

B-Type Natriuretic Peptide in the Cardiology Department

Abstract:

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Abstract

Heart Failure is one of the fastest growing cardiovascular diseases of the 21st century. Echocardiogram is considered the gold standard for diagnosis, but is costly, time consuming and not readily accessible to all patients. Our aim was to assess the diagnostic utility of BNP to risk stratify patients for ECHO. Seventy-four GP referred, non-pregnant patients of e18 years with a working diagnosis of HF were recruited. Patients were given two appointments to attend the Cardiology Department and at each, were examined by the same cardiologist, had their medications recorded and blood drawn for BNP analysis. ECHO was performed at the second visit. The diagnosis of HF was confirmed in 49 of 74 patients (66%). The clinical utility of BNP to rule-in HF was evaluated using ROC curve analysis. The AUC was satisfactory at 0.691 (C.I. 0.573-0.793). The positive likelihood ratio (+LR) was 5.87, negative likelihood ratio (-LR) was 0.58, the positive predictive value was 92% and a negative predictive value was 47%. One-third of patients (n=25) had a BNP >178 pg/mL, 23 of whom had HF confirmed. At this decision threshold BNP correctly classified 23 of 25 patients who were confirmed not to have HF (Specificity for HF of 92%). A BNP of e178 pg/mL can be used to prioritise GP patients for ECHO.

Introduction

The incidence of HF in Ireland is approximately 10,000 new cases yearly with an expected prevalence for the year 2010 of 300,000 cases with half at the prodromal stage². Heart failure is predominantly a disease of the elderly, with a prevalence rate of 80 cases per 1000². Greater longevity, combined with improvements in the treatment of ischaemic heart disease (IHD) account for the increased prevalence. The cost of diagnosing and treating heart failure was put at approximately 2% of healthcare expenditure in 2001³. Hospital In-Patient Enquiry (HIPE) data shows that heart failure accounts for 35% of in-patient stays⁴. The survival rate in myocardial infarction varies across incomes with 1-year mortality about 9.5% in the wealthiest in contrast to 11.5% in the poorest⁵. Up to 50% may go on to develop heart failure. Early diagnosis and treatment are, therefore, of considerable importance.

Heart failure causes dyspnoea, rales and peripheral and pulmonary oedema; a picture shared with chronic obstructive pulmonary disease and other conditions. Conventional diagnosis relies on initial clinical examination together with chest X-ray and electrocardiography (ECG), which may suggest cardiomyopathy increasing the likelihood of heart failure as the cause of the symptoms. The second step in diagnosis is Doppler echocardiography allowing an estimate of the left ventricular ejection fraction (LVEF). A LVEF of less than 45% is used to diagnose heart failure. However, it is estimated that up to 50% of those with HF have normal or near normal LVEF⁶.

B-type natriuretic peptide is used predominantly to rule-out heart failure.^{7,8} The National Institute for Health and Clinical Excellence (NICE) in the UK, guidelines, direct the exclusion of HF on the basis of ECG and /or B-type natriuretic peptide (BNP) measurement where available and recommend the confirmation of suspected HF with echocardiogram (ECHO)⁹. In our institution, both the size, and duration on the waiting list for ECHO is increasing year on year. This is likely to continue as the number of new HF cases each year approximates 10,000. As of May 2010 the waiting time for ECHO was 8 months. This lengthy waiting time prompted the current study to examine the clinical utility of BNP to risk stratify for ECHO, GP referral patients clinically assessed by the cardiology team as having HF. In this context BNP is being used to rule-in HF.

