The Diagnostic Value of B Natriuretic Peptide in Elderly Patients with Acute Dyspnea

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Introduction

The number of emergency department (ED) admissions continues to climb, with a limited number of departments available to handle the volume.¹ The rapid and accurate diagnosis of dyspneic patients is a routine challenge for ED physicians. Unfortunately, the signs and symptoms of congestive heart failure (CHF) — the first cause of dyspnea—are frequently non specific and highly variable especially in older adults or patients with pre-existing respiratory diseases.²–⁴ Indeed, CHF can present as wheezing and mimic acute asthma (so-called cardiac asthma) especially in the elderly.⁵ Recent studies suggested that an appropriate diagnosis and early accurate therapy were associated with a decreased mortality and morbidity from acute dyspnea and CHF.⁶,⁷ Natriuretic peptides (NP) (including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP)) are endogenous hormones that are released by the heart in response to myocardial stretch and overload. In this article, the rationale and value of BNP for emergency patients admitted for acute dyspnea are reviewed.⁶,⁷,⁸

Role of the Natriuretic Peptides in Heart Failure

Physiologic secretion of natriuretic peptides

Cardiac endocrine function is an essential component of the homeostatic regulation network,⁹,¹⁰ including the renin-angiotensin-aldosterone system, vasopressin, endothelins, and sympathetic nervous system, and the counter-regulatory vasodilatory/natriuretic response, mainly represented by NP.¹¹ As cardiac performance decreases, all neurohormonal systems are progressively stimulated in an attempt to sustain cardiac output and circulatory homeostasis.¹² The large increases in circulating concentrations of NP in HF could be related to activation of the neuroendocrine system and thus be considered an adaptive and potentially protective response mechanism in cardiovascular disease.

NP have several physiologic actions, the most important being (a) vasodilation; (b) promotion of natriuresis and diuresis; (c) inhibition of the sympathetic nervous system and of the renin-angiotensin-aldosterone system, endothelins, cytokines, and vasopressin; (d) inhibition of the pathophysiologic mechanisms responsible for ventricular and vascular hypertrophy and remodeling; and (e) beneficial effects on endothelial dysfunction secondary to the atherosclerotic process, including blunting of shear stress and regulation of coagulation and fibrinolysis, as well as inhibition of platelet activation.¹²,¹³

The NP family includes ANP, BNP and its related peptide, whereas CNP and urodilatin are predominantly secreted by noncardiac tissues (endothelium and kidney, respectively). Recently, another
peptide, called dendroaspis natriuretic peptide (DNP), with a structure and biological activities similar to those of the NP family, was identified, but its role is still uncertain.14,15

BNP derives from the precursor pre-proBNP, containing 134 amino acids and including a signal peptide of 26 amino acids. ProBNP, produced by cleavage of the signal peptide, is further split into BNP, which is considered to be the biologically active hormone, and an inactive N-amino terminal fragment, NT-proBNP. NT-proBNP is used in a commercial analytical method and refers to measurement of N-terminal 1–76 fragment. BNP is a 32-aa polypeptide containing a 17-aa ring structure common to all NPs.6 BNP gene expression is a feature of both atrial and ventricular myocytes. In the healthy heart, BNP gene expression occurs mainly in the atria. However, ventricular BNP gene expression is up-regulated in diseases that affect the ventricles, such as CHF. Atrial myocytes contain secretory granules for peptide storage.12 Importantly, atrial granules store both intact proBNP and cleaved products, i.e. bioactive BNP-32. In contrast, ventricular myocytes in the healthy heart do not seem to produce these granules, and do not contain proBNP-derived peptides. The nucleic acid sequence of the BNP gene contains the destabilizing sequence TATTTAT, which suggests that turnover of BNP messenger RNA is high and that BNP is synthesized in bursts. This release appears to be directly proportional to ventricular volume expansion and pressure overload.

