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Review

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Differential diagnosis of acute dyspnea: the value of B natriuretic peptides in the emergency department

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Summary

Congestive heart failure (CHF) is the main cause of acute dyspnea in patients presenting to an emergency department (ED) and is associated with high morbidity and mortality. B-type natriuretic peptide (BNP) is a polypeptide, released by ventricular myocytes in direct proportion to wall tension, which lowers renin–angiotensin–aldosterone activation. For the diagnosis of CHF, both BNP and the biologically inactive NT-proBNP have similar accuracy. Threshold values are higher in an elderly population, and in patients with renal dysfunction. They might also have a prognostic value. Studies have demonstrated that the use of BNP or NT-proBNP in dyspneic patients early following admission to the ED, reduced the time to discharge and total treatment cost. BNP and NT-proBNP should be available in every ED 24 h a day, because the literature strongly suggests the beneficial impact of an early appropriate diagnosis and treatment in dyspneic patients. The purpose of this review is to indicate recent developments in biomarkers of heart failure and to evaluate their impact on clinical use in the emergency setting.

Introduction

The number of emergency department (ED) admissions continues to increase year after year, with very few departments available to handle the volume.[1] The rapid and accurate diagnosis of patients with the most severe conditions is a routine challenge for ED physicians. The diagnosis of congestive heart failure (CHF) is particularly challenging, 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.[5]). However, recent studies suggest that an appropriate diagnosis and early accurate therapy was associated with a decreased mortality in CHF.[6,7] Natriuretic peptides (NP) [including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP)] are endogenous hormones that are released by the heart in response to myocardial stretch and overload. Their production mediates natriuresis,

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inhibition of renin and aldosterone, as well as vasorelaxant, anti-fibrotic, anti-hypertrophic and lusitropic effects. The NP system thus serves as an important compensatory mechanism against neurohumoral activation in heart failure. This provides a strong rationale for the use of exogenous NP in the management of CHF. In this article, the rationale, the value of NP for emergency patients admitted for acute dyspnea and suspicion of CHF are reviewed.[6–8] New data on physiology, confounding factors and new applications of these peptides, allow fresh analysis of the possibilities and limits of their use in a clinical and emergency setting.

Methods

Searches were conducted in MEDLINE for studies published in English between January 1990 and January 2008, using combinations of the key words 'diagnosis', 'acute dyspnea', 'acute respiratory failure', 'heart failure', 'pulmonary edema', 'emergency department', 'natriuretic peptides ''BNP'', ''NT-proBNP'' '. We included only studies limited to human subjects. We included studies that reported the sensitivity specificity, and area under the receiver operating characteristic (ROC) curves of BNP or NT-proBNP for diagnosing HF in ED patients with acute dyspnea. Conceptually the ROC is a plot of sensitivity against specificity for all possible cut-off values. The cut-off point with the best discrimination is the point on the curve closest to the upper left corner of the graph, i.e. the best threshold value is the one that minimized the distance to the ideal point (sensitivity = specificity = 1) on the ROC curve.[9] When area under the curve (AUC) is reported with standard errors or confidence intervals, they allow valuable statistical comparison of diagnostic tests. An AUC of 50% means no discrimination, whereas 100% means perfect discrimination.[10] An AUC of 75–85% means an intermediate to good discriminative properties of a diagnostic test, which allows physicians to use the test for daily clinical practice.

Studies were considered eligible for inclusion if they (i) addressed the usefulness of BNP or NT-proBNP to quantify the probability of HF among patients presenting with acute dyspnea to an ED setting, (ii) included at least 100 patients, (iii) used an optimal design for assessing the accuracy of a diagnostic test, i.e. a prospective blind comparison of the test and the reference standard in a consecutive series of patients from a relevant clinical population and (iv) used a clinical criterion standard, in which the diagnosis of HF was determined by expert physicians with access to all clinical information, including assessment of ventricular function and symptomatic response to treatment. Variables extracted included the study design, the number of patients with and without HF, characteristics of the study population (age distribution, gender, proportion of patients with history of HF and either asthma or COPD), clinical variables evaluated and the diagnostic performance of BNP or NT-proBNP.