Methods

This was a single centre prospective study of nine months duration. GP referral patients aged between 18-85 years were invited to participate, if they presented with dyspnoea, or oedema and a working diagnosis of HF. Individuals less than 18 years of age or pregnant were not included. Following informed consent, patients were given two appointments with the Cardiology Department, Beaumont Hospital. At both appointments, the patients were interviewed and examined by the same cardiologist to assess their clinical status and current medication. The same equipment to assess blood pressure, heart rate and weight was used throughout the study. At both visits blood was drawn for BNP and creatinine analysis. ECHO was performed at the second appointment. 105 patients were recruited to this study, 31 were lost to follow-up. Of the 74 patients (male, n = 41) who completed the study, 49 were confirmed by ECHO to have HF. Of those, 17 had left ventricular systolic dysfunction (LVSD), 5 had Valvular Disease (VAD) and 27 had diastolic dysfunction (DD). The patient demographics and medications of those diagnosed with HF are detailed in Tables 1 and 2 respectively. Ethical Approval for this study was obtained from the Ethics and Medical Research Committee of Beaumont Hospital, Dublin, Ireland.

The Biosite BNP assay using the Beckman Dxl Immunoassay analyser was employed¹⁰. The assay is based on an immobilized 2-site immunoenzymatic assay. The measuring range of this assay is 5-5000 pg/mL with an average analysis time of 15 minutes per test from initiation of assay run. Intra-assay (n=20) coefficient of variation (CV) at BNP concentrations 87.4 pg/mL, 416.1 pg/mL, and 2255.9 pg/mL were 3.6%, 1.7%, and 2.1% respectively. The inter-assay precision (n=20) at BNP concentrations of 85.6 pg/mL, 419.1 pg/mL, and 2204.2 pg/mL were CVs of 5.7%, 6.2%, and 4.4% respectively. The cost per test is approximately 24.

HF was diagnosed on clinical assessment and objective evidence based on ECHO. Transthoracic two-dimensional Doppler ECHO was performed using the Agilent Technologies Sonos 5500 instrument and reported according to the British Society of Echocardiography guidelines. Cardiac abnormalities that may have lead to breathlessness or a raised BNP were documented. Left ventricular function was evaluated by eyeball assessment and the Simpson's rule¹¹ used when a discrepancy arose between observers. Diastolic function was measured in accordance with the Heart Failure and Echocardiography Associations of the European Society of Cardiology criteria, with measurement of trans-mitral Doppler velocity looking at early (E) and late (A) diastolic filling, E/A ratio as well as E deceleration time (DT) from an apical four-chamber view. Tissue Doppler is used to measure the septal and lateral side of the mitral annulus, looking at longitudinal myocardial shortening represented by Eâ¹². ECHO was performed by a cardiac technician and confirmed by a cardiology specialist, who observed all ECHOs performed. Both technicians and clinicians were blind to the BNP results. A consultant cardiologist reviewed the report and patients were graded according to one of four groups: normal, systolic heart failure, diastolic heart failure and valvular disease. ECHO is routinely performed Monday to Friday, each takes 20-30 minutes and costs approximately 170. In this study, the average time between a patient's first appointment at the Cardiology Outpatient Department and having their ECHO was 75 days (range 38-142 days) for men and 80 days (range 21-163 days) for women.

Twenty-three percent of patients were confirmed to have LVSD, 36.5% to have diastolic dysfunction and 6.8% to have HF as a result of valvular disease. 33.8% of those recruited to this study were found not to have HF. The prevalence of HF in this population was 66.2%. Receiver operating characteristic curve (ROC) statistical analysis was used to determine the diagnostic power of BNP to confirm HF in this cohort. The ROC curve was drawn using ECHO as the gold standard for diagnosis and the area under the curve (AUC) calculated. Diagnostic utility was evaluated using sensitivity, specificity, and negative and positive predictive values and likelihood ratios. Statistical analysis was performed using the Analyse-it General and Laboratory Modules software package (Analyse-it Software Ltd, P.O. Box 103, Leeds LS277WZ,UK).

