Brain Natriuretic Peptide

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Heart failure is a nosological entity whose incidence is constantly rising, mostly due to the elevation of the population's mean age. Diagnosis of heart failure is not an easy task, especially in the elderly, in women and in the obese, while particular diagnostic considerations arise for patients with dyspnea and edemas[2]. The prognosis of heart failure remains poor and its causes are not always clarified. For the aforementioned reasons, a simple, cheap and easily performed laboratory test, like the assessment of brain natriuretic peptide (BNP) plasma levels, that could help distinguish patients with heart failure from patients suffering from other causes of dyspnea when classical biochemical and imaging investigations fail to set the diagnosis, seems very appealing.

Structure, synthesis, storage and secretion of BNP

BNP consists of 32 amino-acids, with a central ring of 17 amino-acids created by a disulphide bond between cystine bases. The first natriuretic peptide ever discovered was atrial natriuretic peptide (ANP), a peptide predominantly secreted by atrial myocardial cells[1,2].

BNP is secreted by myocardial cells located on both atria and ventricles, predominantly by left ventricular myocardial cells. The name was given because it was first discovered in porcine brain. BNP's gene is located on the short arm of chromosome 1, close to ANP loci. Its mRNA is translated to a chain of 108 amino-acids (proBNP) that co- exist with ANP in some of the secretory vesicles of the atrial and ventricular myocardial cells. ProBNP is transformed to BNP and to NT- pro BNP, an endocrinologically inactive molecule[2,3].

Although the exact mechanism that regulates BNP production and secretion is unknown, it seems possible that cardiac wall tension and dilation play an important part. Therefore, intense exercise moderately raises BNP plasma level, while this rise is more pronounced in patients with left ventricular hypertrophy or heart failure. In detail, it seems that tension or pressure increase inside the atria are followed by an increase of BNP's mRNA within 60 min, while in the ventricles, where BNP's production depends on hemodynamic loading, BNP's levels increase in a few hours[3,4].

BNP plasma concentrations (as well as ANP's) show a fast discrete rise immediately after birth. By the third month, it is stabilized to the adult level. This fast rise seems to be due to the increase of the left ventricular volume and pressure. BNP plasma concentration also rises in pulmonary hypertension, but in this case the increased secretion by the right ventricle is responsible, as BNP level correlates well with its telodiastolic pressure and volume[2,3].

Natriuretic peptides receptors

Three kinds of receptors have been described for natriuretic peptides: A, B and C. The first two seem to regulate the pep-

tides' biological actions, while the third one has to do with their removal from the circulation. All three types of receptors can be found throughout the human body, but are highly concentrated in the kidneys, the heart, the vascular endothelium, the vascular smooth muscles and the central nervous system.

Physiology of BNP action

1) BNP promotes diuresis, natriuresis, hypotension and smooth muscle relaxation. It exerts its action on the kidneys' glomerulus apparatus and on the proximal renal tubule, inhibiting rennin secretion and increasing the rhythm of diuresis and natriuresis without causing any change in intraglomerular hydrostatic pressure, in the rhythm of glomerular filtration or in the rhythm of blood flow to the kidney. It also inhibits the secretion of aldosterone.
2) There are indications that BNP regulates the autonomic nervous system, as BNP receptors were found on the vertebra ganglions.
3) Recent studies suggest that it prohibits myocardial fibrosis and proliferation of the smooth muscle cells that are situated on the middle layer of the vessels, while it also inhibits the expression of the plasminogen activator inhibitor on the endothelial cells, thus helping to prevent thrombosis.
4) BNP causes dilation of epicardial vessels, inhibits coronary artery spasm that is caused by hyperventilation and dilates pulmonary arteries in healthy individuals, as well as in patients with pulmonary hypertension[2,3].

BNP and N-terminal pro-BNP (NT- proBNP) removal

Nartiuretic peptide removal from circulation is achieved with two mechanisms[2]:

1) Through endocytosis, followed by lysosomatic degradation, which is controlled by C- type natriuretic peptide.
2) Through the enzyme endopeptidase, which degrades the peptide ring.

BNP in non - cardiac disorders

BNP plasma concentration is influenced by non - cardiac disorders (Table 1), as well as by drugs that inhibit its degradation, such as endopeptidase and vasopeptidase inhibitors.

Table 1. Non-cardiac disorders that increase BNP's concentration.

Excess of fluid volume
1. Renal failure
2. Liver cirrhosis with ascites
3. Primary aldosteronism
Renal failure
Inappropriate BNP production from tumors
Thyroid disorders
Increase of circulating glucocorticoids
Hypoxia

B-adrenergic blockers cause a small BNP rise, while inhibitors of the conversion enzyme of angiotensin cause a slight reduction of BNP level. BNP levels reduction is also noticed after stabilization of heart failure, although there is no data for the causes of this reduction.