This article summarizes the up-to-date understanding of the value of BNP and NT-proBNP testing in the patient presenting with acute dyspnea in an emergency setting.

Physiology of the natriuretic peptides

Physiologic secretion of natriuretic peptides

Cardiac endocrine function is an essential component of the homeostatic regulation network,[11,12] including the renin–angiotensin–aldosterone system, vasopressin, endothelins and sympathetic nervous system, and the counter-regulatory vasodilatory/natriuretic response, mainly represented by NP.[13] As cardiac performance decreases, all neurohormonal systems are progressively stimulated in an attempt to sustain cardiac output and circulatory homeostasis.[14] The NP have several physiologic actions (Figure 1), the most important being (i) vasodilation, (ii) promotion of natriuresis and diuresis, (iii) inhibition of the sympathetic nervous system and of the renin–angiotensin–aldosterone system, endothelins, cytokines and vasopressin, (iv) inhibition of the pathophysiologic mechanisms responsible for ventricular and vascular hypertrophy and remodeling and (v) 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.[14,15]

The NP family includes ANP, BNP and its related peptide, whereas C natriuretic peptide and urodilatin are predominantly secreted by non-cardiac tissues (endothelium and kidney). Recently, another peptide, called dendroaspis natriuretic peptide, with structure and biological activities similar to those of the NP family, was identified, but its role is still uncertain.[16,17]

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

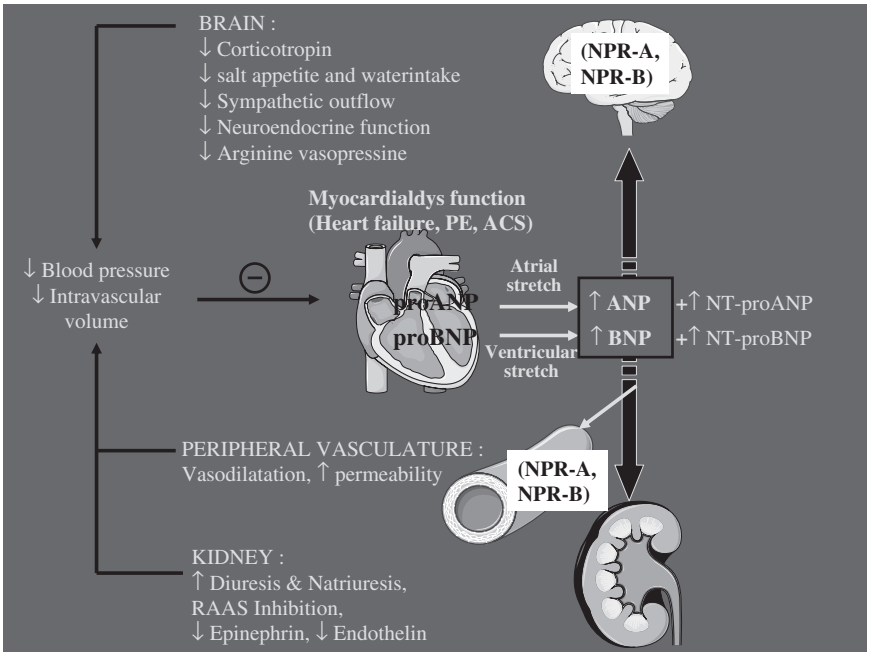

Figure 1. The regulation and actions of NP.

