Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure

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Background: Circulating concentrations of B-type natriuretic peptide (BNP) and the aminoterminal fragment (NT-proBNP) of its prohormone (proBNP) are increased in congestive heart failure in proportion to the severity of symptoms, the degree of left ventricular dysfunction, and cardiac filling pressures. Following the introduction of rapid, automated assays for determination of BNP and NT-proBNP, these peptides are increasingly used for diagnostic and prognostic purposes.

Objective: To review studies evaluating the diagnostic and prognostic value of BNP and NT-proBNP, with special emphasis on their performance as indicators of acute heart failure in the intensive care unit.

Results: In patients presenting with acute dyspnea, both BNP and NT-proBNP are accurate indicators of acute heart failure and provide prognostic information above and beyond conventional risk markers. Increased plasma levels of BNP and NT-proBNP are not specific for heart failure and may be influenced by a variety of cardiac and noncardiac conditions commonly seen in the intensive care unit, including myocardial ischemia, cardiac arrhythmias, sepsis, shock, anemia, renal failure, hypoxia, acute pulmonary embolism, pulmonary hypertension, and acute respiratory distress syndrome.

Conclusions: The diagnostic performance of BNP and NTproBNP as indicators of acute heart failure depends on the clinical setting. In the intensive care unit, particular caution should be used in the interpretation of elevated BNP and NT-proBNP levels. (Crit Care Med 2008; 36[Suppl.]:S17–S27)

KEY WORDS: B-type natriuretic peptide; heart failure; dyspnea; shock; sepsis

cute heart failure can be defined as the rapid onset of symptoms and signs secondary to abnormal cardiac systolic or diastolic function (1). The clinical syndrome of acute heart failure is characterized by one or more of the following: reduced cardiac output, tissue hypoperfusion, increased pulmonary artery occlusion pressure, and tissue congestion. Heart failure can present in patients without previously recognized cardiac dysfunction (*de novo*) or as the acute decompensation of chronic congestive

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heart failure (CHF). Acute heart failure is associated with intense patient discomfort and, despite recent advances in therapy, still carries a high mortality rate. Because acute CHF requires urgent treatment, early evaluation of patients is crucial for appropriate selection and monitoring of therapy. This evaluation can be complex and relies on integration of the bedside evaluation and information available from invasive or noninvasive diagnostic techniques (2). This article reviews the role that B-type natriuretic peptides (BNPs) play in the evaluation of acute heart failure, with special emphasis on their utility in the intensive care unit (ICU).

Biology of B-Type Natriuretic Peptide

BNP was first identified in porcine brain in 1988 and originally was termed *brain natriuretic peptide* (3). Subsequently, it was detected in ventricular cardiomyocytes, and the ventricular myocardium was later recognized as the major source of circulating BNP (4). BNP is commonly regarded as an exclusively ventricular-derived hormone, but the concentration of BNP appears to be higher in atrial than in ventricular tissue. Taking into account tissue weight, however, the total amount of BNP messenger RNA has been suggested to be three times higher in the ventricles than in the atria (5).

BNP shares structural and physiologic features with atrial natriuretic peptide. Despite being encoded by separate genes, the two peptides show a high degree of primary structure homology and share a common ring structure. The second messenger cyclic guanosine monophosphate mediates the main physiologic actions of atrial natriuretic peptide and BNP. Binding to guanylyl cyclase-coupled, highaffinity natriuretic peptide-A receptors on target cells increases intracellular levels of cyclic guanosine monophosphate, resulting in vasodilation, natriuresis, diuresis, and inhibition of renin release and aldosterone production (5, 6).

BNP is synthesized as a longer precursor peptide or prohormone (proBNP) and subsequently split into a biologically active C-terminal and an inactive Nterminal fragment by the enzyme corin

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(5). The processing of proBNP to Nterminal fragment (NT-proBNP) and the 32-amino acid, biologically active BNP probably occurs both intra- and extracellularly. In human cardiac tissue, BNP appears to be found predominantly in the 32-amino acid form, but a significant amount is also stored as the intact 108amino acid precursor peptide, proBNP. ProBNP is only partially stored in granules, and the regulation of BNP synthesis and secretion apparently takes place at the level of gene expression. Both the biologically active 32-amino acid Cterminal fragment (BNP), the 76-amino acid N-terminal fragment (NT-proBNP), and other high-molecular fragments, possibly intact proBNP 1-108, are found circulating in human plasma (7). Interestingly, a recent study using quantitative mass spectral methodology reported the absence of circulating 32amino acid BNP in advanced heart failure, suggesting the existence of altered forms of BNP that contribute to the high levels measured by conventional assays (8). A schematic and simplified drawing showing the cleavage of proBNP into BNP and NT-proBNP is depicted in Figure 1.

