CARDIOVASCULAR MEDICINE

B-type natriuretic peptide identifies silent myocardial ischaemia in stroke survivors

K Y K Wong, S McSwiggan, N S J Kennedy, R S MacWalter, A D Struthers

Heart 2006;92:487-489. doi: 10.1136/hrt.2005.060350

See end of article for
authors' affiliations

Correspondence to:
Dr Kenneth Wong,
Department of Cardiology,
Cardiothoracic Centre-
Liverpool NHS Trust,
Thomas Drive, Liverpool
L14 3PE, UK; kywong@
doctors.org.uk

Accepted 26 August 2005
Published Online First
10 October 2005

Objective: To test the hypothesis that B-type natriuretic peptide (BNP) predicts reversible myocardial ischaemia in stroke survivors who do not have chest pain or previous myocardial infarction.

Methods: 56 stroke survivors (mean (SE) age 68 (8) years) underwent tetrofosmin myocardial perfusion scanning with dipyridamole as the stressor. The degree of ischaemia was assessed by a scoring system (out of 64) by an experienced observer blinded to the results of BNP.

Results: In the whole cohort, BNP was significantly correlated with the degree of myocardial ischaemia on stress scanning (Spearman's $r = -0.475$, $p < 0.001$). BNP also correlated with the degree of reversible ischaemia (stress score – rest score; Spearman's $r = 0.28$, two tailed $p = 0.049$). In the cohort who did not have left ventricular systolic dysfunction ($n = 44$), BNP remained higher in patients with relevant myocardial ischaemia (mean (SE) BNP 20.9 pg/ml, 95% confidence interval (CI) 15.2 to 26.5 v 12.2 pg/ml, 95% CI 5.95 to 18.5; $p = 0.046$); 33 of the 44 patients had no chest pain or history of myocardial infarction. The relation between resting BNP and both inducible ischaemia and dipyridamole stress score remained significant (Spearman's $r = 0.37$ and -0.38 , respectively).

Conclusions: BNP correlates with the degree of reversible myocardial ischaemia in patients who do not have chest pain or a history of myocardial infarction or evidence of left ventricular systolic dysfunction. Stroke survivors with a high BNP deserve further investigations to rule out significant reversible myocardial ischaemia, in order to reduce their risk of cardiac death.

Raised B-type natriuretic peptide (BNP) has a recognised role of identifying left ventricular systolic dysfunction in patients suspected of having heart failure.¹ The Framingham heart study showed that in patients without heart failure, plasma natriuretic peptide concentrations predicted the risk of death and cardiovascular events.² This may be because ischaemic myocardium releases BNP, irrespective of haemodynamic status—for example, raised BNP concentrations are associated with tighter culprit stenosis and, in stable angina, N-terminal proBNP had a close correlation with the extent of coronary disease.^{3,4} Nevertheless, no studies have been published that address the important issue of whether BNP predicts silent myocardial ischaemia in asymptomatic patients who are known to be at high risk of cardiac death but who have no chest pain.

One such cohort of high risk patients are survivors of cerebrovascular disease who often do not exercise enough to develop symptoms of angina. Nevertheless, it is well known that if the patient survives the first six months after a stroke, the most common cause of death in subsequent years is a cardiac death rather than a recurrent stroke. Yet few stroke survivors are routinely investigated for significant myocardial ischaemia despite this being their main cause of death.

We have therefore tested the hypothesis that BNP is increased in asymptomatic stroke survivors with silent but potentially reversible myocardial ischaemia. We tested this hypothesis in patients without significant left ventricular systolic dysfunction. Secondly, we tested the hypothesis that BNP rise correlates with the extent of reversible myocardial ischaemia in stroke survivors who have no symptoms of angina.

METHODS

Patients

Fifty six patients who made a good recovery and were at least one month after a recently documented stroke or transient

ischaemic attack were recruited into the study from the stroke outpatient clinic. Patients who were unable to consent—for example, because of dementia, patients who were living in a nursing home, and those over 90 years of age—were excluded. Patients with atrial fibrillation were also excluded. (It is well known that the presence of atrial fibrillation can result in increased BNP concentrations.) Patients with moderate to severe asthma that contraindicated the use of dipyridamole without steroid cover and patients with severe chronic obstructive pulmonary disease taking theophylline medication were also excluded for ethical reasons. Ethical approval was obtained from the Tayside Committee on Medical Research Ethics. The study also had Administration of Radioactive Substances Advisory Committee approval. All patients gave informed consent to participate in the study.