The elimination of the two peptides is different.16 BNP is cleared by several mechanisms, including the kidneys, specific clearance receptor-mediated degradation (natriuretic peptide receptor type C, NPR-C) and enzymatic degradation, especially neutral endopeptidase. In contrast, NT-proBNP seems to be removed exclusively by the kidneys.17 These differences are responsible for the fact that BNP has a lower absolute plasma concentration. However, Kroll et al. recently recalculated the NT-proBNP half-life and found that it was closer to that of BNP (25 minutes).18 ANP has a half-life of 1 to 5 minutes.19

Factors related to natriuretic peptide secretions
NP are greatly increased in diseases characterized by an expanded fluid volume. The common clinical conditions affecting the circulating concentrations of NPs are shown in Table 1.20 The circulating concentrations of NP are also directly or indirectly modified by several physiologic factors, such as circadian variations, sodium intake and drugs or hormones (including corticosteroids, diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists and adrenergic antagonists) or pro-inflammatory cytokines.19,26

However, the main variations in circulating concentrations of NP in healthy adults are related to weight, aging and gender. In particular, the BNP concentration is about one third higher in women than in men.21 It could be explained by the physiologic stimulation of female sex steroid hormones. The increases in NP with aging may be attributable to physiologic cardiac hypertrophy and kidney’s senescence (decrease in their clearance rate).22 When adjusted for relevant covariates, compared with normal counterparts, overweight and obese patients with acute CHF have lower circulating NT-proBNP and BNP levels, suggesting a body mass index-related defect in natriuretic peptide secretion.23 A recent study suggested that the association between BMI and BNP and NT-proBNP could be mediated by lean mass rather than fat mass.23 In fact, studies on effect of obesity on NP are controversial.24

BNP and NT-proBNP: diagnostic role in dyspnea
BNP is an independent predictor of high left ventricular end-diastolic pressure and of capillary pulmonary artery pressure.25 Both correlate to New York Heart Association classification, to the severity of heart failure, and correlate inversely to left Table 1. Causes of raised BNP and NT-proBNP levels.

| Cause                                |
|--------------------------------------|
| Congestive heart failure (CHF)       |
| Septic shock                         |
| Right or Left ventricular dysfunction, without acute CHF |
| Coronary artery disease, atrial fibrillation |
| Acute respiratory distress syndrome  |
| Acute pulmonary embolism             |
| Chronic obstructive pulmonary disease with cor pulmonale |
| Renal failure                        |
| Liver cirrhosis                      |
| Subarachnoid hemorrhage              |
| Hyperthyroidism                      |
ventricular ejection fraction. Cardiologic studies showed that BNP and NT-proBNP can reliably predict the presence or absence of left ventricular dysfunction on echocardiography.

The potential clinical usefulness of assays of NP for differential diagnosis of dyspnea and for stratification of patients with CHF has been confirmed over the last five years. Thus, the Task Force of the European Society of Cardiology recommended that a BNP assay should be included in the first step of the algorithm for the diagnosis of HF as are electrocardiography (ECG) and chest x-rays.27

Acute dyspnea is the key symptom of most respiratory diseases and CHF, with high related morbidity and mortality.28 Unfortunately, the accuracy in diagnosing CHF by emergency physicians is about 60%.28,29 In the EPIDASA study,28 514 patients older than 65 years with acute dyspnea were included. The in-hospital mortality was 16%, with a higher mortality (21%) in the 219 patients with CHF. Inappropriate emergency treatment occurred in 162 (32%) patients, and led to a higher mortality (25% versus 11%; p < 0.001), highlighting the importance of an early accurate treatment in the ED.

Numerous studies have evaluated and validated both natriuretic peptides in the diagnosis of CHF in middle-aged patients with acute dyspnea26,30–41 (Tables 2 and 3). All studies used the same methodology, with a measurement of BNP at admission in dyspneic patients in the emergency room. The final diagnosis of CHF related-dyspnea was adjudicated by independent experts, who were blinded to the results of the BNP assay, and the complete medical chart. The usual exclusion criteria were patients with severe renal insufficiency patients whose dyspnea was clearly not secondary to CHF (chest trauma), and dyspnea secondary to severe coronary ischemia. The largest studies was performed by Maisel et al.6 In the BNP (breathless not properly) study, value of 100 pg/ml or more for BNP was the strongest independent predictor of CHF, with an odds ratio of 29.60. A BNP cutoff of 100 pg/ml was more accurate (83%) than either the NHANES criteria (67%) or the Framingham criteria (73%), two commonly used sets of criteria for diagnosing CHF. The diagnostic accuracy of BNP was 83.4% with an area under the receiver-operating-characteristic curve (AUC) of 0.91.6 The PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study included 600 patients.42 The ROC curve demonstrated NT-proBNP to be highly sensitive and specific for the diagnosis of acute CHF (AUC of 0.94), with an optimal cutpoint of 900 pg/mL. Increased NT-proBNP was the strongest independent predictor of a final diagnosis of acute CHF (odds ratio 44). NT-proBNP testing alone was superior to clinical judgment alone for diagnosing acute CHF. Using an age categorization of <50 years (n = 144) and ≥50 years (n = 455), Januzzi et al. determined that—for ruling in acute CHF—the optimal cut off points were 450 and 900 pg/mL with areas under the curve of 0.98 and 0.93, respectively. Recently, Moe44 et al. confirmed that clinical judgment alone generated a lower AUC than NT-proBNP (0.83 vs. 0.90) (see below).

