

# The role of natriuretic peptides in defining the diagnosis and prognosis of medical diseases

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### Abstract

Natriuretic peptides, BNP and NT-proBNP are increased in patients who have a higher myocardial wall tension. They have been extensively used to diagnose heart failure in patients presenting dyspnea. BNP and NT-proBNP serum levels are influenced by variables such as age, gender, body mass index and renal function. Lately, their increase in acute coronary syndromes, stable atherosclerotic

coronary artery disease, chronic obstructive pulmonary disease, pulmonary hypertension and sepsis has been investigated. We review the diagnostic and prognostic value of circulating natriuretic peptides in the assessment of several medical diseases.

Key words: BNP, Internal Medicine, prognosis.

### Natriuretic Peptides

In 1981, De Bold and his assistants found out that the endovenous infusion of auricular extract in rats would lead to abundant natriuresis.<sup>1</sup> Such finding led to discovering the auricular natriuretic peptide (ANP),<sup>2</sup> the first of a protein family with natriuretic, diuretic and vasodilatory properties. Subsequent research enabled to identify other members of this family of natriuretic peptides: B-type natriuretic peptide (*brain*) (BNP) and the C-type natriuretic peptide (CNP).

ANP is released in the auricles responding to stretch. In humans, also BNP; initially discovered in brain tissue, is released in the heart, namely the ventricles and its effects are similar to ANP (*Fig. 1*). CNP is confined to the vascular endothelium and central nervous system and has a mild natriuretic and vasodilatory effect.

BNP gene is located on the chromosome 1 codifying the pre-proBNP, a 134 aminoacids protein, which is cleaved into proBNP, made up of 108 aminoacids. The proBNP is, on its turn, cleaved by the proteolytic enzyme furin in its biologically active form, BNP with 32 aminoacids and its terminal-N segment (NT-proBNP).<sup>3</sup>

The stimuli triggering BNP release are an increase on the ventricular volume, pressure overload and an increase on the myocardial wall tension resulting from these.<sup>4,5</sup>

BNP and NT-proBNP are produced in equimolar quantity by the ventricular myocytes, but NT-proBNP half-life is longer.<sup>6,7</sup> In spite of not existing significant concentration differences between these two peptides in normal individuals, this fact becomes evident in patients with a left ventricle dysfunction. In such patients, the levels of NT-proBNP are around four times higher than those of BNP.<sup>8</sup>

Cardiovascular effects of natriuretic peptides are related with the decrease on preload due to an increase on vascular permeability and<sup>9</sup> increased natriuresis and venous capacitance subsequent to a reduced sympathetic tonus.<sup>10,11</sup> On the kidney, natriuretic peptides increase the glomerular filtration pressure dilating the afferent artery whilst contracting the efferent<sup>12</sup> interfering in the absorption mechanisms and tubular secretion,<sup>13</sup> leading to natriuresis. At CNS level, they inhibit thirst<sup>14</sup> reducing the sympathetic activation.<sup>15</sup>

### Natriuretic Peptides and Cardiac Failure

#### ***Dyspnea Differential Diagnosis in the Emergency Unit***

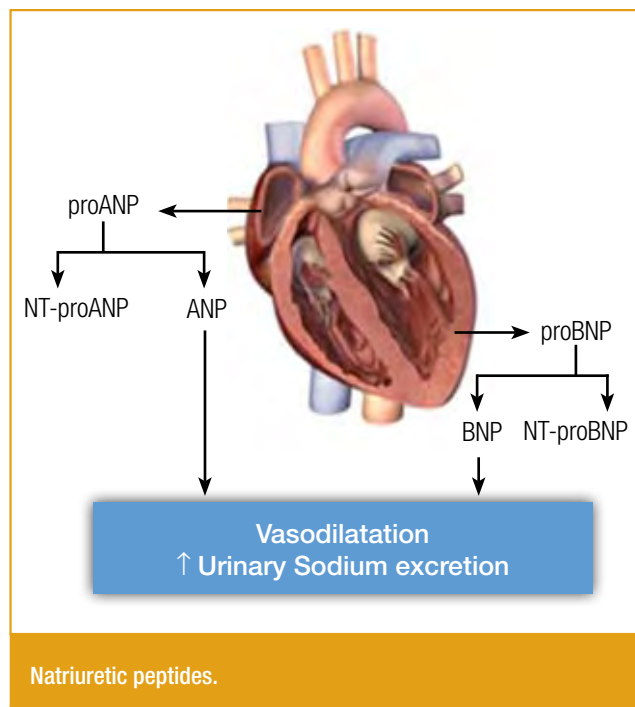
It has been in a context of dyspnea in an Emergency Unit (SU) that the usefulness of determining BNP was better studied and validated. Its determination has shown to be a sensitive and specific method to differentiate dyspnea of cardiac or pulmonary origin.<sup>16</sup>

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Natriuretic peptides.