active hormone and an inactive N-amino terminal fragment, NT-proBNP. NT-proBNP refers to measurement of N-terminal 1–76 fragment. It has no biological activity but is associated with NP in terms of pathophysiology. Despite an equimolarity in terms of synthesis, there is no equivalence in terms of measurement due to different half-life and clearance mechanisms. BNP is a 32-aa polypeptide containing a 17-aa ring structure common to all NP.[6] BNP gene expression is a feature of both atrial and ventricular myocytes. In the healthy heart, BNP gene expression occurs in the atria and partly in the two ventricles. However, ventricular BNP gene expression is up-regulated in diseases that affect the ventricles, such as CHF, which explains that it may be a more specific indicator of ventricular disorders than other NP. It is well-established that atrial myocytes contain secretory granules with small amount of peptide storage, which led to the primary hypothesis about the endocrine heart.[14] This storage is crucial for ANP release, which is linked to burst release of micro-granules. This is not the case for BNP or NT-proBNP, especially in HF patients. In these circumstances, BNP and NT-proBNP are secreted due to RNA m synthesis by an active mechanism. This explains the delay between stimuli like CHF and BNP's detection in blood. 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. More recently many publications have improved our knowledge of NP secretion and synthesis especially in CHF. There is growing evidence of the existence of alternative forms of BNP in severe heart failure.[18,19] Shimizu *et al.*[20,21] have determined on RIA assay and chromatography that there are circulating forms of uncleaved proBNP. Recently Hawkridge *et al.*[22] and others proved in small studies of severe CHF patients that BNP measured in usual point of care immunoassay is mainly composed of altered forms of the peptide without any natriuretic effect. BNP assays only measure uncleaved BNP (i.e. the active molecule) and not the unfunctional BNP.

The clearance of the two peptides is different.[23] 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 only to be cleared by the kidney.[24] These differences are responsible for the fact that BNP has a lower absolute plasma concentration and lower half-life. However, Kroll *et al.*[25] recently re-calculated NT-proBNP half-life and suggested that it was closer to that of BNP (25 min).

Factors related to natriuretic peptide secretion

NP are greatly increased in diseases characterized by an expanded fluid volume or increase of intraventricular end-diastolic pressure. The common clinical conditions affecting the circulating concentrations of NP are reported on Table 1.[26] The circulating concentrations of NP are also directly modified by several physiologic factors, such as circadian variations, sodium intake and drugs and their related hormones (including corticosteroids, diuretics, angiotensin-converting enzyme inhibitors, adrenergic agonists and adrenergic antagonists) or proinflammatory cytokines.[27] It is crucial to note that the impact of the confounding factors is very different from one another. Some conditions like circadian cycle sodium intake or exercise in healthy people lead to a slight increase of NP, and others like complicated pulmonary embolism may lead to a significant increase of NP. 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 at age <50 years.[28] This could be explained by the physiological stimulation of female sex steroid hormones. This elevation of NP was particularly obvious in the oldest women but there is a possibility that the interpretation of NP elevation could be biased by the high prevalence of hypertension or left ventricular hypertrophy in this population even without any sign of HF. Thus, increases in NP with aging may be attributable to physiologic cardiac hypertrophy and age-related kidney dysfunction (decrease of NP clearance rate).[29] NT-proBNP has no clearance receptor, but is only cleared renally. Compared with normal counterparts, overweight and obese patients with acute CHF have lower circulating NT-proBNP and BNP levels, suggesting a BMI (body mass index)-related defect in NP secretion.[30] Some authors have hypothesized that adipocytes act as clearance receptors for BNP but this explanation does not explain the impact of obesity on NT-proBNP. Furthermore, a recent study has suggested that the association between BMI and BNP and NT-proBNP may be mediated by lean mass rather than fat mass.[30] In fact, studies on effect of obesity on NP are controversial.[31] In most of papers, significant obesity (BMI >35–40 kg/m^2) leads to a relative decrease of 40% of NP measurement in healthy and in HF patients. In a clinician perspective, it is proposed to multiply the results of NP measurements by 1.6–1.8 in obese patients before interpretation of the results.

Table 1 Causes of raised BNP and NT-proBNP levels

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, ischemic and hemorrhagic stroke
Hyperthyroidism

It is of importance to note that the method of analysis could directly play a role on the diagnostic value of NP. All NT-proBNP assays use the same antibodies (Roche Diagnostics, Dade Behring, Biomérieux). However for BNP, most of the assays use different antibodies (all but Beckman and Biosite triage have different antibodies). Clinicians should also know that variability is higher for bedside test than for laboratory assays. Due to longer half-life and larger concentrations, NT-proBNP variability is lower than BNP variability especially for the lowest values. This variability has a limited impact in clinical perspective in HF but could play a role in some situations like acute coronary syndrome.

