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**Abstract:** B-type natriuretic peptide (BNP) is a neurohormone produced mainly by ventricular myocytes in response to increased left ventricular end-diastolic pressure. Patients with acute decompensated heart failure often have elevated plasma BNP. However, recent clinical observations have demonstrated that in patients with advanced heart failure, the plasma level of BNP is lower than those with acute heart failure. We hypothesized that a lower circulating BNP level in patients with chronic and advanced heart failure is due to the exhaustion of the biosynthesis mechanisms and is associated with a poor outcome in these patients.
Low levels of B-type natriuretic peptide predict poor clinical outcomes in patients with chronic and advanced heart failure

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Summary

B-type natriuretic peptide (BNP) is a neurohormone produced mainly by ventricular myocytes in response to increased left ventricular end-diastolic pressure. Patients with acute decompensated heart failure often have elevated plasma BNP. However, recent clinical observations have demonstrated that in patients with advanced heart failure, the plasma level of BNP is lower than those with acute heart failure. We hypothesized that a lower circulating BNP level in patients with chronic and advanced heart failure is due to the exhaustion of the biosynthesis mechanisms and is associated with a poor outcome in these patients.

Key words: B-type natriuretic peptide; heart failure; prognosis; mortality.
Introduction

B-type natriuretic peptide (BNP) is a 32-amino-acid polypeptide released from cardiac ventricles in response to myocardial stretch or increased wall tension [1]. BNP is involved in the regulation of blood pressure, blood volume and sodium balance [1]. BNP reduces cardiac preload by causing vasodilatation and increasing vascular capacitance [1]. It also induces natriuresis by its actions on the renal vasculature and tubules [1].

Circulating levels of BNP are elevated in patients with acute decompensated heart failure, due to activation of beneficial compensatory mechanisms [2]. Levels of BNP can be used to confirm the diagnosis of heart failure and to aid in the assessment of prognoses [2-6]. BNP can also be used in risk stratification and in prediction of mortality in patients with acute coronary syndrome [7]. The baseline levels of BNP are correlated with the risk of death, heart failure, and myocardial infarction at 30 days, 6 months and 10 months in patients suffering from acute coronary syndrome [7, 8]. It has also been suggested that even in acute coronary syndrome patients who had no obvious clinical manifestations of heart failure, an increase in plasma BNP is associated with a higher mortality and a poorer prognosis [9].

BNP synthesis and release during acute heart failure

The cellular storage and secretion of proBNP-derived peptides are complex. BNP genes are expressed in several types of cardiac cells, such as atrial, ventricular myocytes and cardiac fibroblasts [10]. In the healthy heart, BNP gene expression occurs mainly in the atria where secretory peptide granules are stored. In contrast, ventricular myocytes
in the healthy heart do not seem to produce these granules, and do not contain proBNP-derived peptides [10]. However, ventricular BNP gene expression is up-regulated in diseases that affect the ventricles, such as dilation of the left ventricle during heart failure. There have been some reports on both secretory granules and proBNP-derived peptides in ventricular myocytes during acute heart failure [10].

In young and healthy subjects, plasma BNP is usually below 20 pg/ml [11]. Plasma BNP concentration is increased in patients with ventricular systolic dysfunction. Many previous studies have demonstrated that in patients with acutely decompensated heart, circulating BNP levels are often above 100 pg/ml [3-8].

The activation of natriuretic peptides system is considered as a compensation mechanism in response to the failing heart. Plasma BNP correlates well with pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, and left ventricular ejection fraction in patients with systolic left ventricular dysfunction [11]. BNP concentration also closely relates to the severity of clinical heart failure assessed by New York Heart Association functional class: the greater the functional class, the higher the circulating BNP levels [3, 4, 6].

**BNP synthesis in advanced heart failure**

During acute heart failure, a higher level of BNP usually indicates an increased risk of death or hospital re-admission, and that lower circulating level reflects a more stable compensated or effectively treated status [12]. However, up to 20% of patients with symptomatic chronic hear failure may have “normal level” (<100pg/ml) of BNP [13, 14]. A relatively small study has found that patients with end-stage heart failure and a poor
prognosis may actually have a lower level of circulating BNP [15]. The investigators analysed whether N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) and BNP levels are related to mortality in 40 patients treated for decompensated chronic heart failure. Cardiovascular mortality during 10-month follow-up was 40%. BNP and NT-pro-BNP levels were lower in patients who died [15].

Our recent observations in 50 patients with advanced congestive heart failure for more than two years have also shown that the correlation between the level of BNP and left ventricular ejection fraction, which is evident in acutely decompensated heart failure, is lost in patients with chronic severe heart failure [16]. The average BNP in the 12 patients who died during follow up was significantly lower (501±72 pg/ml) than those who survived (877±89 pg/ml) [15]. Amongst the non-survivals, three had a BNP less than 100 pg/ml at the beginning of the follow up [16]. Logistic stepwise regression analysis, after adjusting age, sex, duration of heart failure, left ventricular ejection fraction, and serum creatinine levels, demonstrated that a lower BNP level (<520 pg/ml) on admission was an independent predictor for mortality in these patients [16].

**Hypotheses**

Although elevated plasma BNP during heart failure usually indicates a poor clinical outcome and low levels suggests a compensated state, recent data showed that patients with end-stage heart failure and poor short-term survival have lower natriuretic peptide levels than those who survive. Therefore, it is likely that in advanced chronic heart failure, the natriuretic peptide system in the cardiac tissues can no longer contribute adequately to neurohormonal compensation, and low levels of BNP may reflect an
impaired neurohormonal response. Large clinical trials may be required to investigate whether paradoxically low BNP levels during advanced and chronic heart failure are an adverse prognostic marker.
Referentes


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