FIG. 1

Patients with a final diagnosis of cardiac failure showed BNP values significantly higher to those who had been diagnosed with pulmonary dysfunction ( $759 \pm 799$  pg/mL vs.  $61 \pm 92$  pg/mL).<sup>16</sup> A BNP value of 94 pg/ml had a 86% sensitivity and a 98% specificity, with the ability to differentiate between cardiac failure and pulmonary dysfunction of 91%.<sup>16</sup> Even in patients who attended the Emergency Unit with an history of COPD, BNP value has successfully differentiated those with dyspnea caused by cardiac failure from those with dyspnea caused by respiratory dysfunction.<sup>16</sup>

In a similar study, in 1586 patients, to determine BNP proved to be a better option to anticipate cardiac failure as cause of dyspnea than data from the clinical history, physical examination and other laboratory tests.<sup>17</sup> The diagnostic capacity of 100pg/ml was 83,4% with a negative predictive value of 96% for a BNP <50pg/ml.<sup>17</sup> The BNP value has also shown to be an independent indicator of cardiac failure, regardless of other variables. Still, it has shown to be related with the NYHA functional class for cardiac failure. Dyspnea of pulmonary cause in patients with a cardiac failure history pose a diagnostic difficulty to construe BNP values, as there is some overlapping on the BNP concentration range among these diagnostic groups.

In a prospective, controlled random study involving 452 patients attending an Emergency Unit due to acute dyspnea, the quick BNP assessment has improved the evaluation and treatment reducing the admission period and the costs of treatment.<sup>18</sup> To use BNP tests in the Emergency Unit has significantly reduced even the time to the appropriate disease treatment, leading to a smaller number of admitted patients and a small ratio of patients requiring transfer to an Intensive Care Unit.<sup>18</sup> The average admission time has been reduced by 3 days and the treatment costs were significantly reduced. There was no impact on mortality.<sup>18</sup>

### **Natriuretic Peptides and Factors Influencing Diagnostic Values (Table I)**

NT-proBNP values are affected by age and gender that must be considered while construing the results.<sup>19,20</sup> In the general population, to determine NT-proBNP has an equivalent value to determine BNP to anticipate cardiac failure.<sup>19,20</sup> Both present good sensitivity and specificity in the cardiac failure diagnosis. Both increase significantly with age and are higher in the female gender,<sup>19,20</sup> therefore there is a need to set up specific reference values, considering all these variables.

It has been shown that kidney failure has an effect on the BNP threshold value for diagnosing dyspnea related with cardiac failure.<sup>21</sup> Also, NT-proBNP values on diagnosing dyspnea by cardiac failure are influenced by the renal function.<sup>22</sup> In a study involving 381 patients, the threshold values for diagnosing dyspnea caused by cardiac failure increased from 1360pg/mL of NT-proBNP and 290pg/mL of BNP in patients with a glomerular filtration rate (GFR) 60-89mL/min/1,73m<sup>2</sup> to 6550pg/mL and 515pg/mL, respectively, in patients with GFR 15-29mL/min/1,73m<sup>2</sup>.<sup>22</sup>

BNP serum levels have shown to be proportionally inverse to the body mass index (BMI) in patients without cardiac failure<sup>23,24</sup> and with cardiac failure.<sup>25</sup> Possible mechanisms were considered as increase on natriuretic peptides clearance<sup>26,27</sup> and reduced BNP release in obese patients.<sup>28,29</sup> When compared to other variables, obesity remains an independent fact for a smaller concentration of circulating BNP and NT-proBNP.<sup>30</sup> In obese patients, BNP values were below the diagnosis threshold more often than NT-proBNP, and both showed a decreased sensitivity in this population.<sup>30</sup>

Therefore, when defining cardiac failure threshol-

ds for diagnosis it must be taken into account the patient's age, gender, BMI and renal function.

