

# The Circulating NTproBNP Level, a New Biomarker for the Diagnosis of Heart Failure in Patients With Acute Shortness of Breath

Antoni Bayés-Genís

Unidad de Insuficiencia Cardíaca, Servicio de Cardiología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain.

Heart failure, which is now the main cause of in-hospital death among patients over 65 years of age, is the only cardiovascular disease for which the rates of incidence and prevalence are increasing.<sup>1</sup> In addition, it is the most costly cardiovascular disease in the industrialized world. Despite recent therapeutic advances, the prognosis of heart failure is poor, and patients suffer multiple recurrences and re-admissions to hospital. The ability to determine levels of natriuretic peptides—biological indicators of the degree of stress to which the myocardium is subject—is a step forward in the management of these patients.

Currently, the diagnosis of acute heart failure is based on patient clinical history, a physical examination, and the results of complementary tests (mainly echocardiography). However, some 25%-50% of patients that seek help at the emergency room for decompensated heart failure are initially diagnosed incorrectly; unfortunately, echocardiography is not always available in emergency rooms in Spain. New diagnostic tests are therefore required that help to confirm ventricular dysfunction in patients with dyspnea of uncertain origin. The rapid, correct diagnosis of heart failure allows the immediate start of intensive therapy, improving patient prognosis and reducing costs.

As well as modulating the neurohormonal response seen in heart failure, the B-type natriuretic peptides could be diagnostically and prognostically useful biomarkers.<sup>2</sup> The initial studies in this area investigated the usefulness of B-type natriuretic peptide (BNP), but more recent work has shown that the aminoterminal

fragment of BNP (NTproBNP) is also a good diagnostic and prognostic indicator of heart failure. An automated immunoanalytical test for NTproBNP that takes less than 20 min to complete is now available, allowing levels of this marker to be determined in patients with acute dyspnea in the emergency room setting.

B-type natriuretic peptides are initially synthesized as pre-propeptides composed of 134 amino acids. These are turned into proBNP-108, a precursor molecule stored in secretory granules in the myocytes. After its release, proBNP-108 is cleaved by the protease furin into its N-terminal fragment (NTproBNP; a 76 amino acid peptide) and BNP (the biologically active molecule). In humans, BNP and NTproBNP are mainly found in the left ventricle, but they are also detectable in atrial and right ventricular tissue.<sup>3</sup> Animal studies have shown that myocardial induction and the secretion of B-type peptides is rapid in situations of myocardial stress, with detectable values in the blood just a few minutes after stimulus.

Although they are derived from a common precursor, BNP and NTproBNP are different in many respects. The half life of BNP is just 18 min. As a biologically active molecule it is eliminated from the bloodstream by specific receptors; it is also degraded in peripheral blood by neutral endopeptidases. In addition, BNP values are rather unstable in vitro and decrease significantly in the 24 h following blood extraction. Finally, if this blood is stored in glass tubes, the BNP level falls due to the activation of the kallikrein system. NTproBNP, however, is a biologically inert molecule and as such is not actively eliminated by any special system. Its half life is some 60-120 min and in humans it is at least partially cleared by the kidneys. NTproBNP is more stable than BNP; little variation is seen in its plasma concentration 72 h after blood extraction, and this blood can be stored in glass tubes with no problem.

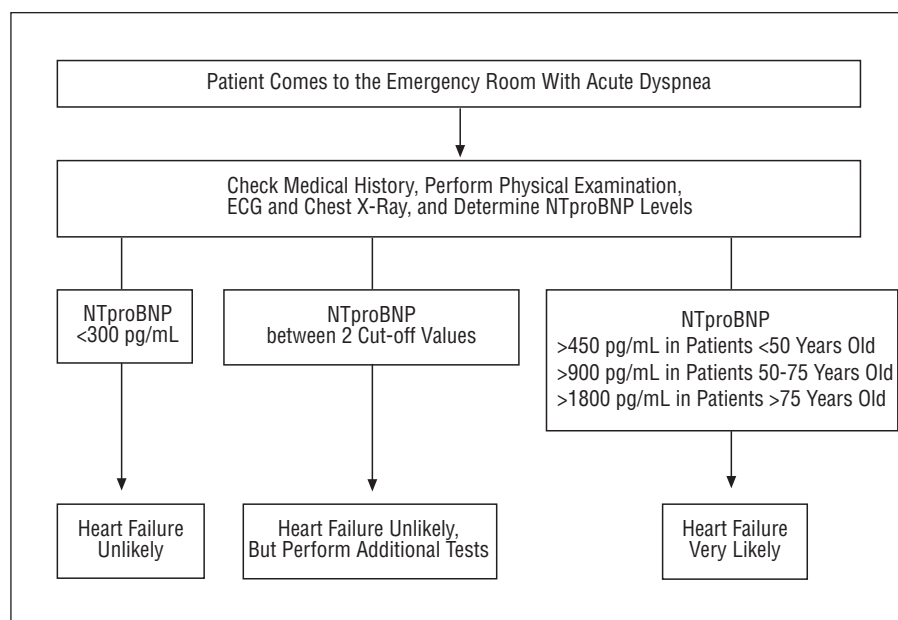
At present, the determination of NTproBNP levels is of diagnostic use mainly in patients with dyspnea in the emergency room setting. The first study that investigated the use of NTproBNP levels as a marker of heart failure was undertaken by the Cardioen-

