The relationship between BNP and risk assessment in cardiac rehabilitation patients

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Key words

B-type natriuretic peptide, cardiac rehabilitation, risk stratification

Br J Cardiol 2008;**15**:161–5

Risk stratification is important in the assessment of cardiac patients enrolled in physical training programmes but is often based on inadequate information. Measuring blood B-type natriuretic peptide (BNP) level, a marker of left ventricular dysfunction, might improve risk assessment. In an observational study blood BNP levels were measured in 100 consecutive patients joining a cardiac rehabilitation programme following acute myocardial infarction. The results were compared with the clinical risk assessment – high, moderate or low. There was a significant correlation between risk category (high, moderate or low) and BNP level (r=0.41, p=0.001). A BNP level of 100 pg/L or more gave a sensitivity of 89% (95% confidence interval [CI] 0.69, 0.97) and a specificity of 61% (95% CI 0.57, 0.63) for predicting high-risk patients with a positive predictive value of 33% (95% CI 0.26, 0.36) and a negative predictive value of 96% (95% CI 0.89, 0.99). A BNP level of less than 100 pg/ml gave a sensitivity of 78% (95% CI 0.55, 0.91) and a specificity of 54% (95% CI 0.43, 0.64) for predicting low-risk patients with a positive predictive value of 27% (95% CI 0.17, 0.40) and a negative predictive value of 92% (95% CI 0.80, 0.97). In conclusion, BNP levels provide information that may improve the accuracy of risk assessment of cardiac rehabilitation patients particularly when other information is limited.

Introduction

Risk stratification is important in the assessment of cardiac patients enrolled in physical training programmes to ensure that these patients receive the appropriate levels of surveillance and exercise intensity. Risk levels, an estimate of the likelihood of future cardiac events, are indicated as low, moderate or high. Poor left ventricular (LV) function is the most important risk factor for death.[1,2]

The gold standard for assessing LV function is echocardiography but this is expensive and is often not available to cardiac rehabilitation co-ordinators. The additional information provided by plasma B-type natriuretic peptide (BNP) levels might be helpful. This has not been studied before.

BNP is excreted into the bloodstream by the ventricular wall when it is stretched and blood levels of BNP are, therefore, raised in patients with LV dysfunction and heart failure.[3,4] Blood levels of BNP, or its precursor N-terminal proBNP, have been found to be the most significant predictors of prognosis in heart failure.[5] A raised level of BNP after acute myocardial infarction is associated with increased risk of LV remodelling, heart failure and death.[6-8] In the presence of a normal echocardiogram a raised BNP also has prognostic significance. A low level of BNP or N-terminal proBNP has been found to be highly predictive of normal LV function and good prognosis.[7-10]

The purpose of this study was to compare BNP level with risk assessment in a group of post-infarct patients joining a supervised exercise-based phase III cardiac rehabilitation programme.

Methods

One hundred consecutive post-infarct patients attending the cardiac rehabilitation programme after discharge from the North Hampshire Hospital coronary care unit were included. A *post hoc* power

calculation indicated that with 100 patients and a sensitivity of predicting high-risk patients of 89%, the true sensitivity can be estimated to within a width of ±6%, with 95% confidence.

All the patients had suffered troponin positive myocardial infarction. Sixty-nine patients had had echocardiograms and 26 had had coronary angiography with ventriculography performed during their admission, but figures giving an estimate of ejection fraction were not available. However, the cardiologist assessing risk level was aware of the results of these investigations.

The patients joined the supervised exercise-based Phase III cardiac rehabilitation programme at three to four weeks after the attack. Blood was taken at their first attendance and BNP levels were measured from whole blood, using the Triage near-testing machine.[11] (BNP levels are expressed as pg/ml and the cut-off point between normal and abnormal is taken as 100 pg/ml for both sexes.) The blood samples were refrigerated and tested within 24 hours. The BNP result was not known to any member of the cardiac rehabilitation clinical team.

Patients completed the Hospital Anxiety and Depression questionnaire[12] to measure psychological state and the Dartmouth Primary Care Cooperative Information Project/World Organization of National Colleges, Academies, and Academic Associations of General Practice/Family Physicians (COOP-WONCA) questionnaire[13] to measure quality of life. They then performed a submaximal treadmill exercise test to a modified Borg score (range 1 to 10) of between 6 and 8 and the predicted peak oxygen uptake was calculated (peak VO_2). All exercise tests were supervised by the same cardiologist.