BNP and NT-proBNP: diagnostic role in acute dyspnea

BNP is an independent predictor of high left ventricular end-diastolic pressure and of capillary pulmonary artery pressure.[32] Both correlate to the NYHA (New York Heart Association) classification, to the severity of the HF and inversely correlate to left ventricular ejection fraction.[33] Some studies have showed that BNP and NT-proBNP can reliably predict the presence or absence of left ventricular dysfunction on echocardiography in symptomatic and asymptomatic HF patients.

The potential clinical usefulness of assays for NP for differential diagnosis of dyspnea and for stratification of patients with CHF has been confirmed in the last 5 years. Thus, the Task Force of the European Society of Cardiology has recommended since 2001 that a NP assay should be included in the first step of the algorithm for the diagnosis of HF as are electrocardiography (ECG) and chest X-ray.[34]

Acute dyspnea is the key symptom of CHF and of most respiratory diseases, with high related morbidity and mortality.[35] Unfortunately, it has

Table 2 Summary of studies which evaluated diagnostic value of BNP (TriageBNP®)

	Logeart[46]	Dao[44]	Lainchbury[45]	Maisel[6]	Ray[49]
Number of patients	166	250	205	1586	308
Mean age	**67**	**ND**	**70**	**64**	**80**
Acute CHF (%)	70	39	34	47	46
Male (%)	67	94	49	56	50
Threshold value (pg/ml)	**300**	**100**	**208**	**100**	**250**
Sensitivity (%)	88 [NA]	94 [89–97]	94 [NA]	90 [88–92]	78 [71–84]
Specificity (%)	87 [NA]	94 [89–97]	70 [NA]	76 [73–79]	90 [84–93]

NA: not available.
Grossly, the higher is the mean age of the population evaluated, the higher is the threshold value of BNP and NT-proBNP; 95% CI for sensitivity and specificity were given when available [CI].

Table 3 Summary of studies which evaluated diagnostic value of NT-proBNP (Elecsys®)

	Bayes-Génis[40]	Januzzi[38]	Ray[48]	Berdague[41]	Moe[65]	Zaninotto[50]
Number of patients	100	599	202	256	500	122
Mean age	**70**	**70**	**80**	**81**	**70**	**78**
Male (%)	59	51	50	48	52	48
Acute CHF (%)	58	37	44	55	46	46
Threshold value (pg/ml)	**1000**	**900**	**1500**	**2000**	**NA**	**1800**
Sensitivity (%)	91 [NA]	87 [NA]	75 [NA]	86 [NA]	NA (about 78 [NA])	80 [71–87]
Specificity (%)	90 [NA]	86 [NA]	76 [NA]	71 [NA]	NA (about 80 [NA])	76 [66–84]

NA: not available.
Grossly, the higher is the mean age of the population evaluated, the higher is the threshold value of BNP and NT-proBNP; 95% CI for sensitivity and specificity were given when available [CI].

been shown that emergency physicians' accuracy in diagnosing CHF is about 60%.[35,36] In the EPIDASA study,[35] 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% vs. 11%; $P < 0.001$), highlighting the importance of correct diagnosis and early accurate treatment in the ED. In a prospective study in UK, the initial general practioner diagnostic of HF was confirmed in only 34% of the cases.[37] Another key point is the importance of clinical indecision at the ED which leads to inappropriate hospitalization and use of potentially dangerous therapy. Thus, in one-third of patients, the ED physician is uncertain of the diagnosis (intermediate probability).[38]

