Review Articles

The role of natriuretic peptides in defining the diagnosis and prognosis of medical diseases

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Abstract
Natriuretic peptides, BNP and NT-proBNP are increased in patients who have a higher myocardial wall tension. They have been extensively used to diagnose heart failure in patients presenting dyspnea. BNP and NT-proBNP serum levels are influenced by variables such as age, gender, body mass index and renal function. Lately, their increase in acute coronary syndromes, stable atherosclerotic coronary artery disease, chronic obstructive pulmonary disease, pulmonary hypertension and sepsis has been investigated. We review the diagnostic and prognostic value of circulating natriuretic peptides in the assessment of several medical diseases.

Key words: BNP, Internal Medicine, prognosis.

Natriuretic Peptides
In 1981, De Bold and his assistants found out that the endovenous infusion of auricular extract in rats would lead to abundant natriuresis.1 Such finding led to discovering the auricular natriuretic peptide (ANP),2 the first of a protein family with natriuretic, diuretic and vasodilatory properties. Subsequent research enabled to identify other members of this family of natriuretic peptides: B-type natriuretic peptide (brain) (BNP) and the C-type natriuretic peptide (CNP).

ANP is released in the auricles responding to stretch. In humans, also BNP; initially discovered in brain tissue, is released in the heart, namely the ventricles and its effects are similar to ANP (Fig. 1). CNP is confined to the vascular endothelium and central nervous system and has a mild natriuretic and vasodilatory effect.

BNP gene is located on the chromosome 1 codifying the pre-proBNP, a 134 aminoacids protein, which is cleaved into proBNP, made up of 108 aminoacids. The proBNP is, on its turn, cleaved by the proteolytic enzyme furin in its biologically active form, BNP with 32 aminoacids and its terminal-N segment (NT-proBNP).3

The stimuli triggering BNP release are an increase on the ventricular volume, pressure overload and an increase on the myocardial wall tension resulting from these.4,5

BNP and NT-proBNP are produced in equimolar quantity by the ventricular myocytes, but NT-proBNP half-life is longer.6,7 In spite of not existing significant concentration differences between these two peptides in normal individuals, this fact becomes evident in patients with a left ventricle dysfunction. In such patients, the levels of NT-proBNP are around four times higher than those of BNP.8

Cardiovascular effects of natriuretic peptides are related with the decrease on preload due to an increase on vascular permeability and an increase on the myocardial wall tension resulting from these.9 Increased natriuresis and venous capacitance subsequent to a reduced sympathetic tonus.10,11 On the kidney, natriuretic peptides increase the glomerular filtration pressure dilating the afferent artery whilst contracting the efferent arteriole interfering in the absorption mechanisms and tubular secretion,12 leading to natriuresis. At CNS level, they inhibit thirst14 reducing the sympathetic activation.15

Natriuretic Peptides and Cardiac Failure

Dyspnea Differential Diagnosis in the Emergency Unit

It has been in a context of dyspnea in an Emergency Unit (SU) that the usefulness of determining BNP was better studied and validated. Its determination has shown to be a sensitive and specific method to differentiate dyspnea of cardiac or pulmonary origin.16
Patients with a final diagnosis of cardiac failure showed BNP values significantly higher to those who had been diagnosed with pulmonary dysfunction (759 ± 799 pg/mL vs. 61 ± 92 pg/mL). A BNP value of 94 pg/ml had a 86% sensitivity and a 98% specificity, with the ability to differentiate between cardiac failure and pulmonary dysfunction of 91%. Even in patients who attended the Emergency Unit with an history of COPD, BNP value has successfully differentiated those with dyspnea caused by cardiac failure from those with dyspnea caused by respiratory dysfunction.

In a similar study, in 1586 patients, to determine BNP proved to be a better option to anticipate cardiac failure as cause of dyspnea than data from the clinical history, physical examination and other laboratory tests. The diagnostic capacity of 100pg/ml was 83.4% with a negative predictive value of 96% for a BNP <50pg/ml. The BNP value has also shown to be an independent indicator or cardiac failure, regardless of other variables. Still, it has shown to be related with the NYHA functional class for cardiac failure. Dyspnea of pulmonary cause in patients with a cardiac failure history pose a diagnostic difficulty to construe BNP values, as there is some overlapping on the BNP concentration range among these diagnostic groups.

In a prospective, controlled random study involving 452 patients attending an Emergency Unit due to acute dyspnea, the quick BNP assessment has improved the evaluation and treatment reducing the admission period and the costs of treatment. To use BNP tests in the Emergency Unit has significantly reduced even the time to the appropriate disease treatment, leading to a smaller number of admitted patients and a small ratio of patients requiring transfer to an Intensive Care Unit. The average admission time has been reduced by 3 days and the treatment costs were significantly reduced. There was no impact on mortality.