Myocardial perfusion imaging

The stroke survivors underwent tetrofosmin myocardial perfusion scanning, with dipyridamole as the stressor, with gated single photon emission computed tomography (SPECT) analysis. An experienced observer blinded to the results of BNP assessed the degree of ischaemia by a scoring system (out of 64). The left ventricle was divided into 16 regions (four apical, three anterior, three lateral, three inferior, and three septal) and each region was assigned a score out of four, indicating the degree of perfusion. The inducible ischaemia score was calculated by the score at rest minus the score during the stress scan. An inducible ischaemia score

Abbreviations: AVERT, atorvastatin versus revascularisation treatment; BNP, B-type natriuretic peptide; BSA, body surface area; EUROASPIRE, European action on secondary prevention through intervention to reduce events; IVSd, intraventricular septal thickness in end diastole; LVH, left ventricular hypertrophy; LVIDd, end diastolic left ventricular internal dimension; LVMI, left ventricular mass index; PWTd, posterior wall thickness in end diastole; SPECT, single photon emission computed tomography

of 3 or more was taken to represent relevant inducible myocardial ischaemia.

Quantified gated spectral analysis for ejection fraction assessment

Gated study allowed accurate measurement of ejection fraction. It was known to correlate well with multiple gated acquisition scanning. Eight frames were taken during each heart beat. This method avoided the need of giving more irradiation to patients. Absence of left ventricular systolic dysfunction was defined as gated SPECT $\geq 50\%$.

BNP assay

Venous blood samples were taken at rest and were then aliquoted into appropriate tubes stored on ice. The samples were spun immediately at 3000 rpm for 10 minutes at 5°C in a Biofuge 28 RS centrifuge (Heraeus Instruments, UK). The BNP samples were stored at -70°C . BNP was extracted from plasma in C_{18} columns and then measured by radioimmunoassay (Bachem (UK) Ltd, St Helens, Merseyside UK).

Echocardiography

Transthoracic echocardiography was done with the Hewlett Packard Sonos phased array imaging system (HP 2000, Hewlett Packard). This is because BNP can be increased in patients with left ventricular hypertrophy (LVH) and abnormal diastolic function. It is therefore important to note whether the cohort with myocardial ischaemia had significantly more patients with LVH or diastolic dysfunction.

Left ventricular mass index estimations

Intraventricular septal thickness in end diastole (IVSd), end diastolic left ventricular internal dimension (LVIDd), and left ventricular posterior wall thickness in end diastole (PWTd) were measured from M mode measurements, obtained at the level of the papillary muscles from parasternal views. When the echocardiogram was of sufficient research quality, left ventricular mass index (LVMI) was calculated according to the American Society of Echocardiography guidelines and measurements were made from leading edge to leading edge: $\text{LVMI} = (0.83 \times [(\text{LVIDd} + \text{PWTd} + \text{IVSd})^3 - (\text{LVIDd})^3]) - 0.6 \text{ g/BSA}$, where BSA (m^2) is body surface area (defined as $0.0001 \times 71.84 \times \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725}$). LVH was defined as $\text{LVMI} \geq 134 \text{ g/m}^2$ in men and 110 g/m^2 in women.

Diastolic function was assessed by the E:A ratio obtained by placing a pulsed wave Doppler signal next to the tips of the mitral valve leaflets to assess mitral inflow during diastole.

No invasive measurements were made by cardiac catheterisation for ethical reasons.

Statistical analysis

Data were statistically analysed with SPSS (SPSS Inc, Chicago, Illinois, USA). Spearman non-parametric tests were used to assess correlations between BNP and the stress scan score, rest scan score, and inducible ischaemia score. The Spearman test was used because this non-parametric test does not assume BNP is normally distributed. Univariate analysis of variance was used to compare the differences between means of continuous variables whose residuals were normally distributed (as evidenced by the one sample Kolmogorov-Smirnov test two tailed $p \geq 0.05$). The Mann-Whitney test was used to assess differences between medians if residuals were not normally distributed. A value of $p < 0.05$ was regarded as significant.

RESULTS

Fifty six patients (39 men) underwent myocardial perfusion scanning with gated SPECT analysis. Their mean (SE) age was 68 (8) years, mean blood pressure 147/79 (17/9) mm Hg, 76% had a history of hypertension, 11% were diabetic, 73% were current or former smokers, and mean total cholesterol was 4.6 (0.77) mmol/l. Thirty one patients had inducible ischaemia (scoring ≥ 3).