### Specific considerations in the elderly

To our knowledge, few studies have specifically evaluated BNP and NT-proBNP in elderly patients32,39,40,43,44 (Table 3). Ray et al. demonstrated that increased BNP was the strongest independent predictor of a final diagnosis of CHF (odds ratio 24.4, p < 0.001), and the accuracy of BNP-assisted diagnosis was higher than that of the emergency physician (0.84 versus 0.77, p < 0.05). They also showed that, whatever the empirical

| Table 2. Summary of studies which evaluated diagnostic accuracy of BNP (TriageBNP®). |
|---------------------------------|-----------------|------------------|-----------------|-----------------|-----------------|
| **BNP**                        | Logeart (37)    | Dao (35)         | Lainchbury (36) | Maisel (6)      | Ray (40)        |
| Number of patients             | 166             | 321              | 205             | 1586            | 308             |
| Mean age                       | 67              | ND               | 70              | 64              | 80              |
| % acute CHF                    | 70              | 42               | 34              | 47              | 46              |
| Threshold value (pg/mL)        | 300             | 94               | 208             | 100             | 250             |
| Sensitivity (%)                | 88              | 86               | 94              | 90              | 78              |
| Spécificity (%)                | 87              | 98               | 70              | 76              | 90              |
probability (from absent to very likely) estimated by the emergency physician for CHF, an elevated level of BNP higher than 250 pg/ml was an accurate predictor of CHF (positive likelihood ratio from 5.9 to 8.8 respectively). Berdague et al. assessed the usefulness of NT-proBNP assay for the diagnosis of CHF in 256 elderly patients (mean age 81 years). The diagnoses made in the ED were incorrect or uncertain in 45% of cases. The median NT-proBNP value was higher (p < 0.0001) in patients with cardiac dyspnea (56%; 7906 pg/ml) than in patients with non-cardiac dyspnea (44%; 1066 pg/ml). NT-proBNP > 2000 pg/ml was the most powerful independent marker of cardiac dyspnea (odds ratio 13.6, p < 0.001). In 241 elderly patients, Arques et al. demonstrated that BNP was as accurate as bedside tissue Doppler echocardiography (0.928 for BNP with a threshold value of 253 pg/ml vs. AUC of 0.846 for echocardiography) for predicting CHF with preserved left ventricular systolic function. In 155 patients presenting with acute dyspnea, Knudsen et al. demonstrated that BNP cut-off was close to 200 pg/mL and that AUC were 0.82 and 0.88 for patients (both genders) aged ≥ 76 and < 76 years, respectively.

**BNP in clinical practice**

Overall, BNP and NT-proBNP threshold values were more elevated in patients aged ≥ 65 years, compared with younger patients. CHF appears to be highly unlikely below a BNP plasma concentration of 100 pg/ml, or a NT-proBNP below 500 pg/mL, and CHF appears to be likely when plasma concentration of BNP is higher than 500 pg/ml, or NT-proBNP is greater 2000 pg/mL (Fig. 1). The choice of these two cut-off 100 and 500 pg/mL is based on the fact that i) the lower cut-off (100 pg/mL) corresponds to the diagnostic threshold level for CHF recommended by the manufacturer and by Maisel’s study; ii) the upper cut-off corresponds to a marked increase in the probability of the diagnosis of CHF. Januzzi et al. found that NT-proBNP and eGFR

