SCIENTIFIC LETTER

Safe use of brain natriuretic protein to rule out the diagnosis of heart failure depends on the selection of cut off value

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The recently published National Institute for Clinical Excellence (NICE) chronic heart failure (CHF) guideline[1] has recommended the use of brain natriuretic peptide (BNP) to help rule out the diagnosis of CHF, and quoted a sensitivity of 90–97%. Moreover, for purposes of medical audit, patients previously labelled as having CHF, but without a confirmation of the diagnosis, may need to be reassessed by measuring their plasma BNP concentrations. Recent papers highlighted that even BNP concentrations below accepted cut off values may actually be associated with elevated cardiovascular risk.[2] When clinicians consider whether to adopt a BNP assay in the diagnostic work up of CHF, one important concern is whether the false negatives could include severe CHF cases and thereby jeopardise their subsequent care through misdiagnosis. We explored this possibility by measuring N-terminal pro-BNP (N-BNP) in a cohort of subjects including those with a confirmed diagnosis of CHF and a wide range of New York Heart Association (NYHA) functional classes and healthy volunteers. Functional cardiac status was quantitatively graded according to aerobic exercise capacity, measured by peak oxygen consumption ($\dot{V}O_2$).[3] Although receiver operating characteristic curves and sensitivity/specificity methods are conventionally used to evaluate diagnostic techniques, for clinicians dealing with individual patients, the simpler method of plotting individual values relative to cut off values is more direct and more easily understood and is therefore employed in this study.

METHODS

Ninety six subjects participated in this study, including 86 consecutive stable CHF patients (diagnosed by practising heart failure specialists according to standard international and national heart failure guidelines: 64% had an underlying ischaemic aetiology, while the remainder had dilated cardiomyopathy (30%) and valve diseases) undergoing cardiopulmonary exercise testing (mean (SD) age 55.7 (12.0) years; 72 male; left ventricular ejection fraction 36.9 (15.2)%, spanning the full range of NYHA functional classes from I to IV), and 10 healthy volunteers (aged 51.8 (11.9) years; nine male). Relevant medications included 59 patients (69%) taking diuretics, 62 patients (72%) taking angiotensin converting enzyme inhibitors, and 37 patients (43%) taking β blockers. A venous blood sample was taken at rest to determine N-BNP using an in house well validated non-competitive assay.[4] The normal ranges of this assay have previously been established in a cohort of 1360 normal subjects,[4] with a median value of 44.8 fmol/ml, and 95th centile of 384 fmol/ml. All subjects underwent cardiopulmonary exercise testing to measure standard parameters including $\dot{V}O_2$. Those within Weber class A (please refer to the appendix for details of Weber classes) ($\dot{V}O_2 > 20$ ml/kg/min) were considered not to have clinically significant functional impairment. The Mann Whitney U test for unpaired samples was performed to assess differences in N-BNP concentrations between patients with CHF and control subjects.

RESULTS

Significantly higher N-BNP concentrations were found in the CHF group (299.3 (interquartile range (IQR) 704.8) fmol/ml) compared with the healthy control group (7.2 (IQR 51.2) fmol/ml) ($p < 0.0001$). In the CHF group, mean $\dot{V}O_2$ was 19.8 (5.9) ml/kg/min. In contrast, the 10 healthy volunteers had a significantly higher $\dot{V}O_2$ (31.8 (6.6) ml/kg/min, $p < 0.00001$). Using the 95th centile of normal population[4] (N-BNP 384 fmol/ml) as the cut off value, we found 14 (16%) CHF patients were in Weber class B or worse, and would have been misdiagnosed as having no CHF. Six patients had $\dot{V}O_2$ values within the potential transplant category ($\dot{V}O_2 < 17$ ml/kg/min) (fig 1).[3] When using half the concentration of N-BNP (192 fmol/ml) as the cut off point, nine (10%) CHF patients were in Weber class B or worse, and would have been misdiagnosed as having no CHF. Two of these patients were within the category for consideration for transplantation (fig 1), and one patient was at that time on the active transplant waiting list and unfortunately died a few months later without receiving a donor heart. When a quarter of the 95th centile (96 fmol/ml) was used as the cut off value, only one CHF patient was in Weber class B (mild functional impairment, fig 1) and none with $\dot{V}O_2$ was < 17 ml/kg/min.

