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Editorial

Redefining heart failure

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1. Introduction

Heart failure is reaching epidemic proportions as a major cause of morbidity and mortality in developed countries. It accounts for at least 5% of hospital admissions in the UK. The overall annual incidence of heart failure is 0.08% rising from 0.02% at age 45–55 years to 1.2% at age 86 years or over [1]. To provide proven beneficial treatments for patients with heart failure, rapid and accurate diagnosis of heart failure is essential. This may be difficult as many conditions can clinically mimic heart failure. Identifying, classifying and grading heart failure are pre-requisites for selection of appropriate therapeutic interventions and require a robust, practical and effective definition of the condition. Currently used definitions all have significant limitations. A definition of heart failure (or any other condition) should, simply and reproducibly, identify a cohort of patients with a common presentation, spectrum of prognosis and response to a unified treatment algorithm.

We propose a change in approach to the definition of heart failure utilising a combination of symptoms and elevation of circulating B-type natriuretic peptide (BNP). We believe this approach has the potential to overcome many of the limitations of current definitions and goes some way to fulfilling the above criteria.

2. The status quo

To fulfil the current definition of heart failure [2], patients must demonstrate appropriate symptoms or clinical signs (such as fluid retention) in the presence of an underlying abnormality of cardiac structure or function. Echocardiography is considered the most practical tool for the detection of ventricular dysfunction and has been described as the investigation of choice by the National Institute of Clinical Excellence (NICE) in the UK. This definition remains, however, imperfect in that it is unreliable for an important subgroup of patients with heart failure; those with few if any echocardiographic features of left ventricular systolic dysfunction. These patients have been described variously as constituting 13–75% of cases of heart failure [3]. In these patients, abnormalities of diastolic function have been proposed and diagnostic criteria have been set [4], but these too have proven controversial and difficult to implement, and remain poorly validated with clinical experience. Significant numbers of patients appear to have heart failure with neither systolic dysfunction nor defined diastolic abnormalities Based on modern echocardiographic criteria, these patients fail to fit into a recognised categories of cardiac structural or functional abnormalities required to diagnose heart failure. In this regard at least, the currently accepted and promoted definitions of heart failure are inadequate.

3. The use of BNP

The use of BNP may resolve some of these difficulties. It is a cardiac neurohormone involved in the regulation of renal and cardiovascular function [5]. It is stored and secreted from membrane granules in the cardiac ventricles in response to ventricular volume expansion, pressure

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overload and resultant increased wall tension [6,7]. It can be measured in the laboratory or at the bedside and unlike echocardiography does not require specialised technical skills and equipment to be brought to the patient's bedside or the doctor's office.

Plasma concentrations of BNP are consistently increased in patients with symptoms of heart failure and left ventricular systolic dysfunction. Furthermore, BNP is an excellent hormonal marker of ventricular diastolic dysfunction using current parameters [8]. As a result, BNP levels may be able to identify patients previously excluded in a definition of heart failure based purely on echocardiographic abnormalities.

The Breathing Not Properly (BNP) Multinational Study compared plasma BNP to initial clinical judgment as to whether heart failure was present [9]. Among patients judged on clinical grounds to have 80% probability of CHF, a plasma BNP > 100 pg/mL was more sensitive (90% versus 49%) but less specific (73% versus 96%) than clinical judgment. Adding BNP to clinical judgment increased diagnostic accuracy (heart failure versus no heart failure) from 74% to 81%. In those participants with an intermediate (21% to 79%) probability of heart failure, BNP at a cut-off of 100 pg/mL correctly classified 74% of the cases. Plasma BNP correctly diagnosed 90% of the patients originally thought to have less than a 21% clinical probability of heart failure.

The value of rapid bedside measurement of plasma BNP for distinguishing between heart failure and a pulmonary cause of dyspnoea was evaluated in a seven-centre, multinational study of 1586 patients presenting to the emergency room with acute dyspnoea [10]. Plasma concentrations of BNP were higher in patients with clinically diagnosed heart failure compared to those without heart failure (mean 675 versus 110 pg/mL). A plasma BNP > 100 pg/mL diagnosed heart failure with a sensitivity, specificity and predictive accuracy of 90%, 76% and 83%, respectively. Lower values were associated with more accurate negative predictive values (for a value of 50 pg/mL, the negative predictive value was 96%). The predictive accuracy of plasma BNP for heart failure was equivalent to or better than other parameters such as cardiomegaly on chest X-ray, a history of heart failure or rales on physical examination. It was also shown that plasma concentration of BNP correlated with NYHA functional class, ranging from a mean of 244 to a mean of 817 pg/mL for classes I to IV.

Other studies have also found high positive and negative predictive values for plasma BNP estimation in the diagnosis of CHF [11–13]. Elevation of plasma BNP can establish the presence of heart failure due to diastolic dysfunction with similar accuracy to that due to systolic dysfunction [12,14,15]. Interestingly, the level of BNP did not differentiate between systolic and diastolic dysfunction.

Other characteristics of BNP support its use within a definition of heart failure. Plasma BNP, measured at presentation, provides prognostic information in patients with heart failure, including those receiving therapy with a beta-blocker and an ACE inhibitor [16,17] and those with asymptomatic or minimally symptomatic left ventricular dysfunction [18–21]. A high level of plasma BNP is an independent predictor of mortality in these patients. Sustained high plasma levels of BNP after additional standard treatment are independent risk factors for mortality in patients with CHF despite improvements in left ventricular ejection fraction and symptoms [20].

BNP is dynamically related to the severity of heart failure. Plasma concentrations of BNP fall after effective pharmacological therapy [16,19] suggesting that measurement of plasma BNP may be helpful in titrating therapy. This issue was addressed in a trial of 69 patients with impaired left ventricular function and clinical heart failure who were randomly assigned to medical treatment guided by plasma BNP concentrations (goal < 200 pmol/L) or standard clinical assessment [22]. At 6 months, a first cardiovascular event occurred less frequently in those undergoing BNP guided therapy (27% versus 53% for clinical assessment).

Overall, these studies support the argument that the diagnosis of heart failure might be better separated from echocardiographic parameters and re-defined in terms of symptoms and elevated BNP. Our proposal parallels the recent (albeit controversial) advance in the definition of myocardial infarction (MI) encapsulated as typical chest pain plus elevated troponins [23].

4. Could this work?

What difficulties might occur? Many treatments for HF are based on evidence gleaned from trials that included only or predominantly cases evaluated by echocardiography. ACE inhibitor and beta-blocker treatments have only been adequately evaluated in heart failure due to systolic dysfunction. Our definition does not exclude subsequent evaluation by echocardiography to determine which interventions are likely to be effective. Other trials in the past have (and increasingly in the future will) included patients with clinical heart failure with varying (including normal) echo parameters. This opens the door for trials of therapies based on BNP where subject definition and recruitment would be eased by the simplicity of the inclusion criteria. For patients post-MI, ACE inhibitor and beta-blocker are appropriate independent of LV function, and spironolactone and diuretics are generally initiated based on clinical rather than echocardiographic parameters.

A temporary difficulty is that currently BNP assays are not standardised. However, experience shows that this can be readily overcome and ranges for BNP (or N terminal BNP) identified just as with other biochemical measurements.

For epidemiological, practical and sound clinical reasons, we therefore propose a new definition of heart failure. Heart failure is present in patients with typical symptoms

(breathlessness, fatigue, fluid retention) and elevated levels of BNP.

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