**Comparison of BNP and NT-proBNP**

There is a strong relationship between heart failure (and thus BNP and NT-proBNP concentrations) and renal function. The central questions are i) how to interpret BNP and NT-proBNP concentrations in patients with renal impairment? ii) is BNP superior to NT-proBNP in case of renal dysfunction? Januzzi et al. found that NT-proBNP and eGFR

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**Table 3. Summary of studies which evaluated diagnostic accuracy of NT-proBNP (Elecsys®).**

| NT-proBNP       | Bayes-Génis (31) | Januzzi (42) | Ray (39) | Berdague (32) | Moe (52) | Zaninotto (41) |
|-----------------|-----------------|--------------|----------|---------------|----------|---------------|
| **Number of patients** | 100             | 599          | 202      | 256           | 500      | 122           |
| **Mean age**    | 70              | 70           | 80       | 81            | 70       | 78            |
| **% acute CHF** | 58              | 37           | 44       | 55            | 46       | 46            |
| **Threshold value (pg/mL)** | **1000**        | **900**      | **1500** | **2000**      | **NA**   | **1800**      |
| **Sensitivity (%)** | 91              | 87           | 75       | 86            | NA (about 78) | 80          |
| **Specificity (%)** | 90              | 86           | 76       | 71            | NA (about 80) | 76          |

Grossly, the higher is the mean age of the population evaluated, the higher is the threshold value of BNP and NT-proBNP.
The diagnostic value of B natriuretic peptide (glomerular filtration rate) were inversely and independently related. McCullough et al. showed that BNP concentrations and cut-off points were influenced by renal function, when eGFR was less than 60 mL/min/1.73 m². Chenevier-Gobeaux et al. showed that i) both NT-proBNP and BNP values were inversely correlated to eGFR, and ii) NT-proBNP and BNP cut-off points rose in line with CKD levels. Ray et al. included 202 patients (mean age of 80 years); 88 (44%) had CHF. The ROC curve showed that BNP and NT-proBNP accurately diagnosed CHF, but the AUC for NT-proBNP was lower than that of BNP (0.80 vs. 0.85, p < 0.05). Using logistic regression, only the diagnosis of CHF predicted the elevation of BNP greater than 250 pg/mL (OR = 27.7, p < 0.001).

Conversely, the diagnosis of CHF (odds ratio 11.7) and a creatinine clearance of less than 60 mL/min (odds ratio 2.7) independently predicted the elevation of NT-proBNP greater than 1,500 pg/mL. Renal dysfunction might at least partly explain the lower accuracy of NT-proBNP observed, because in contrast to BNP, renal excretion is a major route of elimination of NT-proBNP.

However, other studies which compared the diagnostic accuracy of BNP and NT-proBNP did not confirm this finding. In a subgroup (n = 75) analysis of their study, Berdague et al. demonstrated that AUC was 0.86 for BNP measurement compared with 0.88 for NT-proBNP (p = 0.6). In 160 patients over 75 years of age, Alibay et al. demonstrated that the diagnostic value, assessed

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**Figure 1.** Diagnostic strategy based on B-type natriuretic peptide levels in elderly patients admitted for ARF in the emergency department. In the grey zone (BNP between 100 and 500 pg/mL) which represents less than a quarter of patients, further investigations are needed, and ER physicians should consider massive PE, severe exacerbation of COPD or severe pneumonia as possible diagnoses...

**Abbreviations:**
- CXR: chest x-ray
- EKG: Electrocardiogram
- ABG: arterial blood gas analysis
- CHF: congestive heart failure
- ACS: acute coronary syndrome
- CT: computed tomography
- IV: intra-venous
- NIV: non invasive ventilation including continuous positive airway pressure
- ACEi: angiotensin converting enzyme inhibitor
- EC: echocardiography
by the AUC, was similar for BNP (0.82) and NT-proBNP (0.84). Mueller et al. demonstrated that AUC for BNP and NT-proBNP in patients with dyspnoea did not differ significantly (AUC of 0.916 vs. 0.903). In 381 patients (mean age 79 years) with dyspnoea, Chenevier-Gobeaux et al. found that NT-proBNP and BNP concentrations increased in a similar way when eGFR decreased.