Stretching of the atrial and failing ventricular myocardium is a potent stimulus for BNP production, which probably outweighs the influence of other modulating factors of natriuretic peptide production in most patients with heart failure (9). BNP expression and release from cardiomyocytes can be stimulated by a variety of endocrine, paracrine, and autocrine factors activated in CHF as well as factors like norepinephrine, angiotensin II, endothelin-I, glucocorticoids, and proinflammatory cytokines.

Although the N- and C-terminal fragments of proBNP probably are secreted in a 1:1 fashion, circulating levels may differ because of different clearance characteristics. The *in vivo* plasma half-life of BNP has been estimated to be approximately 21 mins (4, 10). Investigations in sheep suggest that the circulating half-life of NT-proBNP is approximately 70 mins (11), but studies in humans have yet to be performed. Clearance of BNP occurs both via binding to clearance receptors and by the actions of enzyme neutral endopeptidase. The mechanisms involved in clearance of NT-proBNP are less well characterized. Renal impairment, a common comorbidity in patients with CHF as well as in many other ICU patients, reduces clearance of both BNP and NT-proBNP



Figure 1. Schematic drawing showing cleavage of prohormone of B-type natriuretic peptide (*proBNP*) into the biologically active C-terminal fragment, B-type natriuretic peptide (*BNP*), and the inactive N-terminal fragment, *NT-proBNP*. *NPR*, natriuretic peptide receptor.

Table 1. Characteristics of B-type natriuretic peptide (BNP) and N-terminal fragment of prohormone of BNP (NT-proBNP)

Characteristic	BNP	NT-proBNP		
Prohormone fragment	C-terminal (proBNP 77–108)	N-terminal (proBNP 1–76)		
Molecular weight, kDa	3.5	8.5		
Physiological activity	Active	Probably inactive		
FDA-approved cutoff values	100	Age <75 yrs: 125		
for heart failure diagnosis, pg/mL		Age >75 yrs: 450		
Clearance mechanisms	Clearance receptors Neutral endopeptidase	Unclear, <mark>renal</mark> clearance may contribute		
Plasma half-life, mins	21	6 <mark>0–120</mark>		
In vitro stability	24 hrs at room temperature	>3 days at room temperature		
Analyzed in	Whole blood and EDTA plasma (plastic tubes)	Serum and plasma		

FDA, Food and Drug Administration.

(12). Characteristics of BNP and NTproBNP are summarized in Table 1.

Assays for BNP and NT-proBNP

During the past few years, several fully automated, rapid assays for determination of BNP and the N-terminal fragment of its prohormone (NT-proBNP) have become commercially available, permitting their use in the clinical setting. These include both high-throughput automated platforms and point-of-care tests. Both preanalytic and analytic issues are important for the proper interpretation of test results, and clinicians should be aware of the following practical points: Plastic tubes containing EDTA are desirable for BNP determination, whereas NT-proBNP can be measured in serum or plasma and collected in glass or plastic tubes. For BNP, refrigeration may be required if the interval between blood collection and analysis is >4 hrs. On the other hand, no significant loss of NT-proBNP immunoreactivity is apparent after 48 hrs at room temperature. Although existing BNP assays correlate closely, BNP assays are not currently analytically equivalent due to lack of assay standardization.

BNP in Cardiovascular Disease

Soon after the discovery of BNP production in the human myocardium, it became clear that tissue and circulating concentrations of BNP are elevated in CHF in proportion to the severity of symptoms (13), the degree of left ventricular dysfunction (14), and cardiac filling pressures (4, 15). Both systolic and diastolic impairment of the left ventricle can result in elevated circulating natriuretic peptide levels (16, 17), even in mildly symptomatic or asymptomatic patients with left ventricular impairment (15, 18).

In addition to systolic and diastolic left ventricular dysfunction, BNP and NTproBNP levels are elevated in a broad spectrum of cardiovascular diseases, including acute coronary syndromes, stable coronary heart disease, valvular heart disease, acute and chronic right ventricular failure, and left and right ventricular hypertrophy secondary to arterial or pulmonary hypertension (6). Activation of neurohormonal systems with vasoconstrictor, antidiuretic, proinflammatory, hypertrophic, and cytoproliferative actions is believed to play a pathophysiological role in the progression of many of these conditions (19). The natriuretic peptides possess beneficial and compensatory properties that counteract these vasoconstrictor neurohormonal systems. Table 2 summarizes some factors associated with higher plasma levels of BNP and NT-proBNP.