**Natriuretic Peptides and Factors Influencing Diagnostic Values (Table I)**

NT-proBNP values are affected by age and gender that must be considered while construing the results. In the general population, to determine NT-proBNP has an equivalent value to determine BNP to anticipate cardiac failure. Both present good sensitivity and specificity in the cardiac failure diagnosis. Both increase significantly with age and are higher in the female gender, therefore there is a need to set up specific reference values, considering all these variables.

It has been shown that kidney failure has an effect on the BNP threshold value for diagnosing dyspnea related with cardiac failure. Also, NT-proBNP values on diagnosing dyspnea by cardiac failure are influenced by the renal function. In a study involving 381 patients, the threshold values for diagnosing dyspnea caused by cardiac failure increased from 1360pg/mL of NT-proBNP and 290pg/mL of BNP in patients with a glomerular filtration rate (GFR) 60-89mL/min/1.73m² to 6550pg/mL and 515pg/mL, respectively, in patients with GFR 15-29mL/min/1.73m².

BNP serum levels have shown to be proportionally inverse to the body mass index (BMI) in patients without cardiac failure and with cardiac failure. Possible mechanisms were considered as increase on natriuretic peptides clearance and reduced BNP release in obese patients. When compared to other variables, obesity remains an independent fact for a smaller concentration of circulating BNP and NT-proBNP. In obese patients, BNP values were below the diagnosis threshold more often than NT-proBNP, and both showed a decreased sensitivity in this population.

Therefore, when defining cardiac failure threshold-
ds for diagnosis it must be taken into account the patient’s age, gender, BMI and renal function.

**BNP vs NT-proBNP**

Some studies compare the determination of BNP and NT-proBNP regarding the diagnosis and prognosis of cardiac failure. In a Val-HeFT substudy, including 3916 patients, both were affected similarly by age, left ventricle (LV) ejection fraction, LV diameter and creatinine clearance. However, NT-proBNP was a better indicator predicting mortality, morbidity and hospitalization due to cardiac failure. These data are supported by other studies suggesting a higher discriminating ability of NT-proBNP regarding BNP, though mild.

Other authors could not discriminate differences in the diagnosis accuracy of both tests, thus the issue is not yet completely solved regarding what is the best test, therefore, both BNP and NT-proBNP are used in the clinical practice with wide evidence supporting the use of both of them.

**BNP and NT-proBNP Prognosis Ability**

A systematic review tried to answer the question of what was BNP prognosis ability. It came to the conclusion that BNP is a strong prognosis predictor in asymptomatic patients and in cardiac failure patients, in all the disease stages. Patients with a BNP not decreasing while responding to treatment seem to be at particular high risk of death or cardiovascular events.

Studies included BNP determination before and after treatment, showed that those values after stabilization with treatment were better death and new events predictors than the initial BNP values.

Even in asymptomatic patients, mortality was related with BNP value, although it is not yet established if there is a continuous link or if the prognosis is defined by a range of BNP values. Consequently, on the 4th and 5th year of studies addressing this issue, the death risk doubled even when low BNP threshold values were used (BNP ≥ 17.9 pg/mL in the McDonagh et al. study, or BNP ≥ 20.0 pg/mL in the male gender and BNP ≥ 23.3 pg/mL in the female gender in the Wang et al. study).

BNP was compared with NT-proBNP in only one multivariate model. Both BNP logarithm (log) as the NT-proBNP logarithm showed statistic significance in multivariate analysis, but only logBNP was kept significant in multivariate analysis.

On admission, BNP showed to be an in-hospital mortality predictor in patients with acute cardiac failure, whether with depressed or preserved systolic function, regardless of other clinical and laboratorial variables. In cardiac failure patients, the relative death risk increased 35% for each increase of 100pg/ml in BNP.

In patients admitted in the Emergency Unit due to dyspnea, NT-proBNP determination was related with mortality to 1 year, regardless of the cause of dyspnea.

In coronary artery disease patients, whether stable or acute, natriuretic peptides have an independent role predicting mortality.

**Natriuretic Peptides and Ischemic Heart Disease**

Acute hypoxia increases the expression of BNP gene leading to a higher myocardial BNP release. This occurs immediately after inducing ischemia and it is related with the degree of ischemia the myocardium was subjected to. NT-proBNP showed to be an independent marker for hemodynamic variables and other biochemical markers in patients with an acute coronary syndrome diagnosis.

Natriuretic peptides role while diagnosing the acute coronary syndrome is not so well clarified. To add BMP to myocardial necrosis syndrome has shown to increase sensitivity in the diagnosis of acute coronary syndrome, at the expense of reduced specificity, in a non controlled study. Therefore it can have a role excluding such diagnosis.

There is no need for necrosis to occur to see an increase on BNP values, as the transitory ischemia, both in humans and animals, induces a BNP increase and transcription of its gene in the absence of a myocardial cell injury. In a population with stable angina
prospectively studied, BNP related with the risk of future cardiovascular events, regardless of the ventricle function and other known risk markers. The determination of NT-proBNP in patients with signs or symptoms of stable coronary disease has shown to be a mortality marker and provided additional prognostic information regarding the conventional risk factors and the evaluation of the ventricle function.

