejection fraction of 35-40%, moderate as 25-35%, and severe as less than 25%. Semiquantitative assessment has previously been shown to correlate closely with formal echocardiographic and radionuclide measurement of left ventricular ejection fraction.[19–21] The assessment was made after the end of the study. An independent investigator (APD) assessed left ventricular function in all patients from videotape recordings of the echocardiography. Analysis was carried out without knowledge of the patients' clinical condition, 12 lead echocardiogram, or natriuretic peptide measurements.

Statistical analysis

Receiver operating curves were generated to visualise the sensitivity and specificity (plotting sensitivity versus 1 – specificity) of each natriuretic peptide through the complete range of plasma concentrations for various measures of left ventricular systolic dysfunction and dilatation. The area under the curve was measured to maximise the diagnostic value of the peptide tests for each measure of dysfunction. A test that correctly classifies all subjects has an area of 1.0 and a test with no discriminatory value has an area of 0.5 or less.

The study was approved by the Greater Glasgow general practitioner ethics committee and all patients were asked for written informed consent before recruitment.

Table 1 Characteristics of 134 patients studied

	No (%) of patients
Mean (range) age (years)	67 (43 to 89)
Men	84 (63)
Medical history:	
Hypertension	51 (38)
Angina pectoris	76 (57)
Symptoms of heart failure	39 (29)
Atrial fibrillation	4 (3)
Coronary artery bypass grafting	28 (21)
Insulin treated diabetes mellitus	4 (3)
Non-insulin treated diabetes mellitus	20 (15)
Asthma/chronic obstructive airways disease	21 (16)
Peripheral vascular disease	32 (24)
Site of myocardial infarction:	
Anterior	24 (18)
Inferior	35 (26)
Lateral	3 (2)
Bundle branch block	10 (7)
No pathological Q wave pattern	62 (46)
Drug treatment:	
Loop diuretic	34 (25)
Thiazide diuretic	7 (5)
β Blocker	60 (45)
Calcium channel blocker	47 (35)
Oral/transdermal nitrate	30 (22)
Angiotensin converting enzyme inhibitor	28 (21)
Aspirin	123 (92)

Results

Table 1 shows the clinical characteristics of the 134 patients. A semiquantitative assessment of left ventricular function was made in all patients. The numbers of patients with preserved function and mild, moderate, and severe dysfunction were 68 (51%), 32 (24%), 26 (19%), and 8 (6%) respectively. M-mode could be measured in only 91 (68%) patients. Ten (11%) patients had substantially reduced fractional shortening (<25%).

Table 2 shows the mean (95% confidence interval) plasma brain natriuretic peptide and *N*-terminal atrial natriuretic peptide concentrations in patients with and without left ventricular systolic dysfunction. Though the mean concentrations of both peptides tended to be highest in those with the most severe left ventricular dysfunction, considerable overlap existed between the range of values in these patients and those with preserved left ventricular function.

Table 3 shows the areas under the receiver operating curves for brain natriuretic peptide and *N*-terminal atrial natriuretic peptide. These indicate their diagnostic value for left ventricular systolic dysfunction. The area under the curve for patients with normal 12 lead electrocardiographic results was 0.93.

Table 2 Plasma concentrations in patients with and without left ventricular systolic dysfunction

Patient group	No of patients (n=134)	Mean (95% CI) brain natriuretic peptide (pg/ml)	Mean (95% CI) *N*-terminal atrial natriuretic peptide (ng/ml)
Preserved left ventricular function and no dilatation*†	34	29.7 (7.0 to 45.4)	5.0 (1.2 to 8.8)
Normal 12 lead electrocardiographic results	29	18.3 (4.6 to 32.1)	3.1 (0.8 to 5.5)
Moderate or severe left ventricular dysfunction	34	35.6 (5.1 to 66.1)	4.3 (0.9 to 7.7)
Severe left ventricular dysfunction	8	50.0 (19.9 to 80.1)	5.6 (1.9 to 9.3)
Fractional shortening <25%†	10	48.9 (15.8 to 82.0)	6.6 (2.7 to 10.1)

*No left ventricular systolic dysfunction and left ventricular end diastolic diameter <55 mm.
† Measurements made in only 91 patients.

