Clinical Applications of B-Type Natriuretic Peptide Assays

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Physiology of the Natriuretic Peptide System

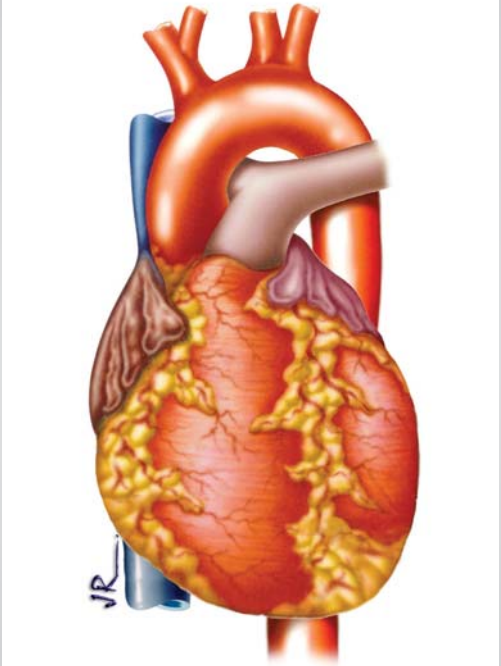
The natriuretic peptide system is activated every time the heart is subjected to injury, whether acute or chronic, as a compensatory mechanism for the effects of vasoconstriction changes that take place in these situations. The primary role of the system is to promote urine output and vasodilation. It is known, however, that a series of additional effects are triggered when these peptides are released, such as the inhibition of the renin-angiotensin-aldosterone system, sympathetic nervous system and smooth muscle cells growth, and possibly the reduction of apoptosis[1].

Three types of peptides are known: type-A peptide (ANP) - released from the atria; type-B (BNP) - released from the ventricles and type-C - released from vascular cells. Because it is released directly from the ventricles, type-B peptide (BNP) is the one that best reflects the condition of the cardiac muscle and, therefore, the one that has obtained greater clinical applicability. The stimulus for its release is the stretching of ventricular muscle cells caused by a pressure or volume overload[1,2]. More recently, it was shown that myocardial ischemia, which leads to an increase in parietal tension due to systolic and/or diastolic dysfunction, can also promote the release of BNP[3].

Before it is released into the blood stream, BNP is present in the form of its precursors. Inside the myocyte, Pro-BNP is split to produce two molecules: BNP, the active portion, and the NT-proBNP portion which is inactive, but can also be measured in the blood.

These peptides bind to specific type-A and type-B receptors. Breakdown and clearance take place by means of binding to type-C receptors, as well as by an enzyme called neutral endopeptidase.

In healthy individuals, BNP levels vary according to sex and age, and are higher in elderly people and in women when compared to men in the same age group[4].



BNP Measurement Techniques

The first BNP measurement techniques developed were time-consuming and difficult to perform, making them inappropriate mainly for emergency situations. With the development of rapid blood tests for BNP (point-of-care), this biochemical marker started to be used in a large variety of clinical setting situations. The first rapid point-of-care blood test performed, and the only utilized up until now, was developed in San Diego, USA, and it has been commercially available in Brazil since 2001. A test for the measurement of NT-Pro-BNP, although not the "point-of-care" type, is also available in Brazil.

BNP is measured by immunofluorescence. Five mL of blood are collected into a tube containing EDTA. One drop is placed on the strip which is then introduced into the

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device, and the result is ready within 15 minutes. BNP remains stable for at least 4 hours at room temperature, for 2 days when refrigerated at 4-8ºC, and for at least 12 months when stored at –20ºC.

Heart Failure

So far, the main application of BNP testing is in the diagnosis and treatment of patients with heart failure (HF). We comment, below, on a few heart failure situations in which BNP testing can be helpful.

LV systolic dysfunction diagnosis

Population studies have shown the usefulness of BNP as a triage test for the diagnosis of left ventricular (LV) systolic dysfunction. In a Scottish study, a blood concentration of BNP over 17.9 pg/mL, showed 76% sensitivity and 87% specificity as a detector of severe ventricular dysfunction (ejection fraction less than 30%). In individuals over 65 years of age, accuracy was even higher[5].