Diagnosis of CHF in the Acutely Dyspneic Patient

The clinical diagnosis of CHF can be challenging, particularly in patients presenting with acute shortness of breath in the urgent care setting. Information ob-

tained from clinical history and physical examination as well as from electrocardiogram and chest radiograph may provide valuable clues as to whether CHF is the cause of symptoms, but additional diagnostic tests, including echocardiography, may be required to obtain a more definite diagnosis (20). However, a helpful history may not be obtainable in the acutely ill patient with dyspnea. Physical signs, including pulmonary rales, edema, a third heart sound, and elevated jugular venous pressure, may be absent, particularly if the patient already receives pharmacologic therapy. Findings on the chest radiograph, including redistribution and interstitial or alveolar edema, are relatively specific but insensitive signs of CHF (21). A normal electrocardiogram is seen infrequently in patients with CHF, but electrocardiographic abnormalities have a low positive predictive value for CHF (22). Many patients with acute shortness of breath may have difficulties in lying still, and obesity and chronic obstructive pulmonary disease, factors commonly seen in acutely dyspneic patients, may result in inferior echocardiographic image quality. A misdiagnosis may have serious consequences, particularly if inappropriate therapy is initiated. For instance, sympathomimetic amines and β -adrenergic agonists may provoke arrhythmias and angina in patients with dyspnea secondary to CHF.

BNP in Patients With Acute Dyspnea

Today, the best documented and most widely used clinical application of BNP testing is for the emergency diagnosis of CHF in patients presenting with acute dyspnea. Although the results of a smallscale study published in 1994 suggested that BNP measurements could be useful in this setting (23), it was not until the development of rapid analytic tests and

Table 2. Major causes of elevated plasma levels of B-type natriuretic peptide (BNP) and N-terminal fragment of prohormone of BNP (NT-proBNP)

Elevated stretch of the myocardium due to impaired systolic and/or diastolic function (e.g., acute
and chronic congestive heart failure, acute and chronic cor pulmonale)
Ventricular hypertrophy (e.g., hypertensive heart disease)
Volume expansion and consequent elevated pressure/distension (e.g., renal or hepatic failure)
Decreased renal clearance (e.g., acute and chronic renal failure, advanced age)
Neurohormonal and cytokine stimulation (e.g., sepsis, shock)
Myocardial ischemia (e.g., unstable angina, acute myocardial infarction)
Hypoxia (e.g., acute pulmonary embolism, cyanotic congenital heart disease)
Tachycardia (e.g., atrial fibrillation, ventricular tachycardia)
Female gender

the publication of the Breathing Not Properly multinational study in 2002 that BNP measurements were introduced into clinical practice. In this landmark multicenter diagnostic test evaluation trial, which included 1,586 patients who visited the emergency department with a main complaint of acute dyspnea, a rapid point-of-care fluorescence immunoassay was used for BNP determination (24). Diagnosis of heart failure was adjudicated by cardiologists blinded to the BNP results. In this study, BNP concentration was found to provide strong and incremental diagnostic information to conventional historical, clinical, or other laboratory tests and to have greater diagnostic accuracy for the diagnosis of heart failure than the emergency department physician, using all other available information. Using a cutoff of 100 pg/mL, the overall diagnostic accuracy was 83.4% and the area under the receiver operating characteristic curve for BNP was 0.91 (95% confidence interval 0.90-0.93) (Fig. 2). Although BNP testing performed slightly better in men than in women and in younger (<70 yrs) than older patients, the overall accuracy was very good regardless of these demographic factors. Importantly, BNP performed well in patients with an intermediate (20% to 80%) pretest probability of heart failure, as evaluated by the emergency department physician (25). In these subjects, who constituted 43% of the total study cohort, the BNP >100 pg/mL cutoff classified 74% correctly.

Very similar results were later reported for NT-proBNP, using a clinical chemistry laboratory-based analytic platform, in the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency department (PRIDE) study (26). This prospective, single-center study included 599 patients with acute dyspnea presenting to the emergency department of Massachusetts General Hospital in Boston, the primary objective being to compare the diagnostic accuracy of NT-proBNP with that of clinical assessment for identifying acute heart failure. In this study, the area under the receiver operating characteristic curve for NT-proBNP was 0.94, which compared favorably with 0.90 for clinical assessment (p = .009). Several decision thresholds were evaluated and the single best cutoff was found to be 900 pg/mL, a cutoff that had an overall diagnostic accuracy of 87% (sensitivity 90%, specificity 85%). Using the lower cutoff of 450 pg/mL

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increased sensitivity to 98% at the cost of a decreased specificity of 76% and an overall diagnostic accuracy of 83%. Table 3 summarizes optimal confirmatory and exclusionary decision limits for acute heart failure based on a pooled analysis of studies evaluating the diagnostic value of NT-proBNP in acutely dyspneic patients (27).

