N-Terminal ProBNP: Marker of Systolic Dysfunction or Nonspecific Indicator of Cardiac Disease?

Torbjørn Omland
Department of Medicine, Akershus University Hospital, Nordbyhagen-Oslo, Norway

The clinical diagnosis of heart failure may represent a considerable challenge, particularly in the obese, in women and in the elderly [1]. Because contemporary heart failure therapy has been shown to significantly reduce mortality and the number of hospital readmissions, an early and correct diagnosis is crucial. The cost and potential side effects associated with heart failure therapy also means that overtreatment should best be avoided.

The clinical syndrome of chronic congestive heart failure is often the end stage of progressive left ventricular dysfunction and is commonly preceded by an asymptomatic or oligosymptomatic latent phase. Congestive heart failure is frequently caused by systolic dysfunction of the left ventricle, but a considerable proportion of patients do have preserved systolic function [2]. Echocardiography is routinely performed by cardiologists to establish the diagnosis of impaired left ventricular systolic function, but this method requires expensive equipment and skilled operators and is not always readily available. During the past few years, B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone, N-terminal proBNP (NT-proBNP) have emerged as promising markers of ventricular dysfunction, and biochemical tests for rapid measurement of these substances have been developed. A point-of-care test for rapid analysis of BNP was first introduced in the year 2000. Very recently, fully automated analytic systems for the determination of BNP and NT-proBNP on large hospital platforms have also become commercially available.

BNP was first identified in porcine brain in 1988 [3], but was subsequently found to be present in ventricular myocardium, which is now known to be the main source of circulating BNP [4]. The main secretory stimulus for BNP (and NT-proBNP) appears to be stretch of cardiomyocytes rather than transmural pressure load [5]; circulating levels of BNP and NT-proBNP are increased in conditions characterized by volume overload and correlate with indices of hemodynamic status and ventricular function [6–8]. Although these peptides share many properties, some differences may have clinical implications. BNP is the biologically active hormone, whereas NT-proBNP appears to be biologically inactive. The in vivo half-life of BNP is approximately 20 min, whereas the half-life of NT-proBNP has been estimated to be approximately 60–120 min [9]. Accordingly, BNP levels may change more rapidly than those of NT-proBNP following therapeutic interventions which affect cardiac filling [10]. Conversely, NT-proBNP may more accurately reflect the average, long-term hemodynamic status of the patient.

Although both BNP and NT-proBNP have been demonstrated to be stable in full blood at room temperature for at least 24 h, the in vitro stability of NT-proBNP in serum or plasma appears to be superior to that of BNP [11]. BNP is cleared from the circulation via binding to specific
clearance receptors as well as via degradation by the zinc metalloprotease, neutral endopeptidase. The clearance mechanisms for NT-proBNP are less well defined, but renal elimination may play a role. It has been argued therefore that the decline in glomerular filtration with age is responsible, at least in part, for the age-dependent increase in NT-proBNP [12, 13]. However, circulating levels of BNP and NT-proBNP are both to some extent influenced by renal function, and comparative data on this topic are sparse.

In this issue of Heart Drug, Gustafsson et al. [14] from Denmark report the results of a study evaluating the utility of NT-proBNP as an indicator of systolic dysfunction of the left ventricle, defined as an ejection fraction less than 40%, in a large group of patients referred from general practice because of symptoms of heart failure. NT-proBNP was found to have a very high negative predictive value, i.e. a normal NT-proBNP value effectively ruled out the presence of systolic dysfunction. The area under the receiver operating characteristics (ROC) curve, an index of overall diagnostic accuracy, was 0.87, meaning that a patient with systolic dysfunction will have a higher NT-proBNP value than a patient with preserved systolic function 87 out of 100 times. The authors appropriately conclude that in this study population, measurement of NT-proBNP proved useful for ruling out left ventricular systolic dysfunction.