In Brazil, Ribeiro *et al* conducted a study on the capacity of BNP testing to detect LV systolic dysfunction in patients with Chagas' disease. In patients with abnormal electrocardiograms or chest X-rays, a BNP value greater than 60.7 pg/mL was an accurate detector of systolic dysfunction, showing 80% sensitivity and positive predictive value (PPV), and 97% specificity and negative predictive value (NPV) [6].

Ambulatory heart failure diagnosis and prognosis

The ambulatory diagnosis of HF may sometimes be difficult to make, especially in primary care settings. Actually, several population studies have shown that less than 40% of patients with suspected HF diagnosed by the general practitioner [GP] had this diagnosis confirmed when evaluated by cardiologists[7]. The Hillindon Heart Failure Study conducted in London indicated that out of 122 patients referred by primary physicians to a specialized clinic, 35 (29%) were confirmed as having HF. BNP testing proved to be very useful in such a population (are under ROC curve was 0.96). With a cut-off value set at 76.4 pg/mL, a high NPV value (98%) and an acceptable PPV value (70%) were obtained. Sensitivity and specificity were 97% and 84%, respectively. The results of this study will be validated by a multicentric study (The UK Natriuretic Peptide Diagnosis Study).

With regards to prognosis, another study evaluated 290 consecutive patients who underwent cardiac catheterism due to asymptomatic or mildly symptomatic LV systolic dysfunction[9]. During a 27-month follow-up period, 24 patients died due to cardiac causes and 25 were hospitalized because of HF or acute myocardial infarction (AMI). BNP levels measured at the time of catheterism correlated independently with cardiac deaths, as well as with cardiac events (death and hospital admissions). There was also a 4% increase in risk for each 10 pg/mL increment in BNP levels.

Another study evaluated patients with recent onset HF. A subgroup of 108 patients, who were part of a population study of individuals diagnosed with HF for the first time, was evaluated in Bromley, London[10]. BNP, NT-proBNP and NT-proANP levels were measured at the first timepoint the patient was seen, that is, before clinical stabilization. During the 38-month follow-up period, 40 patients died, 34 of them due to cardiovascular causes. The three peptide levels were strong predictors of mortality (area under the ROC curve was 0.70, 0.73 and 0.68, respectively).

Therapeutical monitoring

The usefulness of BNP testing in guiding therapy has also been studied, with doses being adjusted according to patient BNP levels. A pilot study showed that the rate of cardiovascular events was smaller in the group with treatment administered according to BNP levels in comparison to the group submitted to conventional treatment[11]. A multicentric study is currently underway to evaluate this issue.

Hospital diagnosis of HF

The primary use of BNP level measurements is in managing hospitalized HF patients. These patients have high BNP levels, which makes it easier to differentiate them from patients without HF. In terms of diagnosis, the largest study was conducted by Maisel *et al*, with 1,538 patients who presented to the emergency department with acute dyspnea[12,13]. In this multicentric study, it was easy to differentiate HF patients from those with other diagnoses. The median BNP values in the HF group and in the non-HF group were 675±5 vs 110±3 pg/mL, respectively. The measurement of plasma BNP levels was superior to two clinical criteria previously utilized for the diagnosis of HF (Framingham and NHALE) and it proved very helpful in excluding a HF diagnosis (NPV 90%). For a cut-off value of 100 pg/mL the sensitivity and the specificity were 90% and 73%, respectively.

At our institution, the use of BNP level measurements was introduced into daily clinical practice in April 2001. At the same time, a protocol was initiated to assess the usefulness of BNP in the diagnosis and prognosis of heart failure patients. Data on the first 70 patients admitted to the emergency department with acute dyspnea were published in 2002[14]. BNP levels in patients with and without HF were 990±550 and 80±67 pg/mL, respectively. At a cut-off level of 200 pg/mL, BNP showed sensitivity, specificity, PPV, and NPV values of 100%, 97.1%, 97.3% and 100%, respectively.

