

# Natriuretic Peptides in Heart Failure: Improving Diagnosis and Management of the Syndrome

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In recent decades, the conceptual development of a new pathophysiological model of heart failure has made it possible to achieve important therapeutic advances through the inhibition of different neurohormonal systems. In spite of these advances, most of our therapeutic actions are applied too late in the long and complex process of myocardial remodeling, which terminates with the appearance of heart failure syndrome. In clinical practice, changes in the dose or classes of medications are made principally when the functional class of the patient deteriorates, fluid retention or lung edema appears, hemodynamic variables deteriorate, left ventricular enlargement occurs, or we observe alterations in the strength of myocardial contraction. Most studies designed to be carried out in patients with heart failure have focused on these endpoints, all of which appear late in the pathophysiological process of heart failure. However, there is a period in the evolution of our patients in which complex active pathophysiological mechanisms are overlooked by the treating physician. Various biochemical markers, such as the plasma concentrations of noradrenaline, renin, aldosterone, and the troponins, among others, have been proposed as a measurable indicator of this process. However, these markers are late or their prognostic value disappears in patients adequately treated with neuroendocrine blockers. In this context, the measurement of natriuretic peptides and, more recently, therapy guided by natriuretic peptide concentrations signal the onset of a new era in the management of patients with heart failure.

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Natriuretic peptides are hormones that are found in different tissues, but are synthesized and stored mainly in the atrial and ventricular myocytes. These molecules bind to specific receptors located in the endothelial cells and smooth muscle fibers, activating guanylate cyclase. The production of intracellular cyclical guanosine monophosphate (cGMP) mediates the physiological effect of these hormones, such as the increase in glomerular filtrate, sodium excretion, and peripheral vasodilation, and the attenuation of the renin-angiotensin, aldosterone, adrenergic, and endothelinergic systems. Of the three known forms of natriuretic peptides, ANP (atrial natriuretic peptide), BNP (brain natriuretic peptide), and CNP (natriuretic peptide type-C), BNP is the most clinically relevant form.

BNP is a peptide of 32 amino acids secreted mainly by ventricular myocytes in response to increased ventricular filling pressure and myocardial stretching. It is stored in the form of pro-BNP and at the time of excretion divides into two molecules, the inactive N-terminal part (NT-proBNP) and active BNP. Both forms are at present easily measurable by radioimmunoanalysis, including ultrarapid techniques.<sup>1</sup>

## BNP MEASUREMENT IN THE GENERAL PRACTITIONER'S OFFICE

At present, the incidence and prevalence of heart failure is growing in a progressively older population, with a larger percentage of isolated diastolic insufficiency and comorbidity. In this "real" population of patients with heart failure, so different from the one studied in recent large therapeutic trials, the diagnosis is difficult and often erroneous.<sup>2</sup>

In this issue of the REVISTA ESPAÑOLA DE CARDIOLOGÍA, Osca et al<sup>3</sup> present a "real" population of patients hospitalized for heart failure in which plasma BNP concentrations correlated independently with the left ventricle shortening fraction. This direct correlation between plasma BNP concentration and

systolic function indices has been described before for the entire clinical spectrum of patients with heart failure. In fact, the measurement of plasma BNP has been shown to be a very sensitive marker of the presence of left ventricular dysfunction in the asymptomatic population<sup>4</sup> and a normal BNP concentration practically excludes the possibility of finding a ventricular function disorder. At the opposite extreme, within the context of patients admitted to the emergency room with sudden dyspnea, plasma BNP concentrations make it possible to identify the patients who really have acute heart failure with systolic dysfunction<sup>5</sup>. In the study by Osca et al, the authors made an extensive statistical analysis of clinical variables associated with BNP concentration. As in earlier studies, the principal correlation was with the indices of myocardial stretching and tension (end-systolic diameter and left ventricular shortening fraction). The other clinical variables, such as type of heart disease, age, or even functional class are clearly related with poor ventricular function, the only independent variable in the statistical analysis made by the authors. As noted earlier, this capacity of BNP concentration to identify patients with an abnormal systolic function is very important within the context of general medicine and makes it possible, among other advantages, to refer patients for echocardiographic diagnosis on a sounder cost-benefit basis.<sup>6</sup>

In no way does plasma BNP concentration replace the findings of physical examination or, when necessary, echocardiographic assessment, but the simplicity, specificity, and low cost of this diagnostic method allows it to occupy a primordial position in general medicine.

## BNP MEASUREMENT IN THE CLINICAL EVALUATION OF HEART FAILURE

High ventricular filling pressures activate neurohormonal systems that mediate the appearance of the symptoms and process of myocardial remodeling. Since the natriuretic peptides reflect cardiac filling pressure and parietal stress, it is reasonable to assume that their plasma concentrations can be used to monitor the effectiveness of pharmacological treatment. A recent controlled study in New Zealand has shown that therapy is more effective when guided by plasma BNP values instead of the usual clinical criteria.<sup>7</sup> The measurement of natriuretic peptides in plasma also has shown its usefulness in determining the prognosis of patients with heart failure, being an important predictor of mortality in populations of advanced age with myocardial infarction or advanced heart failure. It has been observed that serial measurements of BNP allow decompensated patients who are more likely to be rehospitalized to be identified at the time of discharge.<sup>1</sup>

Drugs that reduce the parietal stress of the left ventricle, such as angiotensin-converting enzyme inhibitors, beta-blockers, spironolactone, or diuretics, reduce plasma natriuretic peptide values. Monitoring therapy with plasma BNP concentration allows neuroendocrine blockade to be adjusted to adequate levels. In this sense, not only are high BNP concentrations important. Recently, a less favorable evolution of patients who have a strong neuroendocrine blockade with valsartan, enalapril, and beta-blockers has been observed<sup>8</sup>. It was interesting that this subgroup of patients had relatively lower concentrations of natriuretic peptides than the other study groups (unpublished observation). It is evident that in an era of treatment by neurohormonal blockade, natriuretic peptides are an ideal biochemical marker to guide therapy and determine prognosis for cardiologists.

Also interesting are patients with isolated diastolic heart failure, for which there are no uniformly accepted diagnostic criteria. In the study by Osca et al in this issue, a BNP concentration with sufficient discriminatory value to identify patients with diastolic heart failure could not be determined in spite of the strong correlation between plasma BNP and the shortening fraction. In the interesting statistical analysis by the authors, only extreme concentrations (350 pg/ml) had the necessary specificity to exclude the presence of isolated diastolic dysfunction. Even so, all these patients had notoriously high BNP concentrations, which confirms the diagnostic power of the method in the presence of heart failure of any type, including isolated diastolic dysfunction.<sup>9</sup>

The main contribution of this study is that it confirms the diagnostic value of plasma BNP concentrations in a heterogeneous population of patients with heart failure, such as that observed in daily clinical practice. BNP correlates closely with markers that have a high prognostic impact, such as left ventricular systolic function. It can be expected that in the coming years we will see the routine use of this biochemical marker in clinical practice and in the most sophisticated heart failure clinics.

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