*NYHA = New York Heart Association Classification System

Results

The clinical utility of BNP in this patient cohort was assessed using ROC curve analysis, Figure 1. BNP at a concentration of ≥ 178 pg/mL gave the least number of false positives and false negatives. The AUC was satisfactory at 0.691 (C.I. 0.573-0.793) and was significantly different from the null hypothesis ($p = 0.0021$). At this cut-off, clinical sensitivity was 47% and clinical specificity was 92%. The positive likelihood ratio (+LR) was 5.87, negative likelihood ratio (-LR) was 0.58, the positive predictive value was 92% and the negative predictive value was 47%. The BNP decision threshold of 178 pg/mL was used to rule-in the diagnosis of HF and prioritise patients for ECHO. The diagnosis of HF was confirmed by ECHO in 49 of 74 patients (66%). 25 of the cohort had a BNP ≥ 178 pg/mL, 23 of whom had HF confirmed. 13 of 17 (76.5%) patients with LVSD, 4 of 5 (80%) patients with HF due to valvular disease, and 6 of 27 (22%) patients with DD were identified. Further, BNP at this cut-off correctly classified 23 of 25 (92%) who were confirmed not to have HF.

Figure 1: ROC curve for BNP in the diagnosis of HF confirmed by echocardiography.
(AUC = 0.69; 95% Confidence Interval 0.57-0.79; Significance level P (Area=0.5) = 0.0021).

Discussion

Heart failure is a growing problem in modern medicine and poses significant challenges to the non-specialist physician. NICE guidelines, published in 2003, recommend that patients with suspected HF should have their diagnosis confirmed by ECHO before any treatment is initiated. NICE have recognized the difficulty of patients accessing ECHOs and have recommended that a normal ECG and/or BNP (NT-proBNP) measurement can be used to rule-out HF. In a study by Zaphiriou in 2005 it was estimated that, when ECG is used to classify patients into those with and without HF, up to 20% of patients could be missed. A review published by Penney in the same year suggested that 10% of patients would be missed if ECG is assessed by non-specialists, quoting a sensitivity of 89.1% and a specificity of 45.7% been shown to be superior to ECG in identifying patients with HF but access to BNP by GPs is mixed at best

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All 74 patients in this study had been clinically assessed by the cardiology team to have HF and had been placed on a waiting list for ECHO. BNP was therefore required to act as a confirmatory test i.e. to rule-in a diagnosis of HF. A decision threshold with high specificity is necessary for this purpose to optimize the positive predictive power of the test. BNP at a cut-off of 178 pg/mL had a specificity of 92%. The approach taken to risk stratify those on the list for ECHO was as follows:- Patients having a BNP concentration ≥ 178 pg/mL would have highest priority and have their ECHO within 2 weeks of presentation to Cardiology. The impact on our patient cohort being that one-third of patients screened for ECHO would be prioritized. On consultation with the cardiology department, the consensus view was that this proposal for the care pathway for GP patients referred with a working diagnosis of HF was pragmatic and would positively benefit patient management.

LVSD is clinically the most important form of HF to identify because of the associated higher mortality rate. Detection of LVSD would allow timely treatment with ACE inhibitors and beta blockers, which have been shown to delay the progression to overt CHF. In a study by Philbin, on 1291 hospitalized patients, the mortality was lower in patients with EF >50% than those with an EF < 39%. The Framingham offspring cohort found that the rate of death after 5 years in patients with HF and normal EF is lower at 68% as compared to 82% in those with systolic HF, albeit a fourfold mortality risk compared with healthy subjects¹⁵. Several studies have shown BNP to be a good identifier of LVSD, and this is confirmed in our study population despite the majority of patients being on cardio-active medication. BNP at a concentration of ≥ 178 pg/mL allows the risk stratification for ECHO of those patients with the more aggressive forms of HF as a result of LVSD and valvular disease. Those given the highest priority for ECHO should have the procedure within 2 weeks of presentation to Cardiology. This is a significant improvement over the current situation where the average waiting time on the waiting list for ECHO at this hospital is 4 months. The measurement of BNP should facilitate earlier diagnosis of HF and minimize the delay in the proper work up of an alternate diagnosis.

Acknowledgements

We thank all the patients who made this study possible. Special thanks are extended to Dr Brendan McAdam and Mr David Farrell, Dept of Cardiology and the scientific staff of the Department of Chemical Pathology, Beaumont Hospital.

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