### BNP vs NT-proBNP

Some studies compare the determination of BNP and NT-proBNP regarding the diagnosis and prognosis of cardiac failure. In a Val-HeFT substudy, including 3916 patients, both were affected similarly by age, left ventricle (LV) ejection fraction, LV diameter and creatinine clearance.<sup>31</sup> However, NT-proBNP was a better indicator predicting mortality, morbidity and hospitalization due to cardiac failure.<sup>31</sup> These data are supported by other studies suggesting a higher discriminating ability of NT-proBNP regarding BNP, though mild.<sup>15,32</sup>

Other authors could not discriminate differences in the diagnosis accuracy of both tests,<sup>33,34</sup> thus the issue is not yet completely solved regarding what is the best test, therefore, both BNP and NT-proBNP are used in the clinical practice with wide evidence supporting the use of both of them.

### BNP and NT-proBNP Prognosis Ability

A systematic review<sup>35</sup> tried to answer the question of what was BNP prognosis ability. It came to the conclusion that BNP is a strong prognosis predictor in asymptomatic patients and in cardiac failure patients, in all the disease stages.<sup>35</sup> Patients with a BNP not decreasing while responding to treatment seem to be at particular high risk of death or cardiovascular events.

Studies included BNP determination before and after treatment, showed that those values after stabilization with treatment were better death and new events predictors than the initial BNP values.<sup>36-41</sup>

Even in asymptomatic patients, mortality was related with BNP value, although it is not yet established if there is a continuous link or if the prognosis is defined by a range of BNP values. Consequently, on the 4th and 5th year of studies addressing this issue, the death risk doubled even when low BNP threshold values were used (BNP  $\geq$  17.9 pg/mL in the McDonagh et al. study, or BNP  $\geq$  20.0 pg/mL in the male gender and BNP  $\geq$  23.3 pg/mL in the female gender in the Wang et al. study).<sup>42,43</sup>

BNP was compared with NT-proBNP in only one multivariate model.<sup>44</sup> Both BNP logarithm (log) as the NT-proBNP logarithm showed statistic significance in multivariate analysis, but only logBNP was kept

TABLE I

Factors influencing BNP and NT-proBNP serum levels

Variables	Effect on the BNP/ NT-proBNP levels
Age	↑
Female Gender	↑
Renal Failure	↑
Obesity	↓

significant in multivariate analysis.<sup>44</sup>

On admission, BNP showed to be an in-hospital mortality predictor in patients with acute cardiac failure, whether with depressed or preserved systolic function, regardless of other clinical and laboratorial variables.<sup>45</sup> In cardiac failure patients, the relative death risk increased 35% for each increase of 100pg/ml in BNP.<sup>35</sup>

In patients admitted in the Emergency Unit due to dyspnea, NT-proBNP determination was related with mortality to 1 year, regardless of the cause of dyspnea.<sup>46</sup>

In coronary artery disease patients, whether stable or acute, natriuretic peptides have an independent role predicting mortality.<sup>47,48,49</sup>

### Natriuretic Peptides and Ischemic Heart Disease

Acute hypoxia increases the expression of BNP gene<sup>50</sup> leading to a higher myocardial BNP release.<sup>51</sup> This occurs immediately after inducing ischemia and it is related with the degree of ischemia the myocardium was subjected to.<sup>52,53,54</sup> BNP showed to be an independent marker for hemodynamic variables and other biochemical markers in patients with an acute coronary syndrome diagnosis.<sup>47,48,55</sup>

Natriuretic peptides role while diagnosing the acute coronary syndrome is not so well clarified. To add BMP to myocardial necrosis syndrome has shown to increase sensitivity in the diagnosis of acute coronary syndrome, at the expense of reduced specificity, in a non controlled study.<sup>56</sup> Therefore it can have a role excluding such diagnosis.