Numerous studies have evaluated and validated both NP in the diagnosis of CHF in acute dyspnea in middle-aged patients[32,39–50] (Tables 2 and 3). All studies used the same methodology, with a single measurement of BNP or NT-proBNP at admission in dyspneic patients in the ED. The final diagnosis of CHF-related dyspnea was evaluated by independent experts, blind to the results of the BNP assay, using the complete medical chart and the findings of the cardiologic investigations. The usual exclusion criteria were severe renal insufficiency, patients whose dyspnea was clearly not secondary to CHF (chest trauma), and dyspnea secondary to severe coronary ischemia. The largest studies were performed by Maisel *et al.*[6] for BNP and Januzzi *et al.*[38] for NT-proBNP. A value of 100 pg/ml or more for BNP was the strongest independent predictor of CHF [Odds ratio (OR) = 29.6]. BNP 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 at a cutoff of 100 pg/ml was 83.4% with an AUC of 0.91.[6] In addition, the negative predictive value of this threshold was particularly high (98%). The PRIDE (ProBNP Investigation of Dyspnea in the Emergency Department) study included 600 patients who presented in the ED with dyspnea. 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 cut-point of 900 pg/ml. Increased NT-proBNP was the strongest independent predictor of a final diagnosis of acute CHF (OR = 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 ($n = 455$), they determined that—for ruling in acute CHF—the optimal cut-off points were 450 and 900 pg/ml with AUC of 0.98 and 0.93, respectively. Recently, Moe *et al*. confirmed that clinical judgment alone generated a lower AUC than NT-proBNP (0.83 vs. 0.90) (see further).[43]

Renal dysfunction and elderly patients?

There is a strong inter-relationship between heart failure (and therefore 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 and (ii) is BNP superior to NT-proBNP in case of renal dysfunction? Januzzi *et al*. found that NT-proBNP and GFR (glomerular filtration rate) were inversely and independently related ($P < 0.001$).[51] McCullough *et al*.[52] showed that BNP concentrations and cut-off points were influenced by renal function, when eGFR was <60 ml/min/1.73 m^2. Chenevier-Gobeaux *et al*.[43] 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. Conversely, Ray *et al*.[48] demonstrated that BNP was more accurate than NT-proBNP in elderly patients, because of a decrease in creatinine clearance. They demonstrated that 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 (OR = 11.7) and a creatinine clearance of less than 60 ml/min (OR = 2.7) independently predicted the elevation of NT-proBNP. The renal dysfunction may at least partly explain the lower specificity and accuracy of NT-proBNP observed, because in contrast to BNP, renal excretion is a major route of elimination of NT-proBNP.[48]

In a geriatric point of view (i.e. >75-year old), in European countries, the rate of patients admitted for acute dyspnea older than 75 years is close to 50%.[53–55] To our knowledge, few studies specifically evaluated BNP and NT-proBNP in real elderly population and confirmed that threshold values were higher in a geriatric population[41,49,56,57] (Table 3). From 308 patients >65 years, Ray *et al*. demonstrated that increased BNP was the strongest independent predictor of a final diagnosis of CHF (OR = 24.4), and the accuracy of BNP-assisted diagnosis was higher than that of the emergency physician (0.84 vs. 0.77, $P < 0.05$). They also showed that, whatever the prior 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). Berdagué *et al*. assessed the usefulness of NT-proBNP assay for the diagnosis of CHF in 256 elderly patients (mean age 81 years). NT-proBNP >2000 pg/ml was the most powerful independent marker of cardiac dyspnea (OR = 13.6). In the ICON study, Januzzi *et al*. confirmed that NT-proBNP testing was valuable for diagnostic evaluation in dyspneic subjects with suspected CHF. In this multi-center, international study from pooled data (1256 patients), they established an optimal strategy to identify CHF when using age-related cut-points of 450, 900 and 1800 pg/ml for ages <50, 50–75, and >75, with 90% of sensitivity and 84% of specificity for CHF. Recently, Coste *et al*.[58] have demonstrated that the age has no influence on the threshold used for discriminating HF and non-cardiac cause of dyspnea in the ED. Chenevier-Gobeaux *et al*. also did not find any difference in diagnostic value for BNP and NT-proBNP between elderly patients and oldest-old (>85 years) and that renal function had no impact on their diagnostic performance (manuscript accepted for publication in Clin Biochemistry in press 2008).