The cardiologist then assessed the risk from all the available clinical evidence using the criteria of established guidelines[2] (which did not include the BNP level, of which he was unaware) and allocated each patient to a high-, moderate- or low-risk category.

Statistical analysis

Receiver operating characteristics (ROC) curves were used to assess the quality of the discriminatory power of BNP levels to predict high and low risk as assigned from clinical assessment. Sensitivity, specificity, and positive and negative predictive values were calculated at different cut-off points to ascertain the optimum sensitivity/specificity. All analyses were performed using SPSS version 1.4.0 (SPSS Inc., Chicago, USA).

Results

Of the 100 patients, 30 were women. Forty-three had been treated by percutaneous coronary intervention (PCI) shortly after the attack. The following were the characteristics that might influence BNP levels:

- The age range was 41 to 84 years, mean 63 years. (BNP levels rise with increasing age.[14,15])
- Body mass index ranged from 19.0 to 51.7 kg/m^2, mean 28.1 kg/m^2. Twenty-two patients had body mass indices between 30.0 and 34.9 kg/m^2, three between 35.0 and 39.9 kg/m^2 and three greater than 40.0 kg/m^2. (BNP levels fall with rising body mass index.[16])
- Estimated glomerular filtration rates (eGFR) were performed for all patients during their admission. Three had levels below 30 ml/minute, indicating severe renal disease. (BNP rises with deteriorating renal function.[14,15])
- No patients had uncontrolled hypertension or severe lung disease, though one had diagnosed chronic obstructive pulmonary disease and seven had asthma. (BNP is excreted by the stretched right ventricle as well as with the left.)
- Cardiac troponin taken shortly after the attack ranged from 0.16 to >50 μg/L, mean 14.2 μg/L. (BNP levels rise with increasing cardiac damage.[7])
- Ninety patients were receiving either angiotensin-converting enzyme (ACE) inhibitors or angiotensin blocking agents, which may reduce BNP levels.

Table 1 summarises the relationship between risk category attributed to the patients and BNP level, age, peak oxygen uptake (peak VO_2) and infarct-related troponin level.

There were 18 patients in the low-risk group, 64 in the moderate-risk group and 18 in the high-risk group. There is a clear trend for BNP levels to increase as we move from the low- to the high-risk category. Age tends to increase with risk category as does troponin, whereas peak VO_2 decreases as risk increases.

Figure 1 is the ROC curve for predicting high risk from BNP levels. **Table 2** shows the diagnostic

Table 1. Summary statistics for B-type natriuretic peptide (BNP), age, peak oxygen uptake (peak VO_2) and infarct-related cardiac troponin broken down by risk category (as identified clinically)

	Risk category		
	Low (n=18) mean (SD)	Moderate (n=64) mean (SD)	High (n=18) mean (SD)
BNP (pg/ml)	80 (90)	194 (247)	374 (272)
Age (years)	58.8 (11.2)	62.4 (10.2)	68.5 (7.9)
Peak VO_2 (ml/min/kg)	31.7 (8.5)	22.7 (8.2)	14.6 (5.9)
Troponin (μg/L)	9.1 (12.4)	15.3 (16.0)	15.4 (18.1)

Key: SD = standard deviation

Table 2. Diagnostic characteristics of BNP levels to predict high-risk category

BNP cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
≥100 pg/ml	0.89 (0.69, 0.97)	0.61 (0.57, 0.63)	0.33 (0.26, 0.36)	0.96 (0.89, 0.99)
≥300 pg/ml	0.61 (0.42, 0.78)	0.85 (0.81, 0.89)	0.48 (0.32, 0.61)	0.91 (0.86, 0.95)
≥400 pg/ml	0.39 (0.22, 0.55)	0.92 (0.88, 0.95)	0.50 (0.29, 0.70)	0.87 (0.84, 0.90)

Key: CI = confidence interval

Figure 1. Receiver Operating Characteristics (ROC) curve for prediction of high risk from BNP level. Area under curve = 0.796 (95% confidence interval 0.689, 0.903)