There is no need for necrosis to occur to see an increase on BNP values, as the transitory ischemia, both in humans and animals, induces a BNP increase and transcription of its gene in the absence of a myocardial cell injury.<sup>50,51,57</sup> In a population with stable angina

prospectively studied, BNP related with the risk of future cardiovascular events, regardless of the ventricle function and other known risk markers.<sup>58</sup> The determination of NT-proBNP in patients with signs or symptoms of stable coronary disease has shown to be a mortality marker and provided additional prognostic information regarding the conventional risk factors and the evaluation of the ventricle function.<sup>49</sup>

### Natriuretic Peptides and Pulmonary Diseases

In patients with a previous pulmonary disease to diagnose the causes of dyspnea is more difficult. In this group of patients co-morbidity is even a bigger diagnosis challenge. In this condition, cardiac failure is frequent, and can represent more than a third of the reasons to attend an Emergency Unit.<sup>59</sup> The use for BNP determination in these patients has shown to reduce the need for admission, to reduce its period of time and inherent costs without significant effects in intra-hospital mortality.<sup>59</sup>

Determining NT-proBNP was related to the mortality 1 year after attending the Emergency Unit for dyspnea, regardless of its cause.<sup>46</sup>

High concentrations of BNP resulting of pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD)<sup>60</sup> were described, even in the absence of left ventricle failure.<sup>61</sup> This increase can suggest *cor pulmonale*.<sup>62</sup> In COPD patients, to determine BNP was related with pulmonary hypertension and it was an independent mortality predictor regardless of hypoxemia and pulmonary functional limitation.<sup>63</sup>

It has also been shown the usefulness of determining BNP in patients with primary pulmonary hypertension. The increase on BNP is related with the patient functional limitation and it is parallel to the hemodynamic alterations and the existence of right cardiac failure.<sup>64</sup>

Patients with acute respiratory distress syndrome (ARDS) present a higher BNP concentration.<sup>65</sup> In spite of this, to determine BNP is useful to the differential diagnosis between acute pulmonary edema of cardiogenic cause (EAP) and ARDS, in patients admitted in Intensive Care Units with hypoxemic respiratory failure and bilateral pulmonary infiltrate. ARDS patients show lower BNP concentrations.<sup>66</sup> In the range of serum levels shown by patients with ARDS or EAP, the higher BNP concentration is related with hospital

mortality, without any link with the prognostic value of APACHE II score.<sup>66</sup>

The relationship between BNP value and the pulmonary capillary wedge pressure is controversial, as supported by some data,<sup>67</sup> but in other studies, this correlation was mild.<sup>66</sup>

### Natriuretic Peptides in Septic Shock

Increases in BNP<sup>68</sup> and NT-proBNP<sup>69</sup> in septic shock patients were observed. It was suggested that this increase in natriuretic peptides may reflect in the septic shock a myocardial dysfunction as occurs in cardiac failure. Patients in sepsis and septic shock show hemodynamic changes as an increased diastolic volume and pressures in both ventricles and increase in the pulmonary arterial pressure (PSAP), which might explain the increase in circulating natriuretic peptides. Not all studies are consensual on evaluating the relation between BNP and pulmonary capillary wedge pressure in an ICU setting.<sup>67,70</sup> For this, a contributing factor may be a complex cardiac dysfunction in sepsis, with a possible involvement of the systolic or diastolic dysfunction, affecting the right or left ventricle.<sup>71,72</sup>

A study has tried to verify which natriuretic peptides, ANP or BNP, was related with cardiac dysfunction.<sup>73</sup> In this study, BNP was the only one to relate with the systolic function.<sup>74</sup> However BNP value was not related with the APACHE II score and was not able to differentiate those who survive and those who did not survive.<sup>74</sup>

BNP is increased in endotoxemia animal models.<sup>75</sup> It has been questioned if BNP expression and release in endotoxemia is only due to hemodynamic changes. It was described an exponential transcription of BNP gene by lipopolysaccharides non mediated by other cytokines and independent from the cardiac mechanic load, in animal models.<sup>75</sup> This fact is also supported for higher levels of endotoxins in other diseases evolving with an increase in natriuretic peptides, as cardiac failure.<sup>76</sup> It is known the deleterious effect over the cardiac contraction made by endotoxins.<sup>77,78</sup> Such data led to a research on the endotoxins role modeling the expression and release of natriuretic peptides in humans. *In vitro* studies have shown that cardiomyocytes, in culture stimulated with IL-1 $\beta$  had an increase on BNP gene expression.<sup>79,80</sup> In cardiomyocytes cultures, the stimulation with family IL-6 interleukins leads to an increase of BNP release.<sup>81</sup>

Such findings support the hypothesis that cytokines modulate BNP serum levels in septic shock, regardless of hemodynamic variables.