Assessing BNP and NT- proBNP plasma concentration

There is no general agreement on the best method for assessing BNP and NT- proBNP plasma concentration. Inventing a method that is simple and also sensitive is difficult, due to the structural and metabolic characteristics of the cardiac natriuretic peptides.

The first method used to assess the plasma concentration of natriuretic peptides was radioimmunological (RIA), but its application was impractical, as it was time-consuming, complex and required a relatively large quantity of blood. To overcome these problems, researchers introduced a new immunoradiometric method (IMRA) that used two specific monoclonal antibodies against two loci of the BNP chain. The sole disadvantage of the second method, compared to the first, was its high cost. Recently, a new method was discovered, which gives the results in 15 minutes using a portable device that can be used by the patient's bedside (Biosyte Diagnostics San Diego). The results of this method show a satisfactory correlation to the results of the radio- immunological method[5].

In theory, assessing NT-proBNP is easier than assessing BNP, because of it's higher plasma concentration, yet the aforementioned techniques for assessing BNP plasma levels are unsuitable, as NT-proBNP is a long molecule and has different loci. For this peptide, two assessment methods of high sensitivity and accuracy have been introduced, that can prove useful for clinical practice as their cost is low and there is no radiation involved. Towards the

end of 2001, a new method for assessing NT-proBNP became available. This method takes barely 18 minutes to provide a fairly accurate result (Roche DiagnosticsGmbH, Basle)[6].

BNP plasma concentration increases with age and is slightly higher in women. The proposed normal range of values is 0.5-3.0 pg/mL (0.15- pmol/L), for both RIA and IMRA. The proposed threshold for the diagnosis of heart failure in patients over 55 years old, referring to the method commercially available (Biosite Diagnostics), is 80 pg/mL. For NT-proBNP, proposed normal range of values is 68- 112 pg/mL (8.2-13.3 pmol/L). Yet, we must note that these numbers are based on a small number of studies[5,6].

BNP use in clinical practice

Diagnosis

Heart failure diagnosis can often be rather difficult, especially in the emergency department, where patients present with ankle edema and dyspnea. In several studies, less than 40% of the patients that come to the ER with the above symptoms have a diagnosis of heart failure[2]. Undoubtfully, fast and reliable diagnosis of heart failure can be achieved with ultrasonographic assessment, but this method is not always applicable or available. Therefore, using a method that is simple and cheap and has the potential to verify the clinical suspicion of heart failure or, at least, to exclude patients that do not have heart failure- is quite useful[7,8].

Two years after the discovery of BNP, we already know that it's plasma concentration increases in heart failure, especially in highly symptomatic patients. It has been proposed that patients with BNP plasma concentrations of <20 pmal/ L have very few probabilities of suffering from heart failure, while patients with higher concentrations must be submitted to further investigation of their cardiovascular system. These proposals are consistent with the recent guidelines for the diagnosis of heart failure[8,16].
Coronary artery disease is the commonest cause of heart failure in Western societies, but is not the only one. Diastolic dysfunction and valvular disorders can both lead to the increase of BNP plasma concentration[3].

Patients with increased BNP levels must undergo further investigations, in order to estimate the etiology and pathophysiology of the underlying disease[8,16].

Left ventricular dysfunction diagnosis. Increased levels of BNP do not provide information on the diagnosis of systolic or diastolic dysfunction of the left ventricle. In patients with normal left ventricular systolic function, an increase of BNP plasma level indicates diastolic dysfunction, regardless of the existence of clinical signs. As recent studies in patients with normal systolic function verified ultrasonografically, increased BNP levels correlate well with Doppler measurements confirming diastolic dysfunction of the left ventricle[16].

Patients with asymptomatic dysfunction of the left ventricle are expected to have lower BNP plasma concentrations than patients with severe heart failure. The more severe the dysfunction of the left ventricle, the higher the BNP plasma concentration[16,17].

Diagnosis of left ventricular systolic dysfunction after acute myocardial infarction. BNP plasma concentration increases after acute myocardial infarction and this increase correlates to the severity of the infarction. Patients with smaller infarcts show an increase of BNP 20 hours after the initiation of symptoms. Patients with larger infracts, lower ejection fraction and more frequent signs of heart failure, reach maximum BNP levels 5 days after admission. In the acute phase, BNP values do not reflect patient's hemodynamic profile, but four days later BNP levels correlate well with the ejection fraction of the left ventricle and with pulmonary wedge pressure[9-12].