Forty four patients had no evidence of left ventricular systolic dysfunction as evidenced by gated SPECT ejection fraction $< 50\%$. Table 1 summarises other basic characteristics of the patients.

BNP significantly correlated with the degree of myocardial ischaemia in the whole cohort of patients (stress scan result: Spearman two tailed $p < 0.001$; rest scan result: Spearman two tailed $p = 0.049$; inducible ischaemia score: Spearman two tailed $p = 0.049$) (table 2).

In the cohort of stroke survivors who did not have left ventricular systolic dysfunction—that is, whose gated SPECT ejection fraction was $\geq 50\%$ —resting BNP was significantly correlated with the degree of myocardial ischaemia (stress scan result: Spearman two tailed $p = 0.008$; inducible ischaemia score: Spearman two tailed $p = 0.045$) (table 2). Figure 1 graphically shows that BNP was significantly higher in patients with myocardial ischaemia (inducible ischaemia score ≥ 3) (mean BNP 20.9 pg/ml, 95% confidence interval (CI) 15.2 to 26.5 v 12.2 pg/ml, 95% CI 5.95 to 18.5, univariate analysis of variance $p = 0.046$). The residual for resting BNP was normally distributed (one sample Kolmogorov-Smirnov test two tailed $p = 0.18$).

Thirty three of the 44 patients had no chest pain or history of MI. The relation between resting BNP and both the inducible ischaemia score and the dipyridamole stress score remained significant (Spearman's $r = 0.37$ and -0.38 ,

Table 1 Patient characteristics

	Reversible myocardial ischaemia		p Value*
	Absent	Present	
Women	29%	32%	NS
Age (years)	66.0 (1.6)	69.5 (1.4)	NS
Creatinine ($\mu\text{mol/l}$)	82 (5)	89 (4)	NS
Systolic BP (mm Hg)	146.4 (3.5)	146.1 (3.1)	NS
Diastolic BP (mm Hg)	81 (1.9)	77 (1.7)	NS
History of MI or angina	30%	32%	NS
LVH	43%	22%	NS
Ejection fraction (%)	54.5 (2.3)	55.8 (2.0)	NS
E:A ratio	0.93 (0.084)	0.82 (0.076)	NS

Continuous variables expressed as mean (SE).

*Fisher's exact test was used to assess discrete variables, and univariate analysis of variance was used to assess continuous variables (provided that their residuals were normally distributed as evidenced by one sample Kolmogorov-Smirnov test two tailed $p > 0.05$).

BP, blood pressure; LVH, left ventricular hypertrophy; MI, myocardial infarction; NS, not significant ($p > 0.05$).

Table 2 Relation between B-type natriuretic peptide and the degree of reversible myocardial ischaemia

	Inducible ischaemia score (rest – stress)	Dipyridamole stress score	Resting score
Whole cohort			
Spearman's r	0.280	-0.475	-0.279
Two tailed p	0.049	< 0.001	0.049
Patients without LVSD (gated SPECT $\geq 50\%$)			
Spearman's r	0.319	-0.416	-0.163
Two tailed p	0.045	0.008	0.314
Patients who had no angina or history of MI and no evidence of LVSD			
Spearman's r	0.370	-0.375	-0.124
Two tailed p	0.048	0.045	0.521

LVSD, left ventricular systolic dysfunction; SPECT, single photon emission computed tomography.

Figure 1 B-type natriuretic peptide (BNP) is higher in patients with significant myocardial ischaemia in the absence of left ventricular systolic dysfunction ($p = 0.046$). CI, confidence interval.

respectively, two tailed $p = 0.048$ and 0.045 , respectively) (table 2).

DISCUSSION

We found that BNP concentrations were directly correlated with the degree of reversible myocardial ischaemia. This relation remained true in patients who had neither chest pain, a history of myocardial infarction, nor left ventricular systolic dysfunction. This is the first published study that shows the link between BNP and reversible myocardial ischaemia in asymptomatic patients who are nevertheless at high risk of cardiac death.

In a community based study of 3346 patients without heart failure, plasma natriuretic peptide concentrations predicted the risk of death and cardiovascular events over a mean follow up period of 5.2 years. Such excess risk was apparent at natriuretic peptide concentrations > 20 pg/ml for men and 23.3 pg/ml for women. These concentrations were well below thresholds for diagnosing heart failure (that is, 80 – 100 pg/ml).² In the present study, BNP was higher in stroke survivors with coronary ischaemia, even after patients with left ventricular systolic dysfunction were excluded. In our study, patients with significant myocardial ischaemia had BNP concentrations as low as 20 pg/ml.