Several studies have verified high levels of BNP and NT-proBNP in septic shock patients<sup>68,82,83,84</sup> and NT-proBNP has shown to be a prognosis independent marker<sup>83,84</sup> and may even to be a stronger death predictor than the APACHE II score.<sup>70</sup> In the septic shock, oncological patients NT-proBNP value, the *Logistic Organ Dysfunction score* and the recent transplant of hematopoietic cells were mortality predictors.<sup>82</sup> In an multivariate analysis, NT-proBNP value on the 2<sup>nd</sup> day of admission was the only parameter related with prognosis.<sup>82</sup>

Natriuretic peptides evaluation in sepsis can have a prognostic value and does not depend only on hemodynamic variables, but also reflects the inflammatory response triggered.

## Conclusion

The use of BNP and NT-proBNP determination may have a prognostic value in cardiovascular and pulmonary diseases and in critical patients. To resort to these tests is widely validated in a dyspnea differential diagnosis in an emergency situation. In spite of starting to emerge evidence in the sense of using natriuretic peptides to define the prognosis, is not yet clear if the recognition of patients in risk may lead to therapeutical attitudes with a positive impact in the morbi-mortality. Therefore, there is a need for further studies to validate its generalized use in medical pathology, in a cost-efficiency perspective.

The knowledge of several factors which can lead to natriuretic peptides release is important while construing BNP and NT-proBNP values. Variables as gender, age and BMI must be integrated with laboratorial and clinical data. ■

## References

1. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extracts in rats. *Life Sci* 1981; 28: 89-94.
2. Kangawa K, Matsuo H. Purification and complete amino acid sequence of a -human atrial natriuretic polypeptide ( a-hANP). *Biochem Biophys Res Commun* 1984; 118: 131-139.
3. Hall C. Essential biochemistry and physiology of (NTpro) BNP. *Eur J Heart Fail* 2004; 6: 257-260.
4. Nakagawa O, Ogawa Y, Itoh H et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. *J Clin Invest* 1995; 96: 1280-1287.
5. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; 135: 825- 832.
6. Mair J, Friedl W, Thomas S, Puschendorf B. Natriuretic peptides in assessment of left-ventricular dysfunction. *Scand J Clin Lab Invest* 1999; 59: 132- 142.
7. McCullough PA, Omland T, Maisel AS. B-type natriuretic peptides: a diagnostic breakthrough for clinicians. *Rev Cardiovasc Med* 2003; 4: 72- 80.
8. Hunt PJ, Richards AM, Nicholls MG et al. Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): a new marker of cardiac impairment. *Clin Endocrinol* 1997; 47: 287.
9. Wijeyaratne CN, Moulton PJA. The effect of a human atrial natriuretic peptide on plasma volume and vascular permeability in normotensive subjects. *J Clin Endocrinol Metab* 1993; 76: 343-346.
10. Schultz HD, Gardner DG, Deschepper CF, Coleridge HM, Coleridge JC. Vagal C-fiber blockade abolishes sympathetic inhibition by atrial natriuretic factor. *Am J Physiol* 1988; 155: R6-R13.
11. Yang RH, Jin HK, Wyss JM, Chen YF, Oparil S. Pressor effect of blocking atrial natriuretic peptide in nucleus tractus solitarii. *Hypertension* 1992; 19: 198-205.
12. Marin-Grez M, Fleming JT, Steinhausen M. Atrial natriuretic peptide causes pre-glomerular vasodilatation and post-glomerular vasoconstriction in rat kidney. *Nature* 1986; 324: 473-476.
13. Harris PJ, Thomas D, Morgan TO. Atrial natriuretic peptide inhibits angiotensin-stimulated proximal tubular sodium and water reabsorption. *Nature* 1987; 326:6 97-98.
14. Burrell LM, Lambert HJ, Baylis PH. Effect of atrial natriuretic peptide on thirst and arginine vasopressin release in humans. *Am J Physiol* 1991; 260: R475-R479.
15. Steele MK, Gardner DG, Xie PL, Schultz HD. Interactions between ANP and ANG II in regulating blood pressure and sympathetic outflow. *Am J Physiol* 1991; 260: R1145-R1151.
16. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol*. 2002; 39: 202-209.
17. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002; 347: 161-167.
18. Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004; 350: 647-654.
19. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol*. 2002; 40: 976-982.
20. Costello-Boerrigter LC, Boerrigter G, Redfield MM, et al. Amino-terminal pro-B-type natriuretic peptide and B-type natriuretic peptide in the general community: determinants and detection of left ventricular dysfunction. *J Am Coll Cardiol*. 2006; 47: 345-353.
21. McCullough PA, Duc P, Omland T, et al. B-type Natriuretic peptide and renal function in the diagnosis of heart failure: an analysis from the breathing not properly multinational study. *Am J Kidney Dis* 2003; 41: 571- 579.
22. Chenevier-Gobeaux C, Claessens YE, Voyer S, Desmoulin D, Ekindjian OG. Influence of renal function on N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients admitted for dyspnoea in the Emergency Department: comparison with brain natriuretic peptide (BNP). *Clin Chim Acta*. 2005; 361: 167-175.
23. Wang TJ, Larson MG, Levy D et al. Impact of age and sex on plasma natriuretic peptide levels in healthy adults. *Am J Cardiol* 2002; 90: 254 -258.
24. Wang TJ, Larson MG, Levy D et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004; 109: 594-600.
25. Mehra MR, Uber PA, Park MH et al. Obesity and suppressed B-type natriuretic peptide levels in heart failure. *J Am Coll Cardiol* 2004; 43: 1590-1595.

