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EDITORIAL COMMENT

Heart Failure in the Emergency Department*

Is B-Type Natriuretic Peptide a Better Prognostic Indicator Than Clinical Assessment?

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The clinical diagnosis of heart failure (HF) may be difficult (1), and may pose a particular challenge in patients presenting with acute shortness of breath (SOB) in the emergency department (ED). Elements of clinical history and physical examination as well as information obtained from the electrocardiogram and chest radiograph, may provide valuable clues as to whether HF is the cause of symptoms in the acutely dyspneic patients (2). Additional diagnostic tests, including echocardiography, may be required to obtain a more definite diagnosis. The ED, however, is not an optimal setting for echocardiography. Many patients are very ill and may have difficulties in lying still. A considerable proportion of dyspneic patients may be obese or have chronic obstructive pulmonary disease; these factors tend to reduce image quality. Moreover, echocardiography may not be generally available on a 24-h basis in all hospitals.

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B-type natriuretic peptide (BNP) was first identified in the porcine brain in 1988, but was subsequently found to be present in ventricular myocardium, the main source of circulating BNP (3). The main secretory stimulus for BNP appears to be a stretch of cardiomyocytes rather than transmural pressure load (4), and circulating levels of BNP are increased in conditions characterized by volume overload and correlate with indices of hemodynamic status and ventricular function (3,5). During the past few years, BNP and the N-terminal fragment (NT-proBNP) of its prohormone (proBNP), have emerged as reliable markers of HF, 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. More recently, fully automated analytic systems for the determination of BNP and NT-proBNP on large hospital platforms have also become commercially available.

By 2004, the best documented and most widely used clinical application of BNP measurement is most likely for the emergency diagnosis of HF in patients presenting with acute dyspnea. The first study suggesting that BNP measurement could prove useful in this setting was published in 1994 (6), but it was not until after the publication of the Breathing Not Properly Multinational Study—a multicenter, diagnostic test evaluation study which included 1,586 acutely dyspneic patients—that BNP measurements entered the clinical arena with full power. This seminal study convincingly documented that measurement of BNP on admission provides valuable diagnostic information in this patient group (7), complementary and superior to clinical evaluation (8). These results were recently extended by the B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study, which in a prospective, non-blinded, randomized fashion evaluated the effect of rapid point-of-care BNP testing in the ED on time to discharge and total cost of treatment. Despite a relatively modest sample size of 452 patients, rapid measurement of BNP in the ED was associated with shorter time to discharge, which translated into reduced total cost of treatment (9). This effect could conceivably have been influenced by the open design of the trial.

In this issue of the *Journal*, Maisel et al. (10) present the primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). This 10-center study, which included 464 patients, examined the relation among BNP levels, ED physicians, patient disposition, and outcome at 30 and 90 days in patients presenting with SOB and elevated BNP levels (i.e., >100 pg/ml). Results of this well-conceived, prospective, non-randomized, observational study extend and complement the results of the Breathing Not Properly Multinational Study and the BASEL study, and provide important, new, and provocative data with regard to the prognostic value of BNP and clinical assessment in acutely dyspneic patients with HF.

The hypothesis of the REDHOT study was that BNP would provide prognostic information concerning mortality and HF development independent of physician decision making in the ED. Based on studies assessing the prognostic value of BNP in acute coronary syndromes (11,12) and chronic HF (13), as well as on previous prognostic data from Maisel et al. in acutely dyspneic patients (14), an independent association between BNP levels and outcome would be expected. The REDHOT results confirm that BNP levels obtained on admission provide independent prognostic information in the ED setting. The overall prognostic value of BNP, as assessed by the area under the receiver-operating characteristics (ROC) curve (i.e., 0.67), is not very impressive, but the modest value may partly be explained by the exclusion of patients with normal (i.e., ≤100 pg/ml) values from the analysis. Moreover, it would be unreasonable to

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expect that the area under the ROC curve should be equally large for BNP as a prognostic marker as for BNP as a diagnostic marker (e.g., 0.91 in the Breathing Not Properly Multinational Study). Events in the future are by nature more unpredictable than diagnoses of the moment.

The more novel, and somewhat provocative, findings of the REDHOT study are related to the poor predictive value of the ED physician assessment and the lack of connection among perceived disease severity, disposition, and BNP levels. Although 68% of the 464 patients were designated for hospitalization upon initial evaluation, 90% were eventually hospitalized. Rather surprisingly, BNP levels did not differ between patients who were discharged and those admitted, and no correlation between BNP levels and perceived disease severity, as assessed by the ED physician on admission, was evident. Whereas BNP levels were predictive of mortality, neither the ED physician's classification of perceived disease severity or the intention to admit or discharge was associated with outcome at 90 days. The lack of correlation between BNP levels and New York Heart Association functional class is in contrast to findings in most previous studies, including the Breathing Not Properly Multinational Study. It is not intuitively clear why the results of these two studies differ in this respect, but the discrepancy may be related to study design differences. Whereas assessment of disease severity in the REDHOT study, in most cases, was made early by ED doctors or internists, in the Breathing Not Properly Multinational Study the assessment was made retrospectively by cardiologists who had available medical records, hospital course, and test results, including echocardiograms. Moreover, because of a lag in the upregulation of BNP synthesis following acute decompensation, in some patients circulating levels of BNP may be more closely related to the patient's chronic functional class than to perceived functional class during the acute exacerbation. In contrast, the prognosis may be more closely associated with the patient's chronic functional state than to actual state on admission.

Although BNP measurements have already been implemented in a large number of hospitals in the U.S. and in Europe, the role of BNP determination in the diagnosis and management of HF remains controversial. Proponents of BNP testing have advocated its use for identifying subjects with left ventricular dysfunction in the population and diagnosing HF in general practice, to distinguish responders and non-responders to different therapeutic regimens, and to identify patients who require intensification of therapy (15). Opponents have claimed that BNP levels often are mildly elevated in elderly subjects without HF and non-diagnostic in well-treated patients with HF (16). Moreover, they claim that BNP measurements fail to provide additional information to that obtained by routine clinical assessment, and that BNP results do not have meaningful implications for the initiation and dose titration of drugs proven to be effective for the treatment of chronic HF (16). Clearly, when interpreting BNP results it is crucial to keep in mind that BNP is a non-specific marker of cardiac disease. Mild to moderate elevation of BNP levels is not specific for HF, but may occur in a variety of conditions including left ventricular hypertrophy, cardiac arrhythmias, and renal impairment. Moreover, the utility of BNP will depend on the clinical setting. Measurements of BNP may be far more accurate in the diagnosis of decompensated HF in the ED setting than in the diagnosis of systolic dysfunction in adequately treated patients with chronic HF. Conversely, clinical assessment may be particularly challenging in the ED setting because the clinical picture may change dramatically within a short period of time.

Although a well-designed and well-conducted clinical trial may lead to rejection or acceptance of the hypothesis tested, most study results are not definitive but raise important new questions that need to be addressed in future trials. The REDHOT study results have potentially important implications for clinical practice in the ED. The findings, however, need to be confirmed by larger trials and should not be generalized to settings other than the ED.

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