REVIEW ARTICLES

Significance of Brain Natriuretic Peptide among Patients with Cardiac Dysfunction and in Pregnancy

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Abstract

The cardiac natriuretic peptides or the natriuretic hormones produced and secreted by human cardiomyocyte, form a family of bioactive peptides. Different types of natriuretic peptides have been identified, the most important being atrial natriuretic peptide (ANP) and brain natriuretic peptide the (BNP). These are derived from the N-terminal portion of proANP (NT-proANP) and proBNP (NT-proBNP) chains. The study of natriuretic peptide, and other neurohormonal regulators of the cardiovascular system marked the emergence of a new field of integrated basic and clinical research - cardiovascular endocrinology. The most commonly used in clinical practice are the natriuretic peptide BNP and NT-proBNP. Although the precursor is synthesized and released in both the atria and the ventricles, the main source of release is the left ventricle. BNP/NT-proBNP is secreted in response to the increased tension on the heart wall, as occurs in the case of volume overload of any etiology, and secretion is directly proportional to the degree of wall stress. As a result, scholars have suggested that determination of the cardiac peptides may be clinically relevant for making an early and rapid diagnosis of heart failure, evaluating the severity of cardiac insufficiency and wall stress, as well as for monitoring the efficacy of therapeutic measures

Key words: heart failure, natriuretic peptide, pregnancy complications.

Значение мозгового натрийуретического пептида у пациентов с нарушением функции сердца и у беременных

Сердечный натрийуретический пептид или сердечные натрийуретические гормоны, производимые и выделяемые кардиомиоцитами, образуют семейство биологически активных пептидов. До сих пор было определено несколько видов натрийуретических пептидов, наиболее важными из которых являются: предсердный натрийуретический пептид (ПНП), мозговой натрийуретический пептид (МНП), производные от терминальной части цепи проПНП N-(NT-proANP) и проМНП (NT-проBNP). Исследование натрийуретических пептидов и других нейрогормональных систем, участвующих в нейроэндокринной регуляции функции сердечнососудистой системы, привело к появлению нового комплексного поля фундаментальных и клинических исследований – сердечнососудистой эндокринологии. Наиболее распространенные - натрийуретический пептид МНП и его предшественник NT-проМНП, которые синтезируются и секретируются как в предсердиях, так и в желудочках. МНП/NT-проМНП выделяется в ответ на рост давления на сердечную стенку при повышении объема перегрузки любого генеза, при этом секреция прямо пропорциональна степени напряжения миокарда. Чаще всего, объем перегрузки вызван сердечной недостаточностью при пороках сердца. Исходя из вышесказанного, некоторые ученые полагают, что определение сердечного пептида важно в качестве средства ранней и быстрой диагностики сердечной недостаточности, а также для оценки эффективности лечебных мероприятий.

Ключевые слова: пороки сердца, натрийуретические пептиды, беременности осложнения.

Introduction

Despite advances in the treatment of heart failure, there are still problems in correctly identifying, diagnosing, and stratifying patients with this condition. To initiate optimal and timely treatment it is necessary to identify heart failure early in its course, however diagnosis is often difficult because of nonspecific symptoms and the frequent presence of heart failure in other diseases. Determination of cardiac peptides is at present a straightforward and rapid diagnosis of heart failure, and is also useful for assessing its severity and prognosis as well as the effectiveness of therapeutic measures [1, 20].

Types and mechanisms of action of natriuretic peptides

Cardiac natriuretic peptide or natriuretic hormones produced and secreted by human cardiomyocytes, are a family of bioactive peptides. So far the focus has been on identifying the types of natriuretic peptides, the most important being: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), other peptides derived from N-terminal portion of proANP chains (NT-proANP) and proBNP (NT-proBNP) and C-type natriuretic peptide (CNP), which is produced and secreted by cardiomyocytes and other tissues as well. The discovery of new forms of the natriuretic peptide family actively continues [16].

Identification of the natriuretic peptides, and other neurohormonal systems involved in regulating the cardiovascular neuroendocrine, marked the emergence of a new field of integrated fundamental and clinical research - cardiovascular endocrinology [16].