Table 3 Areas under receiver operating curves (diagnostic value) for brain natriuretic peptide and *N*-terminal atrial natriuretic peptide in patients with left ventricular systolic dysfunction and dilatation*

Patient group	Brain natriuretic peptide	*N*-terminal atrial natriuretic peptide
Moderate or severe left ventricular dysfunction	0.54	0.56
Severe left ventricular dysfunction	0.73	0.55
Fractional shortening <25%	0.71	0.63

*Compared with patients with preserved left ventricular systolic function and no dilatation.

The optimal threshold concentrations of the two peptides were determined as those that gave the best combination of sensitivity and specificity for detection of left ventricular systolic dysfunction. These thresholds were used to calculate the positive and negative predictive values (table 4). Concentrations below the thresholds were useful in excluding severe left ventricular systolic dysfunction but could not discriminate between lesser degrees of systolic dysfunction and preserved function. Table 5 shows the likelihood ratios for each of the natriuretic peptides.

Discussion

We evaluated the potential role of two natriuretic peptides in detecting left ventricular systolic dysfunction in ordinary clinical practice. In our population brain natriuretic peptide and *N*-terminal atrial natriuretic peptide were of clinical value in identifying only patients with severe left ventricular systolic dysfunction, though this was a small subgroup.

Neither test was useful in discriminating between lesser degrees of systolic dysfunction and preserved function. The characteristics of, for example, our patients with moderately severe left ventricular dysfunction suggest that their ventricular impairment was real. Of the 26 patients in this category, 25 had a Q wave infarct pattern or left bundle branch block on their electrocardiogram, significant left ventricular dilatation (left ventricular end diastolic diameter >55 mm), or very low fractional shortening ($<25\%$). Our findings therefore suggest that measurement of blood natriuretic peptide concentrations would not help in identifying most patients with important left ventricular dysfunction (who would be suitable for treatment with an angiotensin converting enzyme inhibitor).

Previous studies

Four published studies have evaluated brain natriuretic peptide and *N*-terminal atrial natriuretic peptide as markers of left ventricular systolic dysfunction in a clinical setting as opposed to epidemiological survey.[14–17] These have all been hospital based, examining patients referred for radionuclide ventriculography or having cardiac catheterisation. In all four studies brain natriuretic peptide had a higher diagnostic value (area under receiver operating curve 0.70, 0.74, 0.85, 0.88) than *N*-terminal atrial natriuretic peptide (0.53, 0.60, 0.60, 0.83). In these studies brain natriuretic peptide also appeared to discriminate between definitely normal left ventricular function, often in patients without cardiovascular disease, and severely reduced left ventricular function.

The relatively selected patients in these studies differ significantly from our general practice cohort. Unlike in our study not all the patients had had a myocardial infarction. In addition, our patients were older and more of them had hypertension, two features increasing the likelihood of left ventricular hypertrophy and diastolic dysfunction. All these factors increase plasma natriuretic peptide concentrations and make it harder to differentiate between normal and impaired left ventricular systolic function.[22–25] Mitral regurgitation is also known to increase natriuretic peptide concentrations, even though left ventricular function may appear spuriously good (though we had only one patient with normal ventricular systolic function and significant mitral regurgitation). Overall, however, few of our patients probably had a "normal" heart. Even previous bypass surgery seems to be associated with increased natriuretic peptide concentrations, possibly due to opening of the pericardium at the time of surgery.[26] More of our patients were also taking β blockers than in the other studies, a treatment known to increase natriuretic peptide concentrations.[27] Digitalis has also recently been shown to increase natriuretic peptide levels.[28]

Table 4 Predictive values of optimal threshold concentrations* of brain natriuretic peptide and *N*-terminal atrial natriuretic peptide for identifying left ventricular systolic dysfunction