In the REDHOT[15] study, which evaluated patients with decompensated HF in the emergency department, a lack of correlation was observed between what the physician at the emergency room classified as a critically ill patient and the clinical progress of that patient. The use of BNP showed a better correlation with the clinical progress than the assessment made by the physician alone. In the BASEL study, it was shown that the use of BNP testing in patients with acute dyspnea helps to speed-up the confirmation or exclusion of heart failure diagnosis, resulting in a shorter hospital stay and lower costs[16].

Diagnosis of diastolic HF

Maisel *et al* evaluated 294 individuals referred for echocardiograms[17]. Patients with echocardiographic diastolic dysfunction had average BNP values of 286±31 pg/mL against 33±3 pg/mL in those with normal function. Patients with restrictive filling patterns showed the highest BNP levels (408±66 pg/mL), and symptomatic patients had high levels of BNP regardless of their diastolic filling pattern. The area under the curve (AUC) for detecting any type of diastolic dysfunction was 0.92, and the cut-off value set at 62 pg/mL showed 85% sensitivity, 83% specificity, and 84% accuracy.

In the multicentric BNP Trial[18], with a BNP cut-off value set at 100 pg/mL, sensitivity was 86%, NPV 96%, and accuracy 75% in detecting diastolic dysfunction. At our institution, patients with HF and LV systolic dysfunction showed higher BNP levels than those with preserved systolic function (1,180±330 vs 753±228 pg/mL, p=0.029). However, it was possible to differentiate HF patients with normal systolic function from patients without HF, whose average BNP levels were 753±228 and 89±28 pg/mL, respectively (p<0.001)[19].

In a population study, however, BNP levels were not good predictors of pre-clinical diastolic dysfunction, suggesting that among patients with diastolic dysfunction, only those with the most marked dysfunction or clinically manifested HF can be identified with the use of BNP[20].

Prognosis of patients hospitalized for HF

In a Veterans' hospital in San Diego, both the BNP levels measured at admission, as well as their variation during hospitalization were predictors of clinical progress[21]. Patients whose BNP levels decreased during their hospital stay had the best prognosis. Those whose BNP levels did not vary had a higher rate of hospital readmission within 30 days, and those with an increase in BNP levels had higher mortality rates while in the hospital and within up to 30 days of follow-up. At our institution, patients with BNP levels over 760 pg/mL at admission had greater rates of mortality or readmission to the hospital within 30 days. Sensitivity and specificity to predict events in patients with BNP above this cut-off value were 72% and 69%, respectively[22].

Acute Coronary Syndromes

BNP testing has proved to be an important prognostic marker in patients with acute coronary syndrome, both those with ST-segment elevation AMI, as well as those with non-ST-segment elevation AMI or unstable angina[23-25]. In the largest study conducted in this area, the baseline BNP determined for AMI patients, with or without ST-segment elevation and with unstable angina, correlated with mortality and with the risk of developing HF or AMI within 30 days and at 10 months. The odds ratio for mortality at 10 months for the second, third and fourth BNP quartiles were 3.8, 4.0 and 5.8, respectively.

Our group assessed the BNP level at admission in 631 patients presenting with chest pain at our emergency department, for the diagnosis of non-ST-segment elevation AMI[26]. Patients with ST-segment elevation were excluded. Upon arrival at the emergency room, patients' levels of BNP, troponin I and CKMB-mass were measured. After 3 hours and 9 hours of admission, the troponin and CKMB-mass measurements were repeated. The final AMI diagnosis was based on a positive result for troponin or CKMB-mass at any timepoint. We tried to evaluate if the BNP measurement upon admission of the patient with chest pain increased the accuracy of an AMI diagnosis during his/her stay in the emergency department. The average BNP values in patients with AMI, unstable angina and diagnoses other than acute coronary heart failure were 200 pg/mL, 78 pg/mL, and 28 pg/mL, respectively. The sensitivity values for CKMB-mass, troponin I, BNP, and the three markers combined were 46%, 51%, 71% and 87%, respectively (p<0.001 to compare BNP alone and all the markers combined relative to CKMB-mass and troponin). The negative