The most commonly used in clinical practice are the natriuretic peptides BNP and NT-proBNP precursor. They are synthesized and released in both the atria and the ventricle, however most of the secretion is mainly from the left ventricle. BNP/NT-proBNP is secreted in response to increased tension on the cardiac walls, as occurs in cases of volume overload of various etioloies, and secretion is directly proportional to the degree of the wall tension.

BNP/NT-proBNP is a natural antagonist of the renin-angiotensin-aldosterone system, acting on the balance of sodium and water, having effects on decreasing peripheral vascular resistance, relaxing vascular smooth muscle, and inducing decrease in blood pressure, natriuresis and diuresis. These effects are achieved by binding to natriuretic peptide receptors on cell surfaces. These receptors are widespread in the cardiovascular system, lungs, kidneys, skin and central nervous system.

Diagnostic capacity

Natriuretic peptides are biomarkers and important means of diagnosis. Currently, plasma levels of natriuretic peptides or their precursors, especially BNP and NT-proBNP are useful in diagnosing heart failure and are included in all guidelines for heart failure [1].

The increased level of natriuretic peptides may indicate left ventricular diastolic dysfunction, left ventricular hypertrophy, valvular, acute or chronic cardiac ischemia, hypertension and pulmonary embolism.

The best predictive value of BNP/NT-proBNP was obtained for detection of severe left ventricular systolic dysfunction with concomitant ventricular hypertrophy: sensitivity 71% and specificity of 86%. Thus the use of BNP/NT-proBNP for the exclusion of the diagnosis of heart failure is based on very high negative predictive value [1]. Negative predictive value of BNP/NT-proBNP in suspected left ventricular systolic dysfunction with concomitant ventricular hypertrophy was 99%, sensitivity of 71%. Thus, BNP/NT-proBNP is able to detect most subjects with severe left ventricular dysfunction and concomitant ventricular hypertrophy with minimal risk of missing the diagnosis of heart failure.

The diagnostic utility of BNP/NT-proBNP in detecting systolic dysfunction, diastolic dysfunction or left ventricular hypertrophy has recently been confirmed in a clinical study of 94 patients, in addition, a population study suggested that measurement of BNP/NT-proBNP are effective method for screening patients with left ventricular dysfunction.

Left ventricular systolic function is preserved in 20-50% of patients with heart failure. Although these patients have a lower mortality compared with patients with left ventricular systolic dysfunction, morbidity is similar. In patients with preserved left ventricular systolic function there is limited information on severity and prognostic factors. Determination of NT-proBNP is a strong test for the diagnosis of heart failure regardless of left ventricular systolic function.

S. Wright has shown that NT-proBNP is present in high levels in cardiac dysfunction and may improve the diagnostic accuracy of heart failure. Atisha Tschope D. and C. [20] have found a good diagnostic accuracy of BNP and NT-proBNP for heart failure, especially in cases of systolic dysfunction as compared with diastolic dysfunction [5, 20]. However, BNP/NT-proBNP allows excellent diagnostic accuracy of isolated diastolic heart failure as well. NT-proBNP can reliably detect isolated diastolic dysfunction in symptomatic patients and is a useful tool to identify patients with reduced exercise tolerance of non-cardiac origin [20]. NT-proBNP may be recommended as a test to exclude patients with heart failure. Moreover, in patients with increased risk of heart failure due to coronary disease, presence of Q waves on ECG or left bundle-branch block major, even if asymptomatic, screening by NT-proBNP may provide relevant diagnostic and prognostic information [1].

In general, the predictive values of BNP/NT-proBNP vary depending on the degree of left ventricular dysfunction, increasing with severity of heart damage and modulated by the presence or absence of ventricular hypertrophy.

Elevated levels of ANP, BNP and NT-proANP were found in patients with cardiac dysfunction of different etiologies (tachycardia, valvular stenosis, or ventricular dysfunction). High circulating levels of natriuretic peptides are associated with: 1) elevated atrial and pulmonary pressures; 2) reduction of systolic and diastolic ventricular function; 3) left ventricular hypertrophy and 4) severe myocardial infarction. Although both peptides, ANP and BNP, are elevated in serum in the presence of left ventricular hypertrophy, BNP is a better indicator for left ventricular hypertrophy.