**Natriuretic Peptides and Pulmonary Diseases**

In patients with a previous pulmonary disease to diagnose the causes of dyspnea is more difficult. In this group of patients co-morbidity is even a bigger diagnosis challenge. In this condition, cardiac failure is frequent, and can represent more than a third of the reasons to attend an Emergency Unit. The use for BNP determination in these patients has shown to reduce the need for admission, to reduce its period of time and inherent costs without significant effects in intra-hospital mortality.

Determining NT-proBNP was related to the mortality 1 year after attending the Emergency Unit for dyspnea, regardless of its cause. High concentrations of BNP resulting of pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD) were described, even in the absence of left ventricle failure. This increase can suggest cor pulmonale. In COPD patients, to determine BNP was related with pulmonary hypertension and it was an independent mortality predictor regardless of hypoxemia and pulmonary functional limitation.

It has also been shown the usefulness of determining BNP in patients with primary pulmonary hypertension. The increase on BNP is related with the patient functional limitation and it is parallel to the hemodynamic alterations and the existence of right cardiac failure.

Patients with acute respiratory distress syndrome (ARDS) present a higher BNP concentration. In spite of this, to determine BNP is useful to the differential diagnosis between acute pulmonary edema of cardiogenic cause (EAP) and ARDS, in patients admitted in Intensive Care Units with hypoxic respiratory failure and bilateral pulmonary infiltrate. ARDS patients show lower BNP concentrations. In the range of serum levels shown by patients with ARDS or EAP, the higher BNP concentration is related with hospital mortality, without any link with the prognostic value of APACHE II score.

The relationship between BNP value and the pulmonary capillary wedge pressure is controversial, as supported by some data, but in other studies, this correlation was mild.

**Natriuretic Peptides in Septic Shock**

Increases in BNP and NT-proBNP in septic shock patients were observed. It was suggested that this increase in natriuretic peptides may reflect in the septic shock a myocardial dysfunction as occurs in cardiac failure. Patients in sepsis and septic shock show hemodynamic changes as an increased diastolic volume and pressures in both ventricles and increase in the pulmonary arterial pressure (PSAP), which might explain the increase in circulating natriuretic peptides. Not all studies are consensual on evaluating the relation between BNP and pulmonary capillary wedge pressure in an ICU setting. For this, a contributing factor may be a complex cardiac dysfunction in sepsis, with a possible involvement of the systolic or diastolic dysfunction, affecting the right or left ventricle.

A study has tried to verify which natriuretic peptides, ANP or BNP, was related with cardiac dysfunction. In this study, BNP was the only one to relate with the systolic function. However BNP value was not related with the APACHE II score and was not able to differentiate those who survive and those who did not survive.

BNP is increased in endotoxemia animal models. It has been questioned if BNP expression and release in endotoxemia is only due to hemodynamic changes. It was described an exponential transcription of BNP gene by lipopolysaccharides non mediated by other cytokines and independent from the cardiac mechanic load, in animal models. This fact is also supported for higher levels of endotoxins in other diseases evolving with an increase in natriuretic peptides, as cardiac failure. It is known the deleterious effect over the cardiac contraction made by endotoxins. Such data led to a research on the endotoxins role modeling the expression and release of natriuretic peptides in humans. In vitro studies have shown that cardiomyocytes, in culture stimulated with IL-1β had an increase on BNP gene expression. In cardiomyocytes cultures, the stimulation with family IL-6 interleukins leads to an increase of BNP release.
Such findings support the hypothesis that cytokines modulate BNP serum levels in septic shock, regardless of hemodynamic variables.

Several studies have verified high levels of BNP and NT-proBNP in septic shock patients, and NT-proBNP has shown to be a prognosis independent marker and may even to be a stronger death predictor than the APACHE II score. In the septic shock, oncological patients NT-proBNP value, the Logistic Organ Dysfunction score and the recent transplant of hematopoietic cells were mortality predictors. In an multivariate analysis, NT-proBNP value on the 2nd day of admission was the only parameter related with prognosis.

Natriuretic peptides evaluation in sepsis can have a prognostic value and does not depend only on hemodynamic variables, but also reflects the inflammatory response triggered.

Conclusion
The use of BNP and NT-proBNP determination may have a prognostic value in cardiovascular and pulmonary diseases and in critical patients. To resort to these tests is widely validated in a dyspnea differential diagnosis in an emergency situation. In spite of starting to emerge evidence in the sense of using natriuretic peptides to define the prognosis, is not yet clear if the recognition of patients in risk may lead to therapeutic attitudes with a positive impact in the morbimortality. Therefore, there is a need for further studies to validate its generalized use in medical pathology, in a cost-efficiency perspective.

The knowledge of several factors which can lead to natriuretic peptides release is important while construing BNP and NT-proBNP values. Variables as gender, age and BMI must be integrated with laboratorial and clinical data.

References