26. Sarzani R, Dessi-Fulgheri P, Paci VM et al. Expression of natriuretic peptide receptors in human adipose and other tissues. *J Endocrinol Invest* 1996; 19: 581-585.
27. Dessi-Fulgheri P, Sarzani R, Rappelli A. The natriuretic peptide system in obesity-related hypertension: new pathological aspects. *J Nephrol* 1998; 11: 296-299.
28. Licata G, Volpe M, Scaglione R et al. Salt-regulating hormones in young normotensive obese subjects: effects of saline load. *Hypertension* 1994; 23: 120-124.
29. Morabito D, Vallotton MB, Lang U. Obesity is associated with impaired ventricular protein kinase C-MAP kinase signaling and altered ANP mRNA expression in the heart of adult Zucker rats. *J Investig Med* 2001; 49: 310-318.
30. Krauser DG, Lloyd-Jones DM, Chae CU et al. Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: a ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) substudy. *Am Heart J*. 2005; 149: 744-750.
31. Masson S, Latini R, Anand IS et al. Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem*. 2006; 52: 1528-1538.
32. Mueller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. *Clin Chim Acta*. 2004; 341: 41-48.
33. El Mahmoud R, Alibay Y, Brun-Ney D et al. Type B natriuretic peptide (BNP) versus n-terminal type B natriuretic propeptide in the diagnosis of cardiac failure in the elderly over 75 population. *Arch Mal Coeur Vaiss* 2006; 99: 201-207.
34. Alibay Y, Beauchet A, El Mahmoud R et al. Plasma N-terminal pro-brain natriuretic peptide and brain natriuretic peptide in assessment of acute dyspnea. *Biomed Pharmacother* 2005; 59: 20-24.
35. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. *BMJ* 2005; 330: 625.
36. Wijesundera HC, Hansen MS, Stanton E, et al. Neurohormones and oxidative stress in nonischemic cardiomyopathy: relationship to survival and the effect of treatment with amlodipine. *Am Heart J* 2003; 146: 291-297.
37. Anand IS, Fisher LD, Chiang YT et al. Changes in brain natriuretic peptide and norepinephrine over time and mortality and morbidity in the Valsartan Heart Failure Trial (Val-HeFT). *Circulation* 2003; 107: 1278-1283.
38. Matsui T, Tsutamoto T, Maeda K, Kusukawa J, Kinoshita M. Prognostic value of repeated 123I-metaiodobenzylguanidine imaging in patients with dilated cardiomyopathy with congestive heart failure before and after optimized treatments— comparison with neurohumoral factors. *Circ J* 2002; 66: 537-543.
39. Maeda K, Tsutamoto T, Wada A et al. High levels of plasma brain natriuretic peptide and interleukin-6 after optimized treatment for heart failure are independent risk factors for morbidity and mortality in patients with congestive heart failure. *J Am Coll Cardiol* 2000; 36: 1587-1593.
40. Cheng V, Kazanagra R, Garcia A et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001; 37: 386-391.
41. Bettencourt P, Ferreira S, Azevedo A, Ferreira A. Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. *Am J Med* 2002; 113: 215-219.
42. Wang TJ, Larson MG, Levy D et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; 350: 655-663.
43. McDonagh TA, Cunningham AD, Morrison CE et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart* 2001; 86: 21-26.
44. Berger R, Huelsman M, Strecker K et al. B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; 105: 2392-2397.
45. Fonarow GC, Peacock WF, Phillips CO et al. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. *J Am Coll Cardiol* 2007; 49: 1943-1950.