Overall, BNP and NT-proBNP might be equally useful as an aid in the diagnosis of CHF in elderly patients presenting to the ED with shortness of breath (Tables 4 and 5). Thus, biologists and physicians should base their decision as to the assay to be performed on reasons and considerations other than their diagnostic value (e.g. cost, bedside utilization, in vitro stability, practical availability, etc.).

Do measurement of B natriuretic peptides improve outcome?
There is now evidence that early measurement of BNP or NT-proBNP following admission to the ED could improve the outcome of dyspneic patients. Mueller et al. conducted a prospective, randomized, controlled study of 452 patients who presented in the ED with acute dyspnea. 225 patients were randomly assigned to a diagnostic strategy involving the measurement of BNP levels with the use of a rapid bedside assay, and 227 were assessed in a standard manner. The use of BNP levels reduced the need for hospitalization (75% vs. 85%), the length of stay (8 vs. 11 days), and their care cost ($5410 vs. $7264) than those whose physicians used conventional assessment. The respective 30-day mortality rates were unchanged. However, a significant reduction in 30-day mortality was observed (9% in the BNP group vs. 17% in the control group; p = 0.039) in the subgroup of patients older than 70 years. Of note (see Fig. 1), in the BNP group, BNP level was associated with strong recommendations for treatment and management, especially if CHF.

Moe et al. also demonstrated that NT-proBNP testing improves the management of 500 patients (Mean age 70) presenting with dyspnea in the ED by prospectively comparing the clinical and economic impact of a randomized management strategy either guided by NT-proBNP results or without knowledge of NT-proBNP concentrations. Knowledge of NT-proBNP results reduced the number of patients re—hospitalized over 60 days by 35% (51 to 33%), and direct medical costs of all ED visits, hospitalizations, and subsequent outpatient services (U.S. $6129 to U.S. $5180 per patient) over 60 days from enrollment. However, knowledge of NT-proBNP results did not result in any major improvement in rate of hospitalization, hospital length of stay, or mortality rates.

Overall, knowledge the level of BNP or NT-proBNP during initial evaluation in the ED is associated with lower costs. There is also evidence that a BNP or NT-proBNP-guided strategy could improve morbidity related to CHF. For example, Jourdain et al. reported that a BNP-guided therapeutic strategy

| Characteristic | BNP | NT-proBNP |
|---------------|-----|-----------|
| Components    | BNP active hormone | NT fragment (1–76) bi-product |
| Molecular weight | 4 kilodaltons | 8.5 kilodaltons |
| Genesis       | Cleavage from proBNP | Cleavage from proBNP |
| Half-life     | 20 minutes | 90 minutes “classically” |
| Clearance mechanism | Neutral endopeptidase | Renal clearance +++ |
|                | Clearance receptors | Renal clearance |
| Increases with aging | +++ | ++++ |
| Correlation with eGFR | -0.20 | -0.60 |
| Approved cutoff(s) for CHF diagnosis | Age ≥75: 250 pg/mL | Age <75: 900 pg/mL |
|                | Age ≥75: 1550 pg/mL |
| Prognostic role in CHF | +++ | +++ |
| Prognostic role in severe PE | ++ | ++ |
Clinical Medicine: Cardiology 2008:2

The diagnostic value of B natriuretic peptide

was superior to a clinically guided approach in 200 NYHA functional class II to III patients (mean age of 65 years) considered optimally treated by CHF specialists.53–55 During a median follow-up of 15 months, fewer patients in the BNP group reached the combined end point of CHF-related death or hospital stay for CHF (24% vs. 52%). The main reason for the more favorable outcome of the BNP group was that mean dosages of ACEIs (angiotensin-converting enzyme inhibitors) and beta-blockers were significantly greater in the BNP group. Other studies are currently conducted to determine whether titration of drug treatment according to plasma NT-proBNP is superior regarding clinical outcomes to that provided by intensive standardized clinical assessment.56

Prognostic values of B natriuretic peptides assessment in acute dyspnea prognostic value in acute dyspnea and CHF

