Use of Brain Natriuretic Peptide and Bioimpedance to Guide Therapy in Heart Failure Patients

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Abstract
The key management goals for the stabilization of patients admitted for acutely decompensated heart failure (ADHF) include relief of congestion and restoration of hemodynamic stability. Nevertheless, in spite of clinical improvement, many patients are discharged with hemodynamic congestion. In response to volume expansion, the heart secretes the brain natriuretic peptide (BNP) with a biological action that counter-regulates the activation of the renin-angiotensin-aldosterone system. Since BNP is released by increased volume load and wall stretch, and declines after treatment with drugs of proven efficacy, on the basis of an improvement in filling pressures the level of BNP has been proposed as a ‘measure’ of congestion. The BNP level of a patient who is admitted with ADHF comprises two components: a baseline, euvolemic ‘dry’ BNP level and a level induced by volume or pressure overload (‘wet’ BNP level). So, the prognostic value of BNP during hospitalization depends on the time of measurement: from the lowest on admission when congestion is present (wet BNP) to the highest on clinical and instrumental stability (dry BNP), following the achievement of normohydration, as determined by fluid volume measurement. Euvolemia can be set as the primary goal of treatment for ADHF with dry BNP concentration as a target for discharge other than improvement of symptoms, because high BNP levels predict rehospitalization and death. Discharge criteria utilizing both BNP and hydration status measurement which account for the heterogeneity of the patient population and incorporate different strategies of care should be developed. This could in the next future offer an aid in monitoring heart failure patients or actively guiding optimal titration of therapy.

Despite advances in pharmacological therapy and intensive application of guidelines [1], acute decompensated heart failure (ADHF) is the leading cause of hospitalization [2] and readmission [3] in many hospitals worldwide. As a
consequence, all intervention strategies for acute heart failure in the field of health economics mainly focus on the early identification of clinical and instrumental indicators, which allow in-hospital treatment and stratification of high-risk patients at discharge [4].

ADHF is a largely hemodynamic disorder, with 90% of hospitalized patients presenting with volume overload (evaluated on a clinical basis) [5]. The key management goals for the initial stabilization of patients include relief of congestion and restoration of hemodynamic stability to prevent renal dysfunction.

Under conditions of blood pressure overload and in response to blood volume expansion, the heart secretes natriuretic peptides with a biological action that counter-regulates the activation of the renin-angiotensin-aldosterone system [6]. Plasma levels of brain natriuretic peptide (BNP) reflect left ventricular dysfunction, with high filling pressures secondary to volume overload, and decrease in concert with a reduction in either filling pressures or body hydration during acute diuretic and vasoactive therapy [7, 8].

In spite of clinical improvement, many patients are discharged with signs and symptoms of ‘hemodynamic’ congestion. It has been demonstrated that most patients hospitalized for acute heart failure show evidence of volume overload at discharge [9]. Furthermore, subclinical volume expansion may cause diuretic undertreatment, leading to symptom worsening and disease progression with an unfavorable outcome [10]. Episodes of decompensation requiring hospitalization are characterized by hemodynamic deterioration and water and sodium retention. A recent review by Gheorghiade and Pang [11] states that strategies for discharge after complete resolution of signs and symptoms compared with earlier discharge with residual symptoms and close follow-up for further optimization should be investigated.

The treatment strategy of patients with ADHF in the hospital setting relies on the understanding of the hemodynamic determinant(s) of elevated BNP levels.

**Rationale for Lowering Natriuretic Peptides in Acute Decompensated Heart Failure**

Since BNP release is triggered by increased volume load and wall stretch [6], the level of BNP/NT-proBNP has been proposed as a ‘measure’ of congestion [12]. The plasma concentrations of BNP increase in unstable patients with ADHF and decline after treatment with drugs of proven efficacy (diuretics, vasodilators, ACE inhibitors, angiotensin receptor blockers, beta-blockers and aldosterone antagonists), on the basis of an improvement in filling pressures [7, 8]. It has been hypothesized that the BNP level of a patient who is admitted with ADHF comprises two components: a baseline, euvolemic ‘dry’ BNP level and a level induced by acute pressure or volume overload (‘wet’ BNP level) [13]. Valle et al. [14] demonstrated that reduction in BNP levels
Use of BNP and Bioimpedance to Guide Therapy in HF Patients

correlates with reduction in fluid overload and improvement of body hydration status (fig. 1).

