Brain natriuretic peptide testing for angina in a rapid-access chest pain clinic

S.B. CONNOLLY1, T. COLLIER2, R. KHUGPUTH1, D. TATAREE1, K. KYEREME1, S. MERRITT1, A.D. STRUTHERS3 and K.F. FOX1

From the 1Cardiovascular Medicine, Charing Cross Hospital, Hammersmith Hospitals NHS Trust, London, 2Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London and 3University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

Received 12 April 2007 and in revised form 27 July 2007

Summary

Background: Patients complaining of chest pain are frequently referred to secondary care, although the majority have pain of non-cardiac origin.

Aim: To investigate whether B-type natriuretic peptide (BNP) levels are predictive of a diagnosis of non-cardiac pain.

Design: Cross-sectional study.

Methods: Consecutive patients (n = 296) presenting to a rapid-access chest pain clinic (RACPC) received the usual clinical assessment plus near-patient BNP testing, with the assessor blinded to the result. After clinical assessment (including exercise stress testing if clinically indicated), pain was diagnosed likely/definitely cardiac or non-cardiac.

Results: Median BNP was higher in those diagnosed with likely/definite cardiac chest pain (26.5 vs. 8 pg/ml) (p < 0.0001, Wilcoxon rank sum test). The odds ratio for cardiac pain in those with BNP <20 pg/ml was 0.25 (95%CI 0.14–0.47) (p < 0.0005); adjusting for age and sex reduced this to 0.41 (95%CI 0.20–0.83) (p = 0.01). The area under the curve (AUC) for the model including BNP, age and sex was 0.70. With BNP as a continuous variable, the AUC for the same model was 0.72.

Discussion: In typical patients presenting to a RACPC, those with a BNP ≤20 pg/ml were significantly less likely to be diagnosed with cardiac pain. Near-patient BNP testing may have a role as a ‘rule out test’ for angina in patients presenting to a RACPC.

Introduction

Chest pain is one of the most common complaints presenting to primary care. Although many of these cases have a low probability for cardiac disease, referral for specialist opinion is frequently made, often for both patient and physician reassurance.

Rapid-access chest pain clinics (RACPCs) are the model of choice in providing the rapid assessment of such patients (National Service Framework1). Our RACPC at Charing Cross Hospital has a proven track record in evaluating patients presenting with suspected cardiac disease, and identifying patients at high risk.2

Similar to other reported data, the majority of our patients are found to have non-cardiac pain,3–5 but making this diagnosis poses a considerable burden on our service’s time. A screening test that could ‘rule out’ angina could have considerable potential in the triage of appropriate referrals to RACPCs.

Address correspondence to Dr S.B. Connolly, Cardiovascular Medicine, 5th Floor, Charing Cross Hospital, Fulham Palace Road, London W6 8RF. email: s.connolly@imperial.ac.uk

© The Author 2007. Published by Oxford University Press on behalf of the Association of Physicians. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org
The role of B-type natriuretic peptide (BNP) testing in the identification of patients with heart failure, particularly that due to left ventricular systolic dysfunction (LVSD) (BNP \( \geq 100 \text{ pg/ml} \)) is now well established.\(^6\) More recently, however, BNP has been found to be an independent predictor of cardiovascular events including mortality, even after adjustment for the presence of LVSD.\(^7\) A mounting body of evidence would suggest that this may, in part, be due to a correlation between increased BNP levels, in the lower range of 20–100 pg/ml, with both the presence and extent of coronary artery disease (CAD).\(^8\)–\(^14\) Indeed, myocardial ischaemia itself has been found to have a direct positive effect on BNP expression.\(^15\)–\(^16\) We therefore investigated whether a low BNP \((\leq 20 \text{ pg/ml})\) was predictive of a diagnosis of non-cardiac pain in patients attending our RACPC.

Methods

Consecutive patients attending the RACPC in Charing Cross Hospital between October 2005 and May 2006 were invited to participate in the study, and informed consent was obtained. Patients were excluded if they were aged <18 years, had cognitive impairment, or had symptoms suggestive of heart failure. The patient was then assessed by the RACPC specialist nurse according to usual clinical practice, including full history, physical examination, laboratory testing, 12-lead ECG and exercise stress testing if clinically indicated. An extra 0.5 ml of blood was drawn for near-patient BNP testing (Roche Diagnostics) and the sample was analysed by a designated member of the cardiac investigations team (specifically not the RACPC nurse assessing the patient) who had received prior training on the use of the BNP assay device.

All clinical and laboratory information was stored on the designated chest pain clinic access database, with the exception of the BNP assay result, which was stored separately, thus ensuring that the RACPC specialist nurse was blinded to the result at all times. The primary outcome of the study was the diagnosis made by the clinical team after the initial evaluation at the RACPC, which was either that of cardiac or non-cardiac pain. The study was approved by the hospital’s ethics committee.

All statistical analyses used Stata, version 9.2 SE. Numbers and percentages were calculated for categorical variables, and means (SD) or medians (IQR) for quantitative variables, as appropriate. Differences between those with and without likely cardiac pain were tested using the Wilcoxon rank sum test for continuous variables and the \( \chi^2 \) test for categorical variables. Odds ratios with 95% CIs were calculated using univariate and multivariate logistic regression. The area under the curve was calculated following the fitting of each logistic model.