In acute dyspnea, studies suggest that high BNP or NT-proBNP levels at admission could be of prognostic importance57–61 Januzzi et al. demonstrated that NT-proBNP at the time of presentation was not only diagnostically useful, but also strongly predicted likelihood for short-term mortality in subjects with CHF, with a more than five-fold increase in risk for death by 76 days among those with marked elevation in NT-proBNP concentrations.60 Gegenhuber et al.58 followed up 251 consecutive patients (mean age of 72 years) admitted for shortness of breath in an ED. Within one year from the time they were enrolled, 62 died and 189 remained alive. Mortality was higher in patients with baseline BNP and NT-proBNP concentrations above the cutoff levels (454 pg/mL and 2060 pg/mL, respectively). Lastly, in a multivariate analysis of the EPIDASA study, elevated NT-proBNP or BNP (odds ratio 2.06) was also predictive of death.28 However, other studies suggest that BNP or NT-proBNP values at pre—discharge,62 and/or percentage change in BNP levels during hospitalization rather than at admission could be more accurate for predicting long-term outcome in patients admitted for acute CHF.61 Logeat et al. demonstrated that patients with BNP <350 pg/ml had the best outcome (16.2% of events at 6 months) compared with patients with BNP between 350 and 700 pg/ml (60%) and patients with BNP >700 pg/ml (93%). Recently, Chenevier-Gobeaux et al. reported that NT-proBNP higher than 3,855 pg/ml— at admission— was associated with significant higher in-hospital mortality in 324 patients aged 75 years and over admitted for dyspnea (17.9% vs. 9.7%). Elevated NT-proBNP concentration at admission was the only variable predictive of death (odds ratio 2.41) Furthermore, mortality in patients with positive cTnI (n = 54) was higher when patients had NT-proBNP ≥3,855 pg/mL than in patients with NT-proBNP <3,855 pg/mL (32.5% vs. 7.1%, p = 0.082).8 Christ et al. also reported that elevated levels of BNP and cardiac troponin I levels were independently associated with an increased risk of death during long-term follow-up.63

Prognostic value in PE

Some subgroups of patients with pulmonary embolism (PE) have a high risk, especially patients with hemodynamic impairment (massive PE), but also hemodynamically stable patients with right ventricular dysfunction (so-called sub—massive PE). Indeed, right ventricular dysfunction is the main determinant of the short-term course of PE and could provide guidance for the early management of patients with PE. Some authors have suggested that thrombolytic therapy could be indicated for submassive PE. BNP and NT-proBNP seem to be useful markers of right ventricular dysfunction and initial myocardial injury in acute PE. Like in acute coronary syndrome,64 studies have suggested

Table 5. Comparison between BNP and NT-proBNP.

|                     | Mueller (38) | Chenevier-Gobeaux (34) | Alibay (30) | Lainchbury (36) | Ray (39) |
|---------------------|--------------|------------------------|-------------|-----------------|--------|
| Number of patients  | 251          | 381                    | 160         | 205             | 202    |
| Mean age            | 73           | 79                     | 81          | 70              | 80     |
| AUC BNP             | 92           | 80                     | 82          | 89              | 85     |
| AUC NT-proBNP       | 90           | 73                     | 84          | 89              | 80     |

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that BNP or NT-pro-BNP were accurate in risk stratification for PE had a high positive negative value for in-hospital death. However, other studies have not shown any prognostic usefulness. In elderly patients, BNP and NT-proBNP do not seem to be solid tests to identify patients with a risk of complicated PE. Thus, in clinical practice the measurement of BNP or NT-proBNP level for each PE admitted to an ED cannot be recommended.

Conclusions
There is strong evidence that BNP and NT-proBNP are reliable markers of CHF in acute dyspnea. Furthermore, they add a prognostic value. Used in conjunction with other clinical information, rapid measurement of BNP or NT-proBNP has been shown to reduce total patient treatment cost. As recommended by current guidelines, their measurements should be strongly promoted in ED.