The prognostic value of BNP during hospitalization depends on the time to measurement: it is the lowest on admission when congestion is present (wet BNP), intermediate during episodes of clinical stability (dry BNP), and the highest after clinical and instrumental stability following the achievement of normohydration as determined by fluid volume measurement (optivolemic BNP) [14].

Bettencourt et al. [9] found that variations of natriuretic peptides during hospitalization (a reduction of >30% from baseline) as well as predischarge levels are predictors of hospital readmission and death within 6 months. Logeart et al. [15] examined the prognostic value of serial admission and discharge BNP measurements among 105 patients surviving hospital stay for decompensated heart failure. Patients with a predischarge BNP level of 350–700 pg/ml had a five times higher risk of death or rehospitalization for heart failure than patients with a predischarge BNP <350 pg/ml. A predischarge BNP level >700 pg/ml was associated with an increased risk of death and rehospitalization for heart failure by a factor of 15 and reached a rate of 90%. Cournot et al. [16] reported data from a prospective cohort study of 61 consecutive patients hospitalized for decompensated heart failure. Cardiac death or readmission were predicted by changes in BNP, with the poorest prognosis in patients who did not achieve a decrease of at least 40%.

Current evidence suggests that whatever the risk profile of the patient studied, a correct interpretation of ‘BNP variations’ in the acute phase has implications for risk stratification as a result of a dynamic process. BNP changes during hospitalization are strongly dependent on resolution of congestion, and elevated BNP levels at discharge usually reflect persistent congestion.

Fig. 1. BNP changes according to hydration status at discharge as determined by BIVA.
BNP concentrations when euvolemia is achieved are closely related to both functional class and prognosis in heart failure, and either ‘predischarge BNP values’ or ‘changes in BNP from admission to discharge’ predict medium-term prognosis [14, 17].

It is well-known that plasma BNP levels are affected by the presence of congestion and volume overload. However, it is worth noting that dry BNP levels at discharge for prognostic purposes are often subjective and loosely based on clinical criteria.

**Use of Bioimpedance Vector Analysis and Brain Natriuretic Peptide to Guide Therapy in Patients with Acute Decompensated Heart Failure**

The prognostic role of neurohumoral markers in ADHF during hospitalization is of great interest and clinical relevance. In patients admitted for ADHF, BNP levels rapidly decrease after short-term therapeutic interventions [7, 8], and the reduction in BNP levels correlates with a reduction in fluid overload and an improvement in body hydration status [14, 18]. However, growing evidence shows that hypervolemia by itself is independently associated with mortality [19–22]. Several indices have been employed to assess hydration status, including changes in body weight and hematologic, urinary, and cardiovascular indices. Nevertheless, targeting a specific reduction of body weight is often challenging because of the difficulty in defining adequate hydration status. Recent studies have suggested minimal weight changes before, during and after an episode of acute heart failure. The ADHERE registry reported that body weight was not decreased but rather increased during hospitalization in about half of the patients admitted for heart failure.