predictive values for the respective markers were 93%, 93%, 95% and 98% (p=0.0016 to compare combined markers relative to CKMB-mass and troponin). The multivariate analysis showed that ST-segment depression (odds ratio of 6.0), BNP>100 pg/mL (OR=2.3), diabetes (OR=2.5), CKMB-mass>5 (RC=11.9), and troponin>1.0 (OR=36.6) were independent predictors of AMI. These data suggest that adding BNP levels to the conventional markers improves the sensitivity and the NPV value of HF diagnosis in patients with non-ST segment elevation acute myocardial infarction.

Predictor of All-Cause Death in Population Studies

A recently published large population study comprising 3,346 patients sought to establish the relationship between BNP and NP-pro-ANP, and the risk of all-cause death. The study aimed also to establish the relationship between the risk to develop a cardiovascular event, HF, atrial fibrillation, cerebrovascular accident or transient ischemic attack, and coronary artery disease[27]. After a 5.2-year follow-up, 119 patients died and 79 suffered a first cardiovascular event. After adjusting for cardiovascular risk factors, each standard deviation increment in BNP logarithmic values was associated with a 27% increase in the risk of all-cause death, 28% in the risk of a first cardiovascular event, 77% in the risk of developing HF, 66% in the risk of developing AF, and a 53% increase in the risk of suffering a cerebrovascular accident or transient ischemic attack. No relationship was observed with the development of events related to coronary artery disease. Similar results were observed with NT-pro-ANP levels.

Sudden Death Predictor (Guiding Referral for the Use of Cardiac Defibrillator)

Among HF patients, BNP measurements can identify those with greatest risk of sudden death, and be a good guiding referral for the use of defibrillator. In an Austrian study[28], only 1% of patients with BNP logarithmic values under 2.11 experienced sudden death compared to 19% of those who had higher values. In this study, 452 individuals were assessed. Within 3 years, 89 patients died, 44 of whom from sudden death. BNP measurement was the only independent predictor of sudden death. The same group is organizing a multicentric study to further confirm these findings.

Aortic Stenosis

In patients with aortic stenosis, BNP values are higher in those who are symptomatic[29]. Since the presence of symptoms is one of the factors taken into consideration in assessing the indication of surgery for such patients, BNP testing could be included in the evaluation and be of help in indicating surgery.

Pulmonary Embolism

When submitted to stress, the right ventricle can produce BNP although in smaller quantities than the left ventricle[1]. Patients with pulmonary embolism, mainly those with right ventricular dysfunction (RV), have slightly increased BNP levels. In patients admitted to the emergency department with dyspnea and a final diagnosis of pulmonary embolism, BNP levels may vary from 100 to 400 pg/mL[12,14]. In patients with pulmonary embolism, BNP values correlate with the presence of RV dysfunction and are predictors of a worse clinical progression[30,31].

Primary Pulmonary Hypertension

In a study involving 60 patients with primary pulmonary hypertension, BNP was an independent predictor of mortality[32]. Patients were treated with prostacyclin and three months after the diagnosis, the BNP level was measured again. During a follow-up of 24 months, the survivors presented a decrease in BNP to levels between the two measurements (217±38 vs 149±30), whereas in those patients who died, there was an increase in BNP levels (365±77 vs 544±68). Survival was extremely low for patients with BNP>180 pg/mL.

Syncope

Tanimoto *et al* conducted a study on 148 consecutive patients with syncope. In sixty-one of these patients the syncope was of cardiac etiology. At a cut-off value of 40 pg/mL, the BNP measurement showed a sensitivity of 82% and specificity of 92% in identifying those patients with a cardiac cause for syncope.

Conclusion

BNP measurement has been gaining an increasingly greater role in clinical practice. Since its initial application, that of identification of LV systolic dysfunction, many other cardiovascular situations have been added to the list of diseases that can be managed with BNP measurement. Its usefulness in treating patients with HF is well established. In other cardiovascular diseases, increasing evidence has been obtained, suggesting that in the near future BNP testing can be added to the management of these patients.

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