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References
[1] McCaig, L.F. and Burt, C.W. 2004. National Hospital Ambulatory Medical Care Survey: 2002 emergency department summary. Adv. Data, 1–34.
[2] Lien, C.T., Gillespie, N.D., Struthers, A.D. and McMurdo, M.E. 2002. Heart failure in frail elderly patients: diagnostic difficulties, co-morbidities, polypharmacy and treatment dilemmas. Eur. J. Heart Fail, 4:91–8.
[3] Mueller, C., Frana, B., Rodriguez, D., Laule-Kilian, K. and Perruchoud, A.P. 2005. Emergency diagnosis of congestive heart failure: impact of signs and symptoms. Can. J. Cardiol., 21:921–4.
[4] Rihal, C.S., Davis, K.B., Kennedy, J.W. and Gersh, B.J. 1995. The utility of clinical, electrocardiographic, and roentgenographic variables in the prediction of left ventricular function. Am. J. Cardiol., 75:220–3.
[5] Jorge, S., Becquemin, M.H., Delerme, S., Bennaceur, M., Insard, R. et al. 2007. Cardiac asthma in elderly patients: incidence, clinical presentation and outcome. BMC Cardiovasc. Disord., 7:16.
[6] Maisel, A.S., Krishnaswamy, P., Nowak, R.M., McCord, J., Hollander, J.E. et al. 2002. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N. Engl. J. Med., 347:161–7.
[7] Mueller, C., Scholer, A., Laule-Kilian, K., Martina, B., Schindler, C. et al. 2004. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. N. Engl. J. Med., 350:647–54.
[8] Chenevier-Gobeaux, C., Allo, J.C., Arthaud, M., Aechkar, R., Claessens, Y.E. et al. 2008. NT-proBNP testing for short-term prognosis in breathless elderly patients. American Journal of Emergency Medicine. In press.
[9] de Bold, A.J., Borenstein, H.B., Veress, A.T. and Sonnenberg, H. 1981. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci., 28:89–94.
[10] Clerico, A., Recchia, F.A., Passino, C. and Emdin, M. 2006. Cardiac endocrine function is an essential component of the homeostatic regulation network: physiological and clinical implications. Am. J. Physiol. Heart Circ. Physiol., 290:H17–29.
[11] Yasue, H., Yoshimura, M., Samida, H., Kikuta, K., Kugiyama, K. et al. 1994. Localization and mechanism of secretion of B-type natriuretic peptide in comparison with those of A-type natriuretic peptide in normal subjects and patients with heart failure. Circulation, 90:195–203.
[12] Levin, E.R., Gardner, D.G. and Samson, W.K. 1998. Natriuretic peptides. N. Engl. J. Med., 339:321–8.
[13] Maisel, A.S. 2003. The diagnosis of acute congestive heart failure: role of BNP measurements. Heart Fail Rev., 8:327–34.
[14] Ruskoaho, H. 2003. Cardiac hormones as diagnostic tools in heart failure. Endocr. Rev., 24:341–56.
[15] Lee, C.Y. and Burnett, J.C. 2007. Natriuretic peptides and therapeutic applications. Heart Fail Rev., 12:131–42.
[16] Anand-Srivastava, M.B. 2005. Natriuretic peptide receptor-C signaling and regulation. Peptides, 26:1044–59.
[17] Austin, W.J., Bhalla, V., Hernandez-Arce, I., Isakson, S.R., Beede, J. et al. 2006. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. Am. J. Clin. Pathol., 126:506–12.
[18] Kroll, M.H., Twomey, P.J. and Srisawasdi, P. 2007. Using the single-compartment ratio model to calculate half-life, NT-proBNP as an example. Clin. Chim. Acta., 380:197–202.
[19] Suttner, S.W. and Boldt, J. 2004. Natriuretic peptide system: physiology and clinical utility. Curr. Opin. Crit. Care, 10:336–41.
[20] Clerico, A., Iervasi, G., Del Chicca, M.G., Emdin, M., Maffei, S. et al. 1998. Circulating levels of cardiac natriuretic peptides (ANP and BNP) measured by highly sensitive and specific immunoradiometric assays in normal subjects and in patients with different degrees of heart failure. J. Endocrinol. Invest, 21:170–9.
[21] Emdin, M., Passino, C., Del Ry, S., Prontera, C., Galetta, F. et al. 2003. Influence of gender on circulating cardiac natriuretic hormones in patients with heart failure. Clin. Chem. Lab. Med., 41:686–92.
[22] Loke, I., Squire, I.B., Davies, J.E. and Ng, L.L. 2003. Reference ranges for natriuretic peptides for diagnostic use are dependent on age, gender and heart rate. Eur. J. Heart Fail, 5:599–606.
[23] Das, S.R., Drazner, M.H., Dries, D.L., Vega, G.L., Stanek, H.G. et al. 2005. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. Circulation, 112:2163–8.
[24] Hermann-Arnhof, K.M., Hanusch-Enserer, U., Kaestenbauer, T., Publig, T., Dunky, A. et al. 2005. N-terminal pro-B-type natriuretic peptide as an indicator of possible cardiovascular disease in severely obese individuals: comparison with patients in different stages of heart failure. Clin. Chem., 51:138–43.
[25] Maeda, K., Tsutamoto, T., Wada, A., Hisanaga, T. and Kinoshita, M. 1998. 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., 135:825–32.
[26] Davis, M., Espiner, E., Richards, G., Billings, J., Town, I. et al. 1994. Plasma brain natriuretic peptide in assessment of acute dyspnea. Lancet, 343:440–4.
[27] Swedberg, K., Cleland, J., Dargie, H., Drexler, H., Follath, F. et al. 2005. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur. Heart J., 26:1115–40.
[28] Ray, P., Birolleau, S., Lefort, Y., Becquemin, M.H., Beigelman, C. et al. 2006. Acute respiratory failure in the elderly: etiology, emergency diagnosis and prognosis. Crit. Care, 10:R82.
[29] McCullough, P.A., Nowak, R.M., McCord, J., Hollander, J.E., Herrmann, H.C. et al. 2002. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: analysis from Breathing Not Properly (BNP) Multinational Study. Circulation, 106:416–22.
[62] Verdiani, V., Nozzi, C., Bacci, F., Cecchin, A., Rutili, M.S. et al. 2005. Pre-discharge B-type natriuretic peptide predicts early recurrence of decompensated heart failure in patients admitted to a general medical unit. *Eur. J. Heart Fail.*, 7:566–71.