Major value of plasma natriuretic peptides in examining patients with suspected cardiac disease is based on the following assumptions: 1) a normal value is not consistent with cardiac disease; 2) significantly higher levels may be an indication for further assessment of the causes of cardiac dysfunction and 3) significant increase in plasma levels of natriuretic peptides after myocardial infarction can identify patients at high risk of death.

Echocardiography is the "gold standard" test for examining patients with suspected left ventricular failure, but cost and availability limit its use for routine screening.

Natriuretic peptides, especially BNP and NT-proBNP, are good markers for the screening of heart failure in symptomatic patients. NT-proBNP has a high sensitivity, excellent prognostic impact, high stability. It is easy to use and is cost-effective. Natriuretic peptides may be used as pre-echocardiography screening test: to assess the need for echocardiography. If NT-proBNP is negative, heart failure is unlikely and further evaluation of this diagnosis may not be necessary. If elevated levels are detected, it is necessary to evaluate the cardiovascular system with further testing, including echocardiography [1].

It has been shown that BNP/NT-proBNP can identify a low left ventricular ejection fraction amongst a general population of hospitalized patients [8] as well as amongst patients with coronary heart disease [7]. In particular, the determination of BNP/NT-proBNP may be useful for differentiating healthy subjects from patients with different stages of heart failure.

Thus, in contemporary clinical practice, BNP and NT-proBNP determination is usually a test to exclude subclinical cardiac disease that has increased wall tension as an underlying factor. This is important both for primary care and specialized medical care. The most widely accepted is the use of natriuretic peptides for heart failure screening to identify patients for further cardiac testing (echocardiography and other investigations evaluating expensive) and pharmacological treatment.

Prognostic value

The BNP/NT-proBNP may be useful for determining the prognosis of long-term survival in patients with heart failure and/or after myocardial infarction.

Studies have shown that in patients with decompensated heart failure, regardless of left ventricular systolic function status, NT-proBNP identifying the risk of complications [5].

The level of BNP/NT-proBNP is a strong and independent predictor of cardiovascular mortality and sudden death in patients with myocardial infarction, chronic heart failure, and acute coronary syndromes [2] as well as in elderly without any known cardiovascular disorders.

In randomized study looking at patients with ejection fraction below 25% and symptoms of chronic congestive heart failure at rest or with minimal effort, NT-proBNP proved to be a strong predictor for subsequent all-cause mortality or hospitalization for heart failure.

Even a single measurement of BNP/NT-proBNP, obtained in the first days after onset of ischemic symptoms, provides sufficient information for use in risk stratification of patients with acute coronary syndromes. BNP is also a useful marker for monitoring severity of right sided heart failure in pulmonary hypertension [4].

Multiple studies suggest that BNP has a better clinical utility than other cardiac natriuretic hormones. Plasma BNP is more useful than plasma ANP to assess mortality in patients with chronic congestive heart failure, as plasma levels of BNP provide prognostic information independent of hemodynamic parameters.

An increased preoperative plasma BNP level is a strong and independent predictor of postoperative atrial fibrillation, in which case prophylactic antiarrhythmic therapy should be considered.

To define the value suggestive of heart failure, many studies [13, 19] use the level of BNP > 100 pg/ml. In all cases of elevated BNP, serum creatinine should be checked to exclude renal dysfunction [19].

Studies that have assessed the value of NT-proBNP, obtained values of "rule out" between 100-160 ng/ml which have provided a negative predictive value of 92-100% and a positive predictive value between 15 and 76%, a sensitivity of 94-98% and a specificity of 35-68% [10]. Currently, there is general agreement for the cutoff value of 125 ng/1 in patients with symptoms suggestive of heart failure [1].

Some studies indicate an increase in natriuretic peptide concentration with age and the female sex hormones in healthy adults, this increase is probably caused by changes in natriuretic peptide metabolism, as well as age-related changes in cardiac and renal functions [8] and should be taken into account in the calculation of reference values for cardiac natriuretic peptide.

So far, there is no consensus on the best methods of quantitative evaluation of cardiac natriuretic peptides. To facilitate widespread clinical applicability of the determination of these hormones, further research is necessary in order to select the most reliable, sensitive, specific and rapid tests.