Evidence from the last decade supports the use of bioimpedance vector analysis (BIVA) to monitor hydration status [23–26]. Notwithstanding certain limitations (e.g. dependence on factors such as skin temperature, food or drink consumption, and body posture during measurement), BIVA is a noninvasive and practical method for assessing total body water. As a consequence, BIVA can be used to guide fluid-related therapies. It allows a rapid, accurate and noninvasive determination of body hydration status, correlates with NYHA class and seems to have a high diagnostic accuracy in the differential diagnosis of heart failure-induced dyspnea [27]. The relationship between body hydration status and BNP levels in patients receiving diuretic therapy remains to be clearly elucidated in the setting of ADHF. The adverse effects of diuretic use on ADHF may also cause acute renal injury by further reducing renal perfusion, glomerular filtration rate, and responsiveness to natriuretic peptides regardless of whether systolic function is decreased or preserved [28]. BIVA adds useful information to standard clinical parameters in monitoring patients with congestion during diuretic treatment. Most importantly, BNP/BIVA-guided management allows
to detect dry BNP values avoiding unnecessary overtreatment of patients with unrecognized body normohydration or dehydration resulting in renal impairment. BNP levels measured during clinical stability should reflect euvolemia or optivolemia defined as the attainment of adequate hydration to maintain renal function. Moreover, BNP levels may be persistently elevated even after adequate hydration has been achieved due to myocardial stretching (dry BNP). BNP concentrations are also found to vary considerably from one measurement to another, with values during clinical stability tightly correlated with the disease state and the underlying cardiac dysfunction. Therefore, it can be reasonably hypothesized that in a sizeable proportion of patients BNP levels at discharge, i.e. during clinical stability, do not truly reflect dry weight BNP, especially in those overtreated with diuretics. As a consequence, decompensated patients show wide fluctuations in BNP concentration that may also exhibit significant increases with respect to values measured during clinical stability.

This concept has been stressed in a recent consensus paper on natriuretic peptides in clinical practice [12]. It suggests predischarge BNP/NT-proBNP as a tool to establish the patient’s ‘dry weight’, although patients often need additional diuresis after discharge. Our aim is to extend this concept to include the use of BIVA as an adjunct to support clinical decision making. In a previous study from our research group, the extent and rapidity of BNP changes during hospitalization (an average of 5.5 days) were shown to be a reliable outcome predictor in ADHF [14]. This study demonstrates that, during hormone-guided treatment, variations in BNP levels and changes in bioelectrical impedance as a surrogate marker for body hydration status allow appropriate timing of patient discharge and predict the occurrence of cardiovascular events at 6 months. We retrospectively evaluated 186 patients admitted with ADHF. Therapy was titrated according to BNP levels, and bioelectrical impedance was measured serially. A target value of <250 pg/ml was reached in 54% of patients. A BNP value of <250 pg/ml at discharge predicted a 16% event rate at 6 months, whereas a BNP value of >250 pg/ml was associated with a far higher rate of adverse events (78%). No significant differences in event rates were found in relation to the time necessary to obtain a reduction in BNP levels below 250 pg/ml (fig. 2). This study is consistent with findings from other authors [7, 8, 18]. In particular, Johnson et al. [8] reported that neurohormonal activation rapidly decreases after short-term therapy tailored to decrease severely elevated filling pressures in patients admitted for class III–IV heart failure. Furthermore, bioelectrical impedance analysis seems to be able to monitor diuretic therapy in acute heart failure as well as to assess serial changes in body fluids [18, 26] and increases the usefulness of BNP as a ‘guide’ to treatment, as previously reported [14, 29]. This study extends these observations to hospitalized patients, showing that BNP can be used to guide treatment during acute heart failure. For strictly clinical purposes, the patients admitted for acute heart failure who respond quickly to intravenous diuretics and experience a decline in BNP values below 250 pg/ml (reaching
euvolemia and clinical stability) may be safely discharged avoiding unnecessary prolonged hospitalizations. Conversely, clinically stable patients with BNP levels still elevated above 250 pg/ml probably deserve further evaluation to ascertain subclinical volume overload amenable to more aggressive treatment, preventing inappropriate discharge.

**Conclusion**

Patients hospitalized for heart failure represent a heterogeneous population, and the identification of those who may benefit from more aggressive intervention is a critical issue that remains challenging.

In patients with congestion, a strong relationship does exist between clinical signs of fluid retention and increased BNP levels. Euvolemia can be set as the primary goal of treatment for ADHF with dry BNP concentration as a target for discharge other than improvement of symptoms, because high BNP levels not only predict rehospitalization within 30 days but also indicate high mortality rates. The addition of BIVA (a simple, noninvasive tool to objectively measure body water) to serial BNP measurement may provide more accurate risk stratification, especially in patients receiving diuretic therapy.

Discharge criteria utilizing both BNP and BIVA which account for the heterogeneity of the patient population and incorporate different strategies of care.

**Fig. 2.** Kaplan-Meier curves showing the cumulative incidence of death and readmission according to predischarge BNP levels.
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References


