B-type natriuretic peptide: where are we?

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Heart failure is often the final stage of various cardiovascular diseases, a common condition among the elderly and responsible for many deaths. It is the leading cause of hospital admissions in industrialized countries (being the cause of about 900,000 admissions and 250,000 deaths among over 65-year-old people in the United States each year). Almost 50% of patients discharged with a diagnosis of heart failure are readmitted to hospital within 6 months (but approximately 30% within 30 days) and the 1-year mortality rate of these patients is 20%. That this is a real epidemic is confirmed by the exponential increase in discharge diagnoses of heart failure, which have escalated in the United States from 377,000 in 1979 to 999,000 in 2000, with an increase of 165% and costs exceeding 24 billion dollars each year.

In this context, the recognition of the value of B-type natriuretic peptide (BNP) as a marker for the diagnosis, prognosis and management of patients with heart failure has been one of the major gains for clinicians dealing with the disease and for the patients affected. The paper by Coppola et al. published in this issue of the Journal, emphasizes all these aspects although some are highlighted with particular strength.

One such aspect is the diagnostic value of BNP in Accident and Emergency (A&E) departments because of the relative ease and speed with which this peptide can be assayed. Many clinical studies have demonstrated the usefulness of BNP assays in reaching an etiological diagnosis of acute dyspnea in first aid and their high negative predictive value. The study by Coppola et al. confirms that BNP is an accurate and sensitive indicator of cardiac dysfunction and that its levels correlate with the severity of the clinical picture. Measuring the plasma levels of BNP can facilitate a correct diagnosis of heart failure. In fact, these levels correlate with end-diastolic pressure, left ventricular wall stress and, in consequence, the functional classification of congestive heart failure. The multinational Breathing Not Properly study evaluated 1586 patients who presented at an A&E department with acute dyspnea and showed that a BNP > 100 pg/mL had a sensitivity of 90% and a specificity of 70% in differentiating dyspnea of cardiac origin from that of other causes. The diagnostic accuracy rose from 74 to 81% when BNP levels were added to clinical criteria. The diagnostic power of BNP was greater than that of either the Framingham criteria or the National Health and Nutrition Examination Survey (NHANES) criteria, which are two of the most widely used sets of diagnostic criteria for heart failure. The study by Coppola et al. does, however, highlight some of the difficulties in using BNP for diagnostic purposes, particularly when concomitant diseases are present. First of all, it is important to remember that the diagnostic cut-off may need to be increased when renal function is impaired, for example from > 100 to > 200 pg/mL in patients with a glomerular filtration rate < 60 mL/min.

Another diagnostically relevant aspect is that BNP, as an expression of wall stress, can also identify patients with heart failure with preserved systolic function. The BNP assay does not, therefore, discriminate patients with systolic dysfunction from those with diastolic dysfunction, although for the same NYHA functional class those with altered systolic function seem to have higher BNP levels.

In their study Coppola et al. highlight that patients at discharge and 30 days postdischarge have significantly lower BNP levels, reflecting the efficacy of treatment. Indeed, one of the developing fields of application of BNP assays is that of patients’ management and optimization of treatment. In a study by Mueller et al., 452 patients who presented at the A&E department with acute breathlessness were randomized into two groups. The diagnostic strategy used for one group included a single measurement of BNP, whereas the standard diagnostic strategy – not including BNP assays – was used in the other group. Knowing the BNP level in the A&E department reduced the number of days spent in hospital (8 vs 11 days, p = 0.001), the percentage of admissions (75 vs 85%, p = 0.008), the frequency of admissions to intensive care (15 vs 24%, p = 0.01) and costs (5410 vs 7264 dollars, p = 0.006).
Although there are no controlled clinical trials on outpatient treatment guided by BNP levels, one prospective clinical study of 69 patients with symptomatic heart failure (NYHA class II-IV; ejection fraction < 40%) provided encouraging support to the idea that BNP levels could indeed be used to guide such a treatment. Patients discharged from hospital or referred to cardiology clinics were randomized into two groups: one in which treatment was guided by BNP (BNP group) and the other in which treatment was guided by traditional clinical criteria (control group). The aim in the BNP group was to reach values < 70 pg/mL and the target in the control group was an end-point standardized by a scoring system. If the patient did not reach the target, drug treatment was increased in accordance with specific protocols and the patient was reassessed again after 2 weeks. The BNP levels in the BNP group decreased by a mean of 273.5 pg/mL from the baseline values, whereas those in the control group increased by 10.4 pg/mL. Most importantly, after 9.5 months of follow-up there had been more events (cardiovascular deaths, hospital admissions for any cardiac event and exacerbations of heart failure in the community) in the control group than in the BNP group (54 vs 19 events, p = 0.02)\textsuperscript{11}. The improved outcome in the BNP group was attributed to the statistically significant higher doses of ACE-inhibitors and diuretics and greater use of spironolactone in this group. This study suggests that BNP assays could play an active role in optimizing pharmacological treatment in heart failure.

Finally, the values of BNP at discharge were correlated with the patient’s long-term prognosis. In a pilot study, Cheng et al.\textsuperscript{12} found that a high level of BNP at discharge was a predictor of death or readmission at 30 days. In a population of patients admitted to a cardiology ward, Logeart et al.\textsuperscript{13} showed that the patients with BNP > 350 pg/mL at discharge had a higher risk of death or readmission at 120 days. Similar results were obtained by Verdiani et al.\textsuperscript{14} in an older population with more comorbid conditions admitted to a general medicine ward. In fact, patients with a discharge BNP > 696 pg/mL had an independent 15-fold higher risk of death or rehospitalization at 30 days than did patients with lower values.

In conclusion, BNP assays are becoming increasingly important in clinical practice, as confirmed by the most recent international guidelines\textsuperscript{15-17} which now endow BNP a central role in the diagnosis of heart failure. Of course there is still much to be done, particularly regarding the prognostic use of BNP and its role in guiding optimization of treatment and the management of patients with heart failure.

### References