Results

During the study period, 414 patients attended the RACPC, of whom 303 agreed to participate in the study (response rate 78.9%). Seven patients were subsequently excluded, as they had a previous diagnosis of CAD. Of the remaining 296 patients, eight had missing BNP measurements, and thus were excluded from further analysis. Sixty-two percent of the patients \((n = 178)\) had exercise stress testing; of these, 72% were normal, 13% abnormal and 12% inconclusive. A further 4% \((n = 12)\) were referred for myocardial perfusion scans. At the end of the consultation with the RACPC nurse (and after exercise testing if performed), 81.6% of study participants \((n = 235)\) were diagnosed with non-cardiac chest pain, while the remainder were diagnosed as having likely/definite cardiac pain. The baseline characteristics of the 288 study participants are displayed in Table 1, with their characteristics when dichotomized by BNP level \(\leq 20 \) or \(>20 \text{ pg/ml}\).

The distributions of BNP values in each group are illustrated in Figure 1. The median BNP level in the group diagnosed with cardiac chest pain was 26.5 pg/ml, compared with 8 pg/ml in those with non-cardiac pain \((p < 0.0001, \text{ Wilcoxon rank sum test})\).

We had postulated that a low BNP \((\leq 20 \text{ pg/ml})\) would be predictive of a diagnosis of non-cardiac pain. Therefore, after dichotomizing BNP levels in this way, the odds ratio for having likely/definite cardiac pain in those with a BNP \(\leq 20 \text{ pg/ml} \) was 0.25 \((95\% \text{ CI } 0.14–0.47, p < 0.0005)\), i.e. the odds of having likely/definite cardiac pain was 75% lower amongst those with a BNP in this range. After adjusting for age and sex, the odds ratio was somewhat attenuated to 0.41 \((95\% \text{ CI } 0.20–0.83)\), but was still statistically significant \((p = 0.01)\). Further adjustment for hypertension, diabetes, dyslipidaemia, PVD or stroke and smoking status had little impact \((OR 0.42, 95\% \text{ CI } 0.20–0.89, p = 0.02)\).

The area under the curve (AUC) for the model including BNP, age and sex was 0.70 (Figure 2). Dividing a continuous variable into two categories using a single cut-point inevitably results in loss of information. The AUC for the same model but with BNP as a continuous variable was 0.72. The calculated sensitivity for a BNP level \(>20 \text{ pg/ml} \) in detecting likely/definite cardiac disease was
calculated at 55%, with a specificity of 77%. The positive predictive value was 35% and the negative predictive value was 88%.

**Discussion**

These data show that, in typical patients presenting to a RACPC, those with a BNP $\leq 20\,\text{pg/ml}$ were significantly less likely to be diagnosed with cardiac pain. These results are in keeping with previous data, suggesting that BNP values of 20–100\,pg/ml are associated with obstructive CAD,\(^8\) but those studies were performed in highly selected clinical groups, in contrast to our extremely heterogeneous study population.
The relatively low sensitivity of a BNP >20 pg/ml in this study in detecting likely/definite cardiac disease reflects the fact that the initial RACPC diagnosis is made prior to coronary angiography, and many of the ‘likely’ subsequently turn out not to have coronary artery disease. However, our RACPC very rarely misses symptomatic CAD, with a 98% negative predictive value at 1 year. Importantly, in this study, the high specificity of 77% and negative predictive value of 88% support the potential role of a low BNP (≤20 pg/ml) as ‘rule out’ test, potentially in the triage of patient referral for RACPC assessment. Triage could potentially be performed in two settings, either in primary care or upon arrival at the RACPC, but it should not lead to dispensing with the usual clinical assessment, including 12-lead ECG. If near-patient BNP testing was performed in primary care, this potentially could reduce the number of referrals to secondary care. If performed in RACPCs, it could potentially reduce assessment time by decreasing the need for exercise stress testing. However, these findings should be validated in further studies before changing clinical practice in this manner. In addition, even if the patient is clearly experiencing non-cardiac pain and has a low BNP level, they should still have a comprehensive cardiovascular risk assessment, including smoking habit, blood pressure, lipid and glucose levels, with appropriate intervention according to national guidelines.

We did not perform echocardiography in this study unless clinically indicated, and thus some of the elevated BNP levels theoretically may have been due to LVSD. However, BNP levels are typically in the range of >100 pg/ml in the presence of LVSD; only 4.3% of the study group (n = 15) had a BNP in this range, and none were >500 pg/ml. Furthermore, median BNP values were used in the statistical analysis in this study. Renal dysfunction has also been shown to contribute to higher BNP, but we did not adjust for this, because we wanted to test the utility of BNP on presentation to the RACPC, when creatinine levels are not usually available. Furthermore, if BNP was being done as a ‘rule out test’, renal dysfunction would only potentially produce more false positives, and one could argue that these patients would benefit from a clinical assessment anyway as they have a higher CVD risk.

We acknowledge that dichotomizing BNP inevitably results in loss of information and consequently some loss of discriminatory power as seen in our results above (AUC 0.70 vs. 0.72). Other limitations of this study include the use of ‘likely/definite cardiac pain’ as an outcome measure rather than the gold standard, namely coronary angiography. However, if coronary angiography had been used, this would likely have served to increase the sensitivity of BNP in detecting coronary disease, for the reasons stated earlier.

In summary, these results suggest that a low BNP ≤20 pg/ml may have a role as a ‘rule out test’ for patients presenting at a RACPC with suspected angina. Indeed, the area under the ROC curve of 0.70 is similar to that of D-dimers for the diagnosis of pulmonary embolism. If these findings are validated in larger studies, the use of BNP as a screening tool has the potential to significantly reduce unnecessary RACPC assessments, and thus permit resources to be redirected to those with genuine CAD.

Acknowledgements

We thank Sri Reddihavari, Rapid Access Clinical Fellow, who obtained local ethical approval for the study. The Triage BNP Test immunoassay and test strips were provided free of charge by Biosite Inc. The researchers involved in this study have no conflict of interest with Biosite Inc. and the research carried out was independent from Biosite Inc.

References