46. Januzzi JL, Sakhujia R, O'donoghue M et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. *Arch Intern Med* 2006; 166: 315-320.
47. de Lemos JA, Morrow DA, Bentley JH et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001; 345: 1014-1021.
48. Sabatine S, Morrow DA, de Lemos JA et al. Multimarker approach to risk stratification in non-ST elevation acute coronary syndromes: simultaneous assessment of troponin I, C-reactive protein, and B-type natriuretic peptide. *Circulation* 2002; 105: 1760-1763.
49. Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005; 352: 666-675.
50. Goetze JP, Gore A, Moller CH et al. Acute myocardial hypoxia increases BNP gene expression. *FASEB J* 2004; 18: 1928-1930.
51. Toth M, Vuorinen KH, Vuolteenaho O et al. Hypoxia stimulates release of ANP and BNP from perfused rat ventricular myocardium. *Am J Physiol* 1994; 266: H1572-H1580.
52. Palumbo B, Siepi D, Lupattelli G et al. Usefulness of brain natriuretic peptide levels to discriminate patients with stable angina pectoris without and with electrocardiographic myocardial ischemia and patients with healed myocardial infarction. *Am J Cardiol* 2004; 94: 780-783.
53. Sabatine MS, Morrow DA, de Lemos JA et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. *J Am Coll Cardiol* 2004; 44: 1988-1995.
54. Marumoto K, Hamada M, Hiwada K. Increased secretion of atrial and brain natriuretic peptides during acute myocardial ischemia induced by dynamic exercise in patients with angina pectoris. *Clin Sci* 1995; 88: 551-556.
55. Morrow DA, de Lemos JA, Sabatine MS et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina/non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. *J Am Coll Cardiol* 2003; 41: 1264-1272.
56. Brown AM, Sease KL, Robey JL, Shofer FS, Hollander JE. The impact of B-type natriuretic peptide in addition to troponin I, creatine kinase-MB, and myoglobin on the risk stratification of emergency department chest pain patients with potential acute coronary syndrome. *Ann Emerg Med* 2007; 49: 153-163.
57. Tateishi J, Masutani M, Ohyanagi M et al. Transient increase in plasma brain (B-type) natriuretic peptide after percutaneous transluminal coronary angioplasty. *Clin Cardiol* 2000; 23: 776-780.
58. Schnabel R, Lubos E, Rupprecht HJ et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina: results from the AtheroGene study. *J Am Coll Cardiol* 2006; 47: 552-558.
59. Mueller C, Laule-Kilian K, Frana B et al. Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J* 2006; 151: 471-477.
60. Ishii J, Nomura M, Ito M et al. Plasma concentration of brain natriuretic peptide as a biochemical marker for the evaluation of right ventricular overload and mortality in chronic respiratory disease. *Clin Chim Acta* 2000; 301: 19-30.
61. Leuchte HH, Neurohr C, Baumgartner R et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. *Am J Respir Crit Care Med* 2004; 170: 360-365.
62. Bando M, Ishii Y, Sugiyama Y, Kitamura S. Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. *Respir Med*. 1999; 93: 507-514.
63. Leuchte HH, Baumgartner RA, Nounou ME et al. Brain natriuretic peptide is a prognostic parameter in chronic lung disease. *Am J Respir Crit Care Med* 2006; 173: 744-750.
64. Leuchte HH, Holzapfel M, Baumgartner RA et al. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. *J Am Coll Cardiol* 2004; 43: 764-770.
65. Mitaka C, Hirata Y, Nagura T, Tsunoda Y, Itoh M, Amaha K. Increased