	Brain natriuretic peptide			*N*-terminal atrial natriuretic peptide		
Patient group	Optimal threshold (pg/ml)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Optimal threshold (ng/ml)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Moderate or severe left ventricular dysfunction	46	0.69 (0.44 to 0.94)	0.55 (0.42 to 0.68)	4.4	0.52 (0.32 to 0.72)	0.51 (0.36 to 0.66)
Severe left ventricular dysfunction	32	0.35 (0.12 to 0.58)	0.92 (0.81 to 1.03)	1.4	0.22 (0.8 to 0.36)	1.00
Fractional shortening <25%	46	0.56 (0.24 to 0.88)	0.86 (0.74 to 0.98)	5.4	0.31 (0.08 to 0.54)	0.82 (0.68 to 0.96)

*Optimal indicates the peptide concentration giving the best combination of sensitivity and specificity.

Table 5 Likelihood ratios* (95% confidence intervals) of brain natriuretic peptide and *N*-terminal atrial natriuretic peptide for identifying left ventricular systolic dysfunction

	Brain natriuretic peptide		*N*-terminal atrial natriuretic peptide	
Patient group	Positive	Negative	Positive	Negative
Moderate or severe left ventricular dysfunction	2.25 (0.77 to 6.61)	0.83 (0.38 to 1.82)	1.08 (0.58 to 2.02)	0.96 (0.51 to 1.79)
Severe left venrticular dysfunction	2.31 (1.24 to 4.35)	0.37 (0.27 to 0.51)	1.21 (1.04 to 1.42)	0
Fractional shortening <25%	4.25 (1.4 to 12.89)	0.57 (0.32 to 1.0)	1.55 (0.7 to 3.4)	0.74 (0.34 to 1.62)

The likelihood ratio of a positive result shows how much more likely a positive result is to be found in a person with the condition than in a person without it. The likelihood ratio of a negative result shows how much more likely a negative result is to be found in a person without the condition than in a person with it.

Key messages

- Plasma concentrations of brain and *N*-terminal atrial natriuretic peptide increase in patients with left ventricular systolic dysfunction
- Both peptides are stable in blood and can be measured relatively quickly and inexpensively.
- In this general practice cohort of survivors of myocardial infarction brain natriuretic peptide had some value in identifying patients with severe left ventricular systolic dysfunction as determined by echocardiography
- Measurement of either peptide concentration was unable to discriminate between patients with moderate left ventricular dysfunction and normal function
- Brain and *N*-terminal atrial natriuretic peptide are not useful for detecting left ventricular systolic dysfunction in ordinary clinical practice

In general practice, therefore, where patients are elderly and have multiple cardiovascular and other problems, the discriminating value of brain natriuretic peptide (and *N*-terminal atrial natriuretic peptide) is clearly limited. Increased brain natriuretic peptide and *N*-terminal atrial natriuretic peptide concentrations may detect an unhealthy heart but do not discriminate between left ventricular systolic dysfunction and the other cardiovascular disorders so commonly seen in this type of population. This is in keeping with another recent report in patients presenting with suspected heart failure.[11]

Other explanations for our findings are unlikely. The peptides measured were stable and the assays reliable in our hands.[13 18] We previously found that peptide measurements did discriminate between healthy subjects and those with a very low left ventricular ejection fraction in an epidemiological study.[18]

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Contributors: JJVMcM is the study guarantor. He had the original idea for the study and coordinated it with SJMcC, LC, and SG. SJMcC interviewed and examined all the patients, took blood for the natriuretic peptide assays, reported on the electrocardiograms, and set up the study database. LC recorded the transthoracic echocardiograms and APD assessed them. SJMcC, JJVMcM, and APD analysed the data. All authors contributed to writing the paper.

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Endpiece

Praise from a patient

There are men and classes of men that stand above the common herd; the soldier, the sailor and the shepherd not infrequently; the artist rarely; rarelier still, the clergyman; the physician almost as a rule. He is the flower (such as it is) of our civilisation.

Robert Louis Stevenson, *Underwood's Foreword* (1887)

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