DISCUSSION

The results from this prospective study have shown that resting plasma N-BNP can indeed be used to help exclude the presence of significant cardiac functional impairment, but it is vital that serious consideration should be given in selecting the cut off value, which should be selected based on the BNP or N-BNP assays employed locally and the usual ranges in the normal and CHF population served. Although the NICE guideline[1] in the UK recommends the use of BNP in the diagnostic process for CHF, it avoided recommending what cut off point to adopt for this diagnostic process. If the cut off value were set at the upper limit of normal healthy subjects ($n > 1300$) for our N-BNP assay (95th centile),[4] then 14 of our patient cohort, including patients being considered for cardiac transplant or already on an active transplant waiting list, would have been false negatives, and given a no CHF label. Such omissions would be considered serious, and judicious selection of cut off value is therefore vital. As shown in our study, a practical cut off value may need to be as low as 25% of this value to avoid mislabelling those with significant CHF as being devoid of CHF. Moreover, N-BNP concentrations may be unrepresentatively low in pharmacologically

Abbreviations: BNP, brain natriuretic protein; CHF, chronic heart failure; N-BNP, N-terminal pro-brain natriuretic protein; NICE, National Institute for Clinical Excellence; NYHA, New York Heart Association; $\dot{V}O_2$, peak oxygen consumption

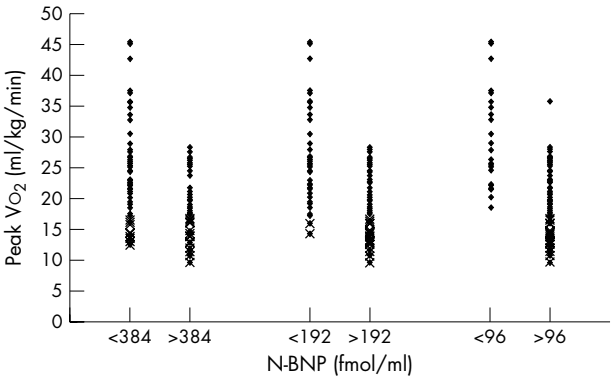

Figure 1 Individual values of $\dot{V}O_2$ in the cohort of participants dichotomised according to cut off values chosen for N-BNP concentrations. Individual points of heart failure patients with severely limited $\dot{V}O_2$ (< 17 ml/kg/min) are indicated with a circle.

treated CHF patients, as diuretic and vasodilator treatment can reduce BNP concentrations.[5] Our study population was recruited from patients on the waiting lists for cardiopulmonary exercise testing in our hospital, and therefore may not be representative of other cohorts of heart failure populations in other hospital departments, or in the community. Nevertheless, in a study of patients with advanced heart failure referred for cardiac transplant assessment, Gardner and colleagues[6] found that the median (IQR) of N-BNP was 1490 (511–3887) pg/ml. This meant that a quarter of the N-BNP values were < 511 pg/ml (60.4 fmol/ml on the Roche Elecys assay system). Our observation with an in house N-BNP assay is therefore very much in keeping with this. It is unknown whether, for the purposes of diagnosing and monitoring heart failure, diuretics may need to be withheld for a short duration before blood is sampled for BNP assay. The period of time for which diuretics should be withheld has yet to be determined.

An alternative approach is to adopt two cut off values as suggested by Mark and colleagues,[2] who recommend BNP concentrations < 100 pg/ml (28.9 fmol/ml) indicating the diagnosis of CHF is unlikely and concentrations > 500 pg/ml (144.3 fmol/ml) indicating it is highly likely. Whether the two cut off values approach is superior to the single cut off approach has yet to be determined.

Previous studies attempting to determine cut off values have variously relied on the area under receiver operating characteristic curves; or the sensitivity/specificity analyses based on comparing BNP/N-BNP concentrations against clinical subjective decision making about the presence or absence of heart failure, or against cut off values of left ventricular ejection fractions (< 40%, 35% or 30%); other echocardiographic means of diagnosing left ventricular dysfunction; or subjective NYHA classification.[5] One problem with such approaches is that if general clinicians (for example, in primary care) repeatedly find patients with severe heart failure to have BNP/N-BNP concentrations below the putative cut off values, confidence in using the assay to rule out CHF may become compromised.

This study is the first to examine cut off values by undertaking a comparison of N-BNP concentrations against an objective, reliable, established method widely employed in assessing patients for cardiac transplantation.[3] The confidence of clinicians in adopting the BNP/N-BNP assay as a reliable means of ruling out CHF must be established upon the basis that none of the patients excluded have serious heart failure. This objective can be confidently achieved if similar studies are conducted using other commercial and in-house assays to determine what would be the respective optimal cut off values for each assay technique, relative to their normal ranges. We strongly believe that BNP and N-BNP are reliable measures of heart failure, but the usual precautions of applying any new medical technology should not be abandoned, and our observation has emphasised the importance of selecting appropriate cut off values.

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APPENDIX

Weber's functional classification of patients according to aerobic exercise capacity:

	$\dot{V}O_2$ (ml/kg/min)
Class A	>20
Class B	16–20
Class C	10–16
Class D	<10

Source: Weber K, Kinasewitz G, Janicki J, Fishman A. Oxygen utilization and ventilation during exercise in patients with chronic congestive heart failure. *Circulation* 1982;**65**:1213–23.

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