SEE ARTICLE ON PAGES 1155-61

Conflicts of interest: Dr Bayés-Genís has a research contract with Roche Diagnostics.

Correspondence: Dr. A. Bayés-Genís.  
Unidad de Insuficiencia Cardíaca. Servicio de Cardiología. Hospital de la Santa Creu i de Sant Pau.  
Padre Claret, 167. 08025 Barcelona. España.  
E-mail: abayesgenis@santpau.es

**Figure.** Proposed algorithm for the diagnosis of acute heart failure (including the determination of NTproBNP levels) in patients coming to the emergency room with acute dyspnea. A similar algorithm might be used for BNP and its respective cut-off values.



doctrine Research Group led by Mark Richards.<sup>4</sup> In a population of 205 consecutive patients it was shown that NTproBNP is as useful as BNP, which at the time was the standard biomarker for diagnosing acute heart failure in patients with dyspnea. Later, our group confirmed that the NTproBNP level was significantly higher in patients with decompensated heart failure, and showed this marker to be useful in the identification of “masked” heart failure, defined as left ventricular dysfunction and concomitant lung disease.<sup>5</sup> Multivariate analysis showed that, with respect to defining the cause of dyspnea, knowledge of the NTproBNP level improved diagnostic precision better than all other types of information, including that gleaned from medical histories, physical examinations and blood analyses. It was then that the need to establish 2 cut-off points was understood: one to rule out and one to rule in a diagnosis of heart failure. These 2 values are required since, in the emergency room, it is just as important to arrive at a rapid diagnosis of heart failure as to determine the absence of cardiac decompensation. More recently, the results of the PRIDE study, which involved 600 patients, showed that NTproBNP is a useful marker for both identifying and excluding heart failure in the emergency room setting.<sup>6</sup> The study by Pascual Figal et al.<sup>7</sup> in this issue of the *REVISTA ESPAÑOLA DE CARDIOLOGÍA* analyses the value of determining the NTproBNP level in patients arriving at the emergency room with acute dyspnea of unknown origin. Previous studies differed from this in that their main criterion for inclusion was the presence of acute dyspnea, independent of whether the attending physician came to an uncertain diagnosis of heart failure. Patients with such a diagnosis are probably those most likely

to benefit from the measurement of their circulating NTproBNP concentration.

The work of Pascual Figal et al.<sup>7</sup> and earlier studies coincide in the usefulness of determining NTproBNP levels in patients in the emergency room, but the small numbers involved make it difficult to accurately establish any cut-off values. The ICON project, which involved 1256 patients with acute dyspnea in Europe, the USA, Australia, and New Zealand, has tried to remedy this.<sup>8</sup> This large study established a rule out level for heart failure of 300 pg/mL (negative predictive power 98%), independent of patient age or sex—a figure that has been incorporated into the heart failure clinical guides of the European Society of Cardiology.<sup>9</sup> To establish the rule in value, sex and age were taken into account since both of these factors can modify the circulating levels of some neurohormones. In this case, sex was found not to significantly affect the results, so the rule in value is based solely on age: 450 pg/mL for patients <50 years of age (sensitivity 97%, specificity 93%), 900 pg/mL for those 50-75 years of age (sensitivity 90%, specificity 82%), and 1800 pg/mL for those aged over 75 (sensitivity 85%, specificity 73%). It should be noted that the cut-off value doubles from one age group to the next. Using these results, Figure 1 shows an algorithm proposed for diagnosing acute heart failure.

Circulating NTproBNP values can be modified by circumstances other than heart failure, and should be taken into account when making a differential diagnosis. For example, high NTproBNP levels can be found in patients with acute coronary syndrome, pulmonary thromboembolism, atrial arrhythmias, and lung disease, etc. Currently, the effects of obesity and kidney dysfunction on circulating NTproBNP levels are under

investigation. Via mechanisms that are still unclear, obesity tends to reduce the circulating concentration, although it is unknown whether this is true in patients suffering from acute decompensation. With respect to kidney function, a recent study from the Maastricht group has shown that renal excretion of NTproBNP is normal even when the glomerular filtrate is reduced. Thus, even though kidney dysfunction is often seen in patients with acute heart failure, it probably does not substantially modify circulating NTproBNP levels.