Therefore, natriuretic peptides are currently considered the most promising markers of cardiac function and cardiovascular prognosis. BNP and NT-proBNP measurement was introduced in clinical practice for diagnosis and risk stratification of CVD, especially in heart failure [1]. Although natriuretic peptides may predict a beneficial treatment in ischemic left ventricular dysfunction, assessing their role in monitoring the treatment remains to be determined.

Natriuretic peptide in pregnant women with CVD

Although clinical and echocardiographic predictors of cardiac complications during pregnancy have been identified [14], current risk stratification does not include adequate assessment of cardiac adaptation of the mother during pregnancy. In addition, because the symptoms of cardiac decompnesation can mimic other pregnancy symptoms, clinical diagnosis of cardiac dysfunction is more difficult in pregnant women. Therefore, there is an important role for the detection of cardiac decompensation using biochemical markers such as serum natriuretic peptides [19].

Serum concentrations of NT-proBNP can be used to monitor heart function during pregnancy, and normal values have been suggested for this purpose [9].

In nonpregnant patients with cardiac disease (congenital or acquired), higher BNP levels at rest are correlated with latent ventricular failure, as evidenced during exercise [12]. In spite of hemodynamic changes in pregnancy, most healthy pregnant women during pregnancy and after birth have elevated levels of BNP that remain stable compared with healthy nonpregnant women [13]. On the other hand, preeclampsia and gestational hypertension are associated with progressively increasing levels of NT- proBNP [9].

NT-proBNP, evaluated and compared with dynamic echocardiographic data, is a better tool for clinical monitoring and management of pregnant women with pre-existing dilated cardiomyopathy [3], severe congenital aortic stenosis, hypertension and preeclampsia [15, 18]. NT-proBNP levels increase in pregnant women with hypertensive disorders, compared with pregnant women with normal blood pressure level (81 pg/ml and 37 pg/ml, respectively, $p < 0.001$) [15], and this increase is progressive. Depending on the severity of the disease, proBNP levels can reach different peaks: gestational hypertension (64 pg/ml), mild preeclampsia (89 pg/ml) and severe preeclampsia (157 pg/ml) [15]. Moreover, the elevated value of NT-proBNP early in the pregnancy course can help predict the occurrence of future complications [3].

Results of the first prospective study to examine the BNP levels in pregnant women with cardiac dysfunction were

published in 2010. The study had two objectives (estimating BNP levels in pregnant women with cardiac dysfunction, and assessing the relationship between BNP levels and cardiac complications of pregnant women) and found higher mean values of BNP levels in women with cardiac dysfunction compared with healthy women. All women with complications during pregnancy had a higher BNP level of 100 pg/ml [19].

There is a subgroup of pregnant women with cardiac disease who have high BNP levels during pregnancy, but no clinical cardiac complications. But the significance of this finding requires further study [13].

In women with a risk score (low risk for cardiac complications), the rate of maternal cardiac complications during pregnancy was 0% in women with BNP levels < 100 pg/ml and 8% in women with BNP levels > 100 pg/ml. Women with a score of l (intermediate risk for cardiac complications), the rate of maternal cardiac complications during pregnancy was 0% in women with BNP levels < 100 pg/ml and 60% in women with BNP levels > 100 pg/ml ($p < 0.03$) [19].

There is some evidence that suggests that pregnancy adversely affects the natural course of cardiac function in women with left ventricular systolic dysfunction [12] and could have delayed effects on ventricular function in the future [20]. Therefore, this group of women, especially those with an abnormally high BNP level during pregnancy should continue surveillance after pregnancy.

Thus, normal BNP levels during pregnancy in women with CVD predict a low risk for maternal cardiac complications. No women with BNP levels < 100 pg/ml showed any cardiac complications, with a negative predictive value of 100% for identification of cardiac complications during pregnancy [19].

Heart failure is a particular risk in pregnant women with acquired valvular heart disease. For a sensitive diagnosis, an early and less costly screening method may be proposed - the determination of terminal fragment BNP or NT-proBNP levels, which increases proportionally with the degree of heart failure.

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