So why would patients with reversible myocardial ischaemia have higher concentrations of BNP? In patients with acute coronary syndromes, increased BNP concentrations (> 80 pg/ml) were associated with tighter culprit lesion diameter stenosis, slower flow in the culprit artery, and culprit lesion located in the left anterior descending coronary artery or more proximally.³ This raises the possibility that BNP, which is stored in secretory granules of atrial and ventricular myocytes, may be released during myocardial ischaemia or relative hypoxia. Indeed, very recently it was shown in isolated human atrial myocytes that hypoxia was a direct stimulus for A-type natriuretic peptide and BNP secretion.⁵ It is possible that myocardial ischaemia, even in the absence of left ventricular dysfunction, augments cardiac BNP gene expression and increases plasma BNP and proBNP concentrations.⁶ Thus, there is evidence to suggest that ischaemic myocardium makes more BNP in situ and releases more BNP when hypoxic.^{5, 6}

Risk stratification of survivors of cerebrovascular disease should be improved if a BNP measurement is routinely assessed. This may lead to perfusion scans in those stroke survivors with a high BNP, and coronary angiography may be considered for those with significant reversible ischaemia. In the many stroke survivors who would not be candidates for revascularisation, an abnormal BNP concentration and

myocardial perfusion scan may prompt the doctor to achieve tighter risk factor (such as blood pressure) control than usual, since the EUROASPIRE (European action on secondary prevention through intervention to reduce events) studies show how poor usual risk factor control is in the real world. In this latter way, BNP may lead to the highest risk stroke survivors getting the best risk factor control, which obviously enhances the cost effectiveness of secondary prevention in general. Asymptomatic patients with reversible myocardial ischaemia may also benefit from intensified statin treatment—for example, atorvastatin 80 mg/day. Sixteen per cent of patients in the AVERT (atorvastatin versus revascularisation treatment) trial were asymptomatic.⁷

Limitations of the study

The study population was small and did not permit adjustments for other factors known to be associated with increased BNP. However, reassuringly, there is no significant difference in age, history of chest pain or myocardial infarction, blood pressure, ejection fraction, E:A ratio (for want of a more accurate invasive measure of diastolic function), and proportion of patients with LVH between the cohorts of patients with and those without myocardial ischaemia.

Conclusions

BNP identifies reversible yet asymptomatic myocardial ischaemia in stroke survivors without left ventricular systolic dysfunction. Asymptomatic ischaemia should be treated to lower target concentrations of blood pressure and cholesterol. Further work is required to assess how best to respond in the case of an individual patient flagged by BNP concentration to have silent myocardial ischaemia.

ACKNOWLEDGEMENTS

We acknowledge the help of Lesley McFarlane and Valerie Godfrey at the Department of Clinical Pharmacology and Therapeutics, Ninewells Hospital and Medical School, for their contribution in laboratory assays.

Authors' affiliations

K Y K Wong, S McSwiggan, R S MacWalter, A D Struthers, Division of Medicine and Therapeutics, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK
N S J Kennedy, Department of Nuclear Medicine, Ninewells Hospital and Medical School, Dundee, UK

This study was supported by the British Heart Foundation and Dr Kenneth Wong was supported by a fellowship from the British Heart Foundation.

Competing interest: none declared

REFERENCES

- Davis M, Espiner E, Richards G, *et al*. Plasma brain natriuretic peptide in assessment of acute dyspnoea. *Lancet* 1994;**343**:440–4.
- Wang TJ, Larson MG, Levy D, *et al*. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004;**350**:655–63.
- Sadanandan S, Cannon CP, Chekuri K, *et al*. Association of elevated B-type natriuretic peptide levels with angiographic findings among patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004;**44**:564–8.
- Weber M, Dill T, Arnold R, *et al*. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. *Am Heart J* 2004;**148**:612–20.
- Hopkins WE, Chen Z, Fukagawa NK, *et al*. Increased atrial and brain natriuretic peptides in adults with cyanotic congenital heart disease: enhanced understanding of the relationship between hypoxia and natriuretic peptide secretion. *Circulation* 2004;**109**:2872–7.
- Goetze JP, Christoffersen C, Perko M, *et al*. Increased cardiac BNP expression associated with myocardial ischemia. *FASEB J* 2003;**17**:1105–7.
- Pitt B, Waters D, Brown WV, *et al*. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus revascularization treatment investigators. *N Engl J Med* 1999;**341**:70–6.