The work of Pascual Figal et al<sup>7</sup> also shows that NT-proBNP levels can provide prognostic information during hospitalization. In this work, eight patients died after admission (6 of cardiac causes and 2 of non-cardiac causes); NTproBNP values of  $\geq 5500$  pg/mL in the emergency room identified these patients with 77% precision. Studies with more patients are clearly required to confirm this result, but it would appear that extreme NTproBNP levels at the time of admission can identify those patients most risk at risk. Some studies have analyzed the prognostic value of NT-proBNP in admitted patients after their discharge and during follow-up. Richards et al<sup>10</sup> found that the plasma concentrations of BNP and NTproBNP during hospital stay were the most important markers of risk of death during a 2 year follow-up period. Similarly, O'Brien et al,<sup>11</sup> whose study involved 34 patients, reported that the pre-discharge NTproBNP level was an independent predictor of cardiovascular death or re-admission for heart failure. Bettencourt et al<sup>12</sup> analyzed the percentage reduction in NTproBNP levels during hospitalization and found that patients who showed a reduction of  $>30\%$  had a better prognosis than those with reductions of  $<30\%$ . In this study it was also noted that increasing NTproBNP levels were a sign of poor prognosis; mortality was close to 80% at 6 months in these patients.

In summary, NTproBNP is a useful biomarker for both the exclusion and diagnosis of acute heart failure in patients with acute dyspnea in the emergency room. Although some authors advocate determination of NT-proBNP levels in all patients with dyspnea, this marker is at its most useful in patients with acute dyspnea of uncertain origin. The plasma concentration of NT-proBNP should be interpreted within the clinical context of the patient and as a function of age. The prog-

nostic value of determining the NTproBNP level is currently being analyzed in several multicenter studies; the preliminary results indicate that it could also provide information to physicians that will help in making therapeutic decisions.

## REFERENCES

1. Heart disease and stroke statistics: 2003 update. Dallas: American Heart Association; 2002.
2. Roig E. Utilidad clínica de los marcadores neurohormonales en la insuficiencia cardíaca. *Rev Esp Cardiol*. 2004;57:347-56.
3. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: molecular aspects. *Eur J Heart Fail*. 2004;6:261-8.
4. Lainchbury JG, Campbell E, Frampton CM, Yandle TG, Nicholls MG, Richards AM. Brain natriuretic peptide and N-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. *J Am Coll Cardiol*. 2003;42:728-35.
5. Bayés-Genís A, Santalo-Bel M, Zapico-Muniz E, López L, Cotes C, Bellido J, et al. N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. *Eur J Heart Fail*. 2004;6:301-8.
6. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal pro-BNP investigation of dyspnea in the emergency department (PRIDE) Study. *Am J Cardiol*. 2005;95:948-54.
7. Pascual-Figal DA, Cerdán-Sánchez MC, Noguera-Velasco JA, Casas-Pina T, Muñoz-Gimeno L, García-Rodríguez R, et al. Utilidad del NTproBNP en el manejo urgente del paciente con disnea severa y diagnóstico dudoso de insuficiencia cardíaca. *Rev Esp Cardiol*. 2005;58:1155-61.
8. Januzzi JL, van Kimmenade RJJ, Lainchbury J, Bayes-Genís A, Pinto Y, Richards AM. Value of NT-proBNP for the evaluation of acute CHF: a multi-center, international pooled analysis of 1256 subjects: primary results from the international collaborative of NT-proBNP (ICON) Study. *J Am Coll Cardiol*. 2005;45 Supl A:140.
9. Nieminen MS, Böhm M, Cowie MR, Drexler H, Filippatos GS, Jondeau G, et al. Guías de Práctica Clínica sobre el diagnóstico y tratamiento de la insuficiencia cardíaca aguda. Abridged version. *Rev Esp Cardiol*. 2005;58:389-429.
10. Richards M, Troughton RW. NTproBNP in heart failure: therapy decisions and monitoring. *Eur J Heart Fail*. 2004;6:351-4.
11. O'Brien R, Squire IB, Demme B, Davies JE, Ng LL. Pre-discharge, but not admission, levels of NTproBNP predict adverse prognosis following acute LVF. *Eur J Heart Fail*. 2003;5:499-506.
12. Bettencourt P, Azevedo A, Pimenta J, Frioes F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in HF patients. *Circulation*. 2004;110:2168-74.