[63] Christ, M., Laule, K., Klima, T., Hochholzer, W., Breidthardt, T. et al. 2007. Multimarker strategy for risk prediction in patients presenting with acute dyspnea to the emergency department. *Int. J. Cardiol.*

[64] Morrow, D.A., de Lemos, J.A., Blazing, M.A., Sabatine, M.S., Murphy, S.A. et al. 2005. Prognostic value of serial B-type natriuretic peptide testing during follow-up of patients with unstable coronary artery disease. *Jama*, 294:2866–71.

[65] Binder, L., Pieske, B., Olschewski, M., Geibel, A., Klostermann, B. et al. 2005. N-terminal pro-brain natriuretic peptide or troponin testing followed by echocardiography for risk stratification of acute pulmonary embolism. *Circulation*, 112:1573–9.

[66] Kostrubiec, M., Pruszczyk, P., Bochowicz, A., Pacho, R., Szulc, M. et al. 2005. Biomarker-based risk assessment model in acute pulmonary embolism. *Eur. Heart J.*, 26:2166–72.

[67] Kucher, N., Printzen, G., Doernhoefer, T., Windecker, S., Meier, B. et al. 2003. Low pro-brain natriuretic peptide levels predict benign clinical outcome in acute pulmonary embolism. *Circulation*, 107:1576–8.

[68] Logeart, D., Lecuyer, L., Thabut, G., Tabet, J.Y., Tartiere, J.M. et al. 2007. Biomarker-based strategy for screening right ventricular dysfunction in patients with non-massive pulmonary embolism. *Intensive Care Med.*, 33:286–92.

[69] Kucher, N., Printzen, G. and Goldhaber, S.Z. 2003. Prognostic role of brain natriuretic peptide in acute pulmonary embolism. *Circulation*, 107:2545–7.

[70] Ray, P., Maziere, F., Medimagh, S., Lefort, Y., Arthaud, M. et al. 2006. Evaluation of B-type natriuretic peptide to predict complicated pulmonary embolism in patients aged 65 years and older: brief report. *Am. J. Emerg. Med.*, 24:603–7.

[71] Maziere, F., Birolleau, S., Medimagh, S., Arthaud, M., Bennaceur, M. et al. 2007. Comparison of troponin I and N-terminal-pro B-type natriuretic peptide for risk stratification in patients with pulmonary embolism. *Eur. J. Emerg. Med.*, 14:207–11.