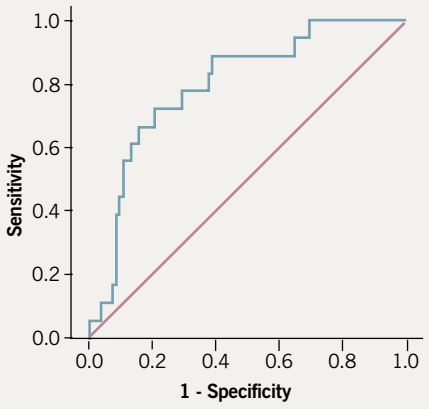
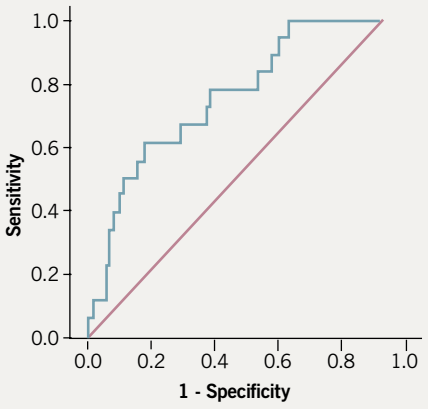


Figure 2. Receiver Operating Characteristics (ROC) curve for prediction of low risk from BNP level. Area under curve = 0.743 (95% confidence interval 0.622, 0.864)



characteristics of BNP levels at different cut-off points. The optimum level of BNP to predict high risk was 100 pg/ml or more which gave a sensitivity of 89% (95% confidence interval [CI] 0.69, 0.97) and a specificity of 61% (95% CI 0.57, 0.63) with a positive predictive value for being in the high-risk category of 33% (95% CI 0.26, 0.36) and a negative predictive value of 96% (95% CI 0.89, 0.99).

Figure 2 is the ROC curve for predicting low risk from BNP levels. Using a BNP level of <100 pg/ml to predict low risk gave a sensitivity of 78% (95% CI 0.55, 0.91) and a specificity of 54% (95% CI 0.43, 0.64) with a positive predictive value of 27% (95% CI 0.17, 0.40) and a negative predictive value of 92% (95% CI 0.80, 0.97).

Two patients in the high-risk category had BNP levels below 100 pg/ml. One was included in this category because she had suffered cardiogenic shock in the coronary care unit, with a very high BNP level in hospital of 920 pg/ml (this figure was not known to the clinical team) and echocardiographic evidence of 'severe left ventricular damage' – but had subsequently been found to have normal coronary arteries and no evidence of permanent LV damage. The second had been included in this category because he had suffered an anterior Q-wave myocardial infarction with a low exercise tolerance when he first attended cardiac rehabilitation. His echocardiogram indicated 'mildly impaired left ventricular systolic function'.

Four patients in the low-risk category had BNP levels higher than 100 pg/ml and none had a BNP level higher than 270 pg/ml. All had been able to perform more than six minutes of the Bruce protocol on the treadmill but one had had an extensive right ventricular infarct, another had suffered a previous infarct and a third was over the age of 80 years.

Table 3 shows summary statistics for the relationship between BNP levels and risk category – age, fitness level and infarct related troponin level. Patients with BNP ≥100 pg/ml were, on average older, had lower levels of peak VO_2 and higher post-infarct troponin levels.

Table 3. Summary statistics for age, peak oxygen uptake, infarct-related cardiac troponin broken down by BNP category

	BNP category	
	<100 pg/ml mean (SD)	≥100 pg/ml mean (SD)
Age (years)	58.2 (8.9)	67.9 (9.6)
Peak VO_2 (ml/min/kg)	26.2 (9.5)	19.2 (7.9)
Troponin (μg/L)	11.7 (14.4)	16.7 (18.2)

Key: SD = standard deviation; VO_2 = peak oxygen uptake

No patients were re-admitted during the course of the study and 10 patients suffered problems during the exercise programme including breathlessness, chest pain and hypotension. All had been included in the moderate-risk category but four had BNP levels above 300 pg/ml.

Discussion

This study demonstrates a relationship between BNP levels and risk assessment in patients joining a cardiac rehabilitation programme following acute myocardial infarction. Patients with a BNP level below 100 pg/ml are unlikely to be at high risk and those with a BNP level of 300 pg/ml or more are almost certainly at medium or high risk. In most cases the increased risk is associated with greater LV damage. In this group of patients the BNP level would, if known to the clinicians involved, have resulted in reclassification of one apparently high-risk and three apparently low-risk patients.