In clinical practice

One of the problems in most of these studies is that the methodology used is based on ROC analysis which is useful for the analysis of one threshold performance, but is unable to analyze the performance of two threshold values as recommended for NP.[59,60] Indeed, an interventional study reported that the early use of BNP based upon two separated threshold values could improve outcome and lower costs.[7]

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 when BNP plasma concentration is below 100 pg/ml or a NT-proBNP is 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 (Figure 2). The choice of these two different cut-offs (100 and 500 pg/ml) is based on the following: the lower cut-off (100 pg/ml) corresponds to the diagnostic threshold level for CHF recommended by

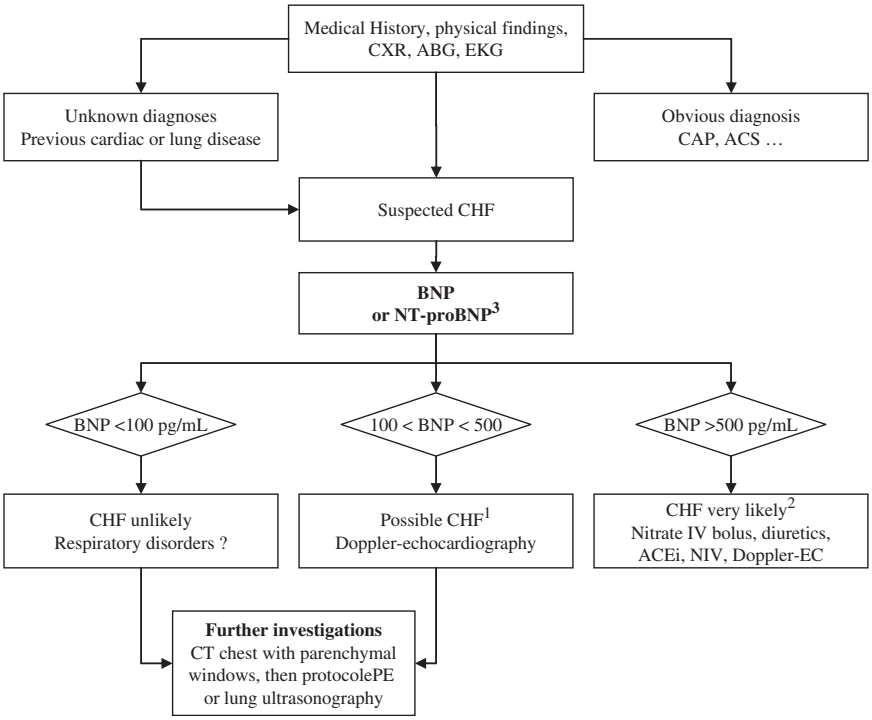

Figure 2. Diagnostic strategy based on BNP levels in elderly patients admitted for acute respiratory failure (ARF) in the ED.
[1]In the 'grey' zone (BNP between 100 and 500 pg/ml), which represents less than a quarter of patients, further investigations are needed, and ER physicians should still consider CHF, as well as massive PE, severe exacerbation of COPD or severe pneumonia.
[2]Physicians should be keep in mind that half of elderly patients with ARF has more than one, i.e. a BNP >500 pg/ml strongly suggests CHF, but other diagnosis could have precipitated CHF.
[3]For NT-proBNP, the cut-off values are 500 and 2000 pg/ml.
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.

most of the studies. The upper cut-off corresponds to a marked increase in the probability of diagnosis of CHF. Indeed, in the BNP study, from 472 patients with BNP values >500 pg/ml, 87% had CHF.[49,61,62] Furthermore, Mueller *et al*. used the same threshold values in their Basel's study (see further).[7]

Meanwhile (the so-called 'grey zone' recently modelized by Coste *et al*.[34]), other investigations are needed (Doppler-echocardiography, CT chest, etc.) because a lot of causes might be suspected [CHF, atrial fibrillation without CHF, decreased BMI, complicated pulmonary embolism (PE), COPD exacerbation].[49,61,62] Thus, in the BNP study, there were 428 patients with BNP values between 100 and 500 pg/ml, and of these, 61% had CHF. Other predictors of elevated BNP levels included a decreased blood hemoglobin concentration and increased age.[49,61,62]

All these results strongly support the position adopted by recently published HF consensus guidelines that advocate the use of NT-proBNP and BNP as a complement and not an alternative to clinical assessment.[34,63] However, BNP and NT-proBNP cannot differentiate between systolic and preserved function HF, in dyspneic patients. So NP cannot replace the echocardiography in the etiologic analysis of HF. Echocardiography remains a mandatory exam during the hospitalization for acute CHF for identifying the underlying mechanism of HF and treatment adjustment.