plasma concentrations of brain natriuretic peptide in patients with acute lung injury. *J Crit Care* 1997; 12: 66-71.

66. Karpaliotis D, Kirtane AJ, Ruisi CP et al. Diagnostic and prognostic utility of brain natriuretic peptide in subjects admitted to the ICU with hypoxic respiratory failure due to noncardiogenic and cardiogenic pulmonary edema. *Chest* 2007; 131: 964-971.

67. Forfia P, Watkins S, Rame J et al. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol* 2005; 45: 1667-1671.

68. Charpentier J, Luyt CE, Fulla Y et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. *Crit Care Med* 2004; 32: 660-665.

69. Hoffmann U, Bruckmann M, Bertsch T et al. Increased plasma levels of NT-proANP and NT-proBNP natriuretic peptide as markers of cardiac depression in septic patients[abstract]. *J Am Coll Cardiol* 2004; 43(Suppl A): 170A.

70. Januzzi JL, Morss A, Tung R et al. Natriuretic peptide testing for the evaluation of critically ill patients with septic shock in the intensive care unit: a prospective cohort study. *Crit Care* 2006; 10: R37.

71. Jardin F, Brun-Ney D, Auvert B, Beauchet A, Bourdarias JP. Sepsis-related cardiogenic shock. *Crit Care Med* 1990; 18: 1055-1060.

72. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. *Intensive Care Med* 1997; 23: 553-560.

73. Witthaut R, Busch C, Fraunberger P et al. Plasma atrial natriuretic peptide and brain natriuretic peptide are increased in septic shock: impact of interleukin-6 and sepsis-associated left ventricular dysfunction. *Intensive Care Med* 2003; 29: 1696-1702.

74. Tomaru Ki K, Arai M, Yokoyama T et al. Transcriptional activation of the BNP gene by lipopolysaccharide is mediated through GATA elements in neonatal rat cardiac myocytes. *J Mol Cell Cardiol* 2002; 34: 649-659.

75. Anker SD, Egerer KR, Volk HD, Kox WJ, Poole-Wilson PA, Coats AJ. Elevated soluble CD14 receptors and altered cytokines in chronic heart failure. *Am J Cardiol* 1997; 79: 1426-1430.

76. Court O, Kumar A, Parrillo JE, Kumar A. Myocardial depression in sepsis and septic shock. *Crit Care* 2002; 6: 500-508.

77. Perera PY, Qureshi N, Christ WJ, Stütz P, Vogel SN. Lipopolysaccharide and its analog antagonists display differential serum factor dependencies for induction of cytokine genes in murine macrophages. *Infect Immun* 1998; 66: 2562-2569.

78. Thaik CM, Calderone A, Takahashi N, Colucci WS. Interleukin-1 $\beta$  modulates de growth and phenotype of neonatal rat cardiac myocytes. *J Clin Invest* 1995; 96: 1093-9.

79. He Q, LaPointe MC. Interleukin-1 $\beta$  regulation of the human brain natriuretic peptide promoter involves Ras-, Rac-, and p38 kinase-dependent pathways in cardiac myocytes. *Hypertension* 1999; 33: 283-289.

80. Kuwahara K, Saito Y, Harada M et al. Involvement of cardiotrophin-1 in cardiac myocyte-nonmyocyte interactions during hypertrophy of rat cardiac myocytes in vitro. *Circulation* 1999; 100: 1116-1124.

81. Chua G, Kang-Hoe L. Marked elevations in N-terminal brain natriuretic peptide levels in septic shock. *Crit Care* 2004; 8: R248-R250.

82. Brueckmann M, Huhle G, Lang S et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. *Circulation* 2005; 112: 527-534.

83. Roch A, Allardet-Servent J, Michelet P et al. NH2 terminal pro-brain natriuretic peptide plasma level as an early marker of prognosis and cardiac dysfunction in septic shock patients. *Crit Care Med* 2005; 33: 1001-1007.

84. Mokart D, Sannini A, Brun JP et al. NT-proBNP as an early prognostic factor in cancer patients developing septic shock. *Crit Care* 2007; 11: R37.