The optimum cut-off level for BNP of ≥100 pg/ml which we found for detecting the likely correlations between BNP and risk is similar to the findings from previous work. Studies of BNP levels in patients with heart failure have suggested that levels below 100 pg/ml made the diagnosis of heart failure unlikely, whereas levels above 500 pg/ml make it very likely.[17] In acute

dyspnoea a cut-off level of 100 pg/ml gave the best sensitivity and specificity for distinguishing between heart failure and other causes for breathlessness.[18] In stable coronary heart disease figures of between 52 and 100 pg/ml have been found to give the best cut-off values for predicting reduced LV ejection fraction or subsequent mortality.[4,19,20] Following acute myocardial infarction, the optimal cut-off levels for predicting heart failure or death have been found to lie between 52 and 180 pg/ml.[4,21,22] One study of remodelling in a group of acute myocardial infarction patients undergoing cardiac rehabilitation found that LV remodelling occurred exclusively in those with a BNP above 150 pg/ml at the start of the programme.[23]

In this study, the risk assessment was made by a cardiologist who had access to much more information than is available to most cardiac rehabilitation co-ordinators in the UK, i.e. physical findings and treadmill exercise test performance and, in most cases, the results of previous echocardiography or ventriculography. Even so the BNP level, had it been known, would have changed the risk assignation in one high-risk and three low-risk patients. The identification of risk category of cardiac rehabilitation patients is important. The exercise training of cardiac patients should be tailored to the individual patient and depends upon the needs, ability and level of risk. Those at high risk need more gradual increase in exercise duration and intensity and a longer period of supervised training before they are safe to be discharged to exercise without supervision. On the other hand low-risk patients need very little monitoring and can safely be discharged from formal supervised Phase III cardiac rehabilitation into unsupervised Phase IV exercise after a short period of supervision. Where facilities are at a premium, low-risk patients may be sent straight into Phase IV while the limited resources of the Phase III cardiac rehabilitation programme are concentrated on higher-risk patients. Most cardiac rehabilitation centres in the UK tend to take on relatively low-risk patients with very low long-term mortality yet do not have the capacity to treat more than a fraction of those who might benefit.[24] BNP level should not be used on its own as an indicator of risk since other factors provide additive information.[25] However, routine measurement of BNP levels might allow co-ordinators to identify with confidence low-risk patients so that they could free up space on the programme to take on a greater proportion of eligible patients, more of whom would be the high-risk patients who have the most to gain from cardiac rehabilitation.

The usefulness of BNP as an indicator of risk may be limited by influences other than LV damage. BNP levels are higher in women than men.[15] N-terminal proBNP level but not BNP levels rise with age in subjects with normal hearts. The positive correlation between age and BNP in this study was probably due to worsening of LV function with increasing age.

There are several limitations of this study. The sample size is small, with only 18 patients falling into each of the high- and low-risk categories. With the limited number of patients and the limited follow-up there were insufficient adverse events to validate the risk assessments as predictors of death or future events. We have, therefore used the clinical risk assessment, the best available predictor of prognosis, as the gold standard against which to compare the predictive power of BNP level. Our assessment of the utility of BNP level to predict risk may be confounded by age and by exercise capacity and post-infarct troponin level. The small sample size prevented the use of modelling techniques to try to account for these potential confounders. We have used BNP rather than N-terminal proBNP levels, which may be more readily available in centres where measurements are made by the pathology laboratories. However, evidence suggests that the two give very similar risk prediction though the blood levels of N-terminal proBNP are approximately three times those of BNP[26]

Conflicts of interest

None declared.

Ethical approval

Ethical approval for this study was granted by North & Mid Hampshire Local Research Ethics Committee on 17 April 2003.

Acknowledgement

Dr Hugh Bethell is in receipt of National Health Service Research & Development funding.

Key messages

- Risk stratification is important in the assessment of cardiac rehabilitation patients
- The information needed for accurate risk stratification is not always available to cardiac rehabilitation co-ordinators
- B-type natriuretic peptide (BNP) blood levels are closely related to risk assessment levels
- BNP levels may help to improve the accuracy of risk stratification in cardiac rehabilitation patients

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