Comparison of BNP and NT-proBNP

Ray *et al*. suggested a higher diagnostic accuracy of BNP compared to that of NT-proBNP.[33] However, the other studies which compared diagnostic accuracy of BNP and NT-proBNP did not confirm that result.[41,64] In a subgroup ($n = 75$) analysis of their study, Berdagué *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*.[64] demonstrated that the diagnostic value, assessed by the AUC, was similar for BNP (0.82) and NT-proBNP (0.84). Mueller *et al*.[47]

Table 4 Characteristics of BNP vs. NT-proBNP

Characteristic	BNP	NT-proBNP
Components	BNP active hormone	NT fragment (1–76) bi-product
Molecular weight	4 kDa	8.5 kDa
Genesis	Cleavage from proBNP	Cleavage from proBNP
Half-life	20 min	90 min 'classically'
Clearance mechanism	Neutral endopeptidase Clearance receptors Renal clearance	Renal clearance +++
Increases with aging	+++	++++
Correlation With eGFR	−0.20	−0.60
Approved cutoff(s) for CHF diagnosis	100 pg/ml Age ⩾75:250 pg/ml	Age <75:900 pg/ml Age ⩾75:1800 pg/ml
Prognostic role in CHF	+++	+++
Prognostic role in severe PE	++	++

Table 5 Comparison between BNP and NT-proBNP

	Mueller[47]	Chenevier-Gobeaux[43]	Alibay[39]	Lainchbury[45]	Ray[48]
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

*$P < 0.05$ vs. AUC NT-proBNP.

demonstrated that AUC for BNP and NT-proBNP in patients with dyspnea did not differ significantly (AUC of 0.916 vs. 0.903). Overall, BNP and NT-proBNP might be equally useful as an aid in the diagnosis of CHF in 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.). As stated below, *in vitro* stability is variable according to different assays. It is beyond this article to compare different assays. However, we believe that daily practices in the clinical department and laboratory organizations are the first arguments to consider when choosing a NP assay.

Does use of NP improve outcome and management?

There is now evidence that measuring BNP or NT-proBNP as early as in an ED could lower the cost of management 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%). Patients in the BNP group spent less time in the hospital (8 vs. 11 days), and their care cost less ($5410 vs. $7264) than those whose physicians did not have that single test result. 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 sub-group of patients older than 70 years.[7]

Moe *et al*.[65] also demonstrated that NT-proBNP testing improved the management of patients presenting with dyspnea to 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 rehospitalized over 60 days by 35% (51% to 33%), and direct medical costs of all ED visits, hospitalizations and subsequent outpatient services (US$6129 to US$5180 per patient) over 60 days from enrollment. However, knowledge of NT-proBNP results did not result in any major improvement in clinical outcomes, including lack of significant differences in the initial rate of hospitalization, hospital length of stay or mortality rates. These results are far less impressive than Mueller's ones. However, we believe that it is explained by the population involved (less severe with a lower rate of adverse events), and the methodology used (no specific recommendations to emergency

physicians were given with NT-proBNP levels unlike Mueller's study with BNP). Overall, knowing 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.[66–68] Initially, Throughton *et al*. suggested that NT-proBNP used for optimizing therapy in CHF reduced hospitalization for HF and cardiac events. However, this study was based on a very small population and mainly on diuretics and ACEI use. Jourdain *et al*. reported that a BNP-guided therapeutic strategy was superior to a clinically guided approach in 220 NYHA functional class II to III patients considered optimally treated by CHF specialists.[66–68] During a median follow-up of 15 months, fewer patients in the BNP group (with an aim of decreasing BNP below 100 pg/ml) reached the combined end point of CHF-related death or hospital stay for CHF, mainly as the result of a reduced hospitalization rate. The major reason for the more favorable outcome of the BNP group was that mean levels of ACEIs, β-blockers, spironolactone and diuretics were significantly greater in the BNP group. Other studies are currently underway 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.[69] Overall, measurements of BNP and NT-proBNP should be promoted in ED, in order to improve outcome and to lower cost.