Theoretically, NT- proBNP is better in identifying patients with heart failure. It's increase is greater than that of BNP and it's plasma concentration more stable[13,14].

In summary, one must emphasize that BNP assessment can not replace ultrasound study as the method of choice for the evaluation of the left ventricular function after acute myocardial infarction.
Asymptomatic left ventricular dysfunction in the general population. The clinical usefulness of BNP assessment as a screening test of the asymptomatic systolic dysfunction in the general population remains to be proven.

Anthracycline cardiotoxicity Anthracycline dosage used in the chemotherapy of several malignant diseases is limited by its cardiotoxicity, which is dose-related. There are no encouraging data concerning the early diagnosis of left ventricular dysfunction in such cases using BNP.

Right ventricular failure. Patients with pulmonary hypertension have increased BNP levels because of it's increased production in the right ventricle. The

level of the increase correlates well with the level of dysfunction of the right ventricle in patients with pulmonary hypertension (primary or thromboembolic) or congenital heart failure. Pressure loading of the left ventricle increases BNP plasma concentrations more than volume loading[3,4,15].

Prognosis

Heart failure prognosis. Until today, published studies indicate that BNP (or NT-proBNP) plasma concentration provides important information on the prognosis of heart failure patients and support it's use as an adjuvant to clinical assessment, especially in centers where risk stratification is of great importance (i.e. transplantation units). Further research is necessary to clarify whether BNP plasma levels are a satisfactory means of identifying patients with low risk for future hospitalizations[15-17].

Prognosis after acute coronary syndrome. Increased BNP levels on admission in patients that have had an acute coronary syndrome without ST elevation, increases the possibility of both short-term and long-term complications. Recent studies indicate that the prognostic value of NT-pro BNP assessment in patients with coronary syndrome is very high and that NT-proBNP is an independent predictive factor of the severity of the coronary artery disease. Patients with NT-proBNP > 1654 ng/L had 27 times greater risk of dying than patients with NT-proBNP< 122 ng/L[17-19].

Prognosis in the general population. In all studies, BNP plasma concentration represents an independent predictive factor for survival, irrespective of the existence of coronary artery disease. Assessing NT-proBNP concentration didn't seem to add further information[20].

Prognosis in pulmonary hypertension. In pulmonary hypertension patients, prognosis is worse for those with higher BNP plasma levels - a 4-fold increase of mortality within 2 years has been noted in patients with BNP values twice above the normal[3,4,15].

Therapy assessment

Pharmacological therapy of heart failure targets the improvement of symptoms and signs of the disease and uses the best possible dosages of angiotensin conversion enzyme inhibitors and b - adrenergic blockers, according to large, randomized clinical trials. There are indications that assessing BNP levels and adjusting therapy (dosage increase) according to it, can achieve the best possible treatment of heart failure[2].

Increase of BNP plasma concentration can be achieved either with i.v. administration of the peptide or with inhibition of the endopeptidase that is partially responsible for it's removal from circulation.

Intravenous administration of BNP. Per os administration is useless, as the peptide is destroyed in the gastric tube (due to 3D structure destruction). Intravenous administration of synthetic human BNP (nesiritide) in heart failure patients causes dilation of the arteries and veins without causing any change to the heart rhythm, thus leading to increased cardiac output due to increased stroke volume. It also promotes diuresis, either because of the increased cardiac output or because of a direct natriuretic action. Studies have been conducted using the peptide for up to seven days with no allergic reactions noted. An average dose of 0.030 mg/kg/min diminishes pulmonary wedge pressure from 28 mmHg to 18 mmHg in patients with heart failure due to systolic dysfunction of the left ventricle and increases cardiac index from 1.9 to 2.3 L/min/m^2. The most important side effect is hypotension, which is, nonetheless, dose- related (administration of 0.030 mg/kg/min decreases systolic pressure about 10 mmHg). Ten to fifteen percent of the patients were withdrawn from the treatment due to hypotension. In July 2001, the FDA approved the administration of BNP in the treatment of heart failure. Although BNP administration causes pulmonary artery dilation, there are no large studies of patients with cor pulmonale or pulmonary hypertension due to other causes. In patients with heart failure caused solely by diastolic dysfunction, BNP administration reduces the exercise- induced increase of left atrial pressure[1].

In summary, assessing BNP plasma level seems to be an important method for heart failure diagnosis and for prognosis evaluation. Nonetheless, it can in no way replace heart ultrasound as the method of choice for the evaluation of left ventricular function in patients with acute dyspnea or in patients after acute myocardial infarction.

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