The results reported by Gustafsson et al. [14] are quite similar to those previously reported by Cowie et al. [15] for BNP, but clearly superior to results obtained in two other recent studies evaluating the diagnostic value of BNP in primary care patients [16, 17]. The differences in diagnostic accuracy are not surprising, however, given the characteristics of the study populations. The studies of Gustafsson et al. [14] and Cowie et al. [15] included mainly untreated patients with a low prevalence of systolic dysfunction (9%) [14] or heart failure (27%) [15], whereas the two other studies included patients on treatment with a high prevalence (60%) of systolic dysfunction [16] and long-term survivors after myocardial infarction [17]. Consequently, the diagnostic accuracies of NT-proBNP and BNP depend on whether patients are receiving treatment for heart failure or not, as well as on the spectrum of disease in the population investigated.

A very high negative predictive value (99–100%) was found for NT-proBNP in the study of Gustafsson et al. [14], regardless of whether the recommended European (gender-specific) or US (age-specific) discrimination limits were used. Conversely, modest positive predictive values (15–18%) were observed, i.e. a large proportion of patients with elevated NT-proBNP did not have systolic dysfunction. When interpreting these results, one should keep in mind that predictive values depend critically on the prevalence or a priori probability of disease. In the study of Gustafsson et al. [14], the a priori probability of systolic dysfunction was 9%. The corresponding a posteriori probability (after NT-proBNP was measured) was 15–18%. Conversely, the a priori probability of preserved systolic function was 91%; i.e. even before NT-proBNP was measured, the likelihood of preserved systolic function was very high.

Do the recommended discrimination limits for NT-proBNP make clinical sense? If the goal is to rule out systolic dysfunction, they do seem appropriate. However, the high false-positive rate means that they are less useful if the objective is to accurately identify patients with systolic dysfunction. Even after NT-proBNP measurement, 5–6 patients with elevated levels would have to be referred to echocardiographic investigation to detect 1 patient with systolic dysfunction. Although this is a significant reduction from the a priori requirement of 10 echocardiograms to detect 1 case, the question remains whether NT-proBNP really provides diagnostic information superior to readily obtainable data from the medical history (e.g. history of myocardial infarction) and the electrocardiogram (e.g. Q waves) of the patient. For instance, in another study of 466 patients referred for echocardiography because of symptoms of heart failure, a 5-point clinical score derived from elements of the medical history, the electrocardiogram and the chest radiograph was of similar diagnostic accuracy to BNP [18]. Documentation of diagnostic information above and beyond that obtained from the medical history, physical examination and electrocardiogram is a requirement that needs to be fulfilled before NT-proBNP measurements can be generally recommended as a screening test for systolic dysfunction.

What is the reason for the high false-positive rate? Small to medium rises in NT-proBNP levels are seen not only in systolic dysfunction, but in a variety of other cardiac conditions, including diastolic dysfunction of the left ventricle, left ventricular hypertrophy, pulmonary hypertension, valvular heart disease and arrhythmias such as atrial fibrillation [8, 12, 19]. Accordingly, in the study by Gustafsson et al. [14], echocardiography revealed cardiac abnormalities other than systolic dysfunction in 78% of patients with NT-proBNP elevation. In addition, NT-proBNP levels are influenced by the age, gender and renal function of the patient, and these factors may also contribute to the misclassification observed [8, 12].

Clinical Significance of N-Terminal proBNP

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What is the take home message from the study by Gustafsson et al. [14]? Although predominantly derived from the ventricular myocardium, mild to moderate elevation of NT-proBNP is not specific for left ventricular systolic dysfunction. NT-proBNP should rather be regarded as a sensitive marker of a wide range of cardiac abnormalities. Consequently, in the absence of renal impairment and advanced age, mild to moderate elevation of NT-proBNP indicates some sort of cardiac disease and should in most cases prompt further cardiac investigations, including echocardiography. Low levels of NT-proBNP effectively rule out systolic dysfunction and probably also most other cardiac structural abnormalities, whereas very high levels of NT-proBNP will identify patients with heart failure, systolic or diastolic, with a high degree of certainty. When used in the appropriate clinical setting and interpreted with caution, NT-proBNP measurements should provide very useful diagnostic information for the clinician.

References