Other potential interests of natriuretic peptides in acute dyspnea

Studies suggest that high BNP or NT-proBNP level at admission and during follow-up have prognostic importance.[70–74] Januzzi *et al*.[73] demonstrated that the presenting NT-proBNP was not only useful for diagnosis, but also strongly predicted likelihood for short-term mortality in subjects with CHF, with a more than 5-fold increase in risk for death by 76 days among those with marked elevation in NT-proBNP concentrations. Gegenhuber *et al*.[71] followed up 251 consecutive patients admitted for shortness of breath in an ED. Within 365 days from the time they were enrolled, 62 died and 189 stayed alive. Mortality was higher in patients with baseline BNP and NT-proBNP concentrations above 454 and 2060 pg/ml, respectively. In another study of dyspneic elderly patients, values of BNP >250 pg/ml (25% vs. 12%, $P < 0.001$) and NT-proBNP greater than 1500 pg/ml (23% vs. 12%, $P < 0.001$) were associated with greater in-hospital mortality.[49] Finally, in a multivariate analysis of the EPIDASA study, elevated NT-proBNP or BNP (OR = 2.06) was also predictive of death.[35] Recently, Chenevier-Gobeaux *et al*.[8] reported that an NT-proBNP level higher than 3855 pg/ml at admission was associated with higher in-hospital mortality in 324 patients aged 75 years and over—admission for dyspnea (17.9% vs. 9.7%, $P = 0.045$). An elevated NT-proBNP concentration at admission was predictive of death (OR = 2.41). Furthermore, mortality in patients with positive cTnI ($n = 54$) was higher when patients had NT-proBNP ⩾3855 pg/ml than in patients with NT-proBNP <3855 pg/ml (32.5% vs. 7.1%, $P = 0.082$).[8] Christ *et al*.[75] also reported that elevated levels of BNP ($P < 0.001$) and cardiac troponin I levels ($P < 0.002$) increased risk of death during long-term follow-up of 305 patients with acute dyspnea [death occurred in 123 (40%) patients within 24 months of follow-up].

Cournot *et al*.[76] included 61 consecutive patients >70 years (mean age, 83 years) hospitalized for CHF. They demonstrated that cardiac death or readmission were best predicted by the change in BNP levels, with the poorest prognosis in patients who did not achieve a decrease of at least 40%. However, studies suggest that BNP or NT-proBNP values at predischarge[77] and/or percentage change in BNP levels during hospitalization rather than at admission could be accurate in predicting long-term outcome in patients admitted for acute CHF.[74] Logeart *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% of events at 6 months).

Pulmonary embolism

Some subgroups of patients with PE have high risk, especially patients with hemodynamic impairment (massive PE), and also hemodynamically stable patients with right ventricular dysfunction (so-called submassive PE).[75] Indeed, right ventricular dysfunction is the main determinant of the short-term course of PE and can guide early management of patients with PE. Thus, some authors have suggested that thrombolytic therapy may be indicated for submassive PE. NP seem to be accurate biomarkers of right ventricular dysfunction and initial myocardial injury in acute PE. Furthermore, studies have suggested that BNP or NT-pro-BNP (as cardiac troponin) were accurate in risk stratification for PE in a middle-aged population and had a high positive negative value for in-hospital death.[78–81] However, other studies did not show any prognostic usefulness.[82,83] Thus, in clinical practice we do not recommend

measurement of BNP or NT-proBNP level for each case PE admitted to an ED.

Conclusions

There is strong and conclusive evidence that BNP and NT-proBNP are reliable and useful biomarkers in acute dyspnea where they have a diagnostic and prognostic value. Used in conjunction with other clinical information, rapid measurement of BNP or NT-proBNP reduced the total treatment cost of patients. As recommended by guidelines, their measurement should be strongly promoted in ED. Due to their prognostic usefulness, some authors suggest that NP should be measured in all the patients with clinical signs of CHF at the ED even if the diagnosis is evident. A careful history and examination of the patient and a systematic search for complicating factors is necessary for the appropriate analysis and the correct use of these biomarkers.

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