Another important study suggesting that BNP determination on presentation to the emergency department can translate into improved management and reduced cost was the B-type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) study (28). This prospective, randomized trial evaluated the effect of rapid point-of-care BNP testing on time to discharge and total cost of treatment in 452 acutely dyspneic patients. A diagnostic strategy including a single rapid measurement of BNP in the emergency department was associated with reduced need for intensive care and shorter time to discharge, which together translated into reduced total cost of treat-

	1.0 T							
		\mathcal{A}	BNP, 50	pg/ml				
		BN BN	IP, 80 pg/ml					
	0.8-	/ BNP,	100 pg/ml					
		BNP, 12	5 pg/ml					
		BNP 150 r	na/ml					
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S	0.47							
		Area under	the receiver-op	erating-charac	teristic curve,			
	11	0.91 (95% confidence interval, 0.90–0.93)						
	0.2	1						
	1/							
	0.0-4							
	0.0	0.2	0.4	0.6	0.8	1.0		
			1–Sp	ecificity				
				POSITIVE	NEGATIVE			
				PREDICTIVE	PREDICTIVE			
	BNP	SENSITIVITY	SPECIFICITY	VALUE	VALUE	ACCURACY		
	pg/ml	(95 percent confidence interval)						
	50	97 (96-98)	62 (59–66)	71 (68–74)	96 (94–97)	79		
	80	93 (91-95)	74 (70-77)	77 (75-80)	92 (89-94)	83		
	100	90 (88-92)	76 (73–79)	79 (76–81)	89 (87–91)	83		
	125	87 (85-90)	79 (76-82)	80 (78-83)	87 (84-89)	83		
	150	85 (82-88)	83 (80-85)	83 (80-85)	85 (83-88)	84		

Figure 2. Main results of the Breathing Not Properly Multinational study. See text for details. Reprinted with permission from Maisel et al (24). *BNP*, B-type natriuretic peptide.

ment, compared with those diagnosed in a standard manner without BNP assessment. These results were recently corroborated by the Canadian IMPROVE-CHF study, which included 501 patients presenting with shortness of breath to seven emergency departments across Canada (29). One major objective of this randomized, controlled study was to evaluate whether the measurement of NT-proBNP improves the overall management of patients presenting with suspected acute heart failure and whether the knowledge of NT-proBNP levels on presentation resulted in reduced resource utilization and hospital cost. Although it was reported that NT-proBNP measurements were associated with an average cost saving of nearly \$1,000, duration of ICU or total hospital stay did not differ between the usual care and NT-proBNP group. Moreover, in the report it was not clear whether the savings were related to better and more rapid treatment or to less use of diagnostic testing.

The clinical utility of BNP testing clearly depends on the clinical setting. BNP may be far less discriminative in the diagnosis of systolic dysfunction in welltreated patients with chronic CHF and mild symptoms than in acutely decompensated patients with severe shortness of breath (30). Moreover, the results obtained in studies of acutely dyspneic patients cannot be extrapolated to heart failure patients who present with predominantly low-output symptoms (e.g., fatigue or anorexia).

Can BNP Be Used as a Surrogate for Specific Hemodynamic Measurements?

After the realization that BNP levels are increased in heart failure, a logical next step was to evaluate whether BNP can be used as a surrogate marker of

Table 3. Recommended decision thresholds for N-terminal fragment of prohormone of B-type natriuretic peptide (NT-proBNP) in the diagnosis of acute heart failure

Age, yrs	Optimal Cutoff, pg/mL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Confirmatory (rule in) decision limits						
<50	450	97	93	76	99	95
50-75	900	90	82	82	88	85
>75	1800	85	73	92	55	83
Overall		90	84	86	66	86
Exclusionary (rule out) decision limit	200	00	60		00	00
All ages	300	99	62	55	99	83

PPV, positive predictive value; NPV, negative predictive value. Adapted from Januzzi et al (27).

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hemodynamic measurements and ventricular function, including ventricular filling pressures and ejection fraction. Early small-scale studies suggested that BNP levels could be used to identify patients with acute myocardial infarction and ejection fraction <40% (31). Subsequent studies, including substantially larger patient populations, in most cases failed to confirm a close correlation between BNP levels and ejection fraction (15, 27, 32, 33). Although a significant correlation exists between BNP and systolic function, this correlation is not sufficiently strong to make BNP or NT- proBNP reliable surrogate indicators of ejection fraction (Fig. 3). Similarly, although ventricular stretch clearly represents a major stimulus for BNP release, the correlations between BNP and pulmonary artery occlusion pressure (PAOP) or left ventricular end-diastolic pressures are only moderately strong, not permitting reliable information to be obtained concerning filling pressures based on a BNP or NT-proBNP test in individual patients (15, 34). The lack of a close correlation between BNP and filling pressures may seem surprising, given that ventricular stretch is the predominant stimulus



Figure 3. Association between N-terminal fragment B-type natriuretic peptide (*NT-proBNP*) and left ventricular ejection fraction. Reprinted with permission from Januzzi et al (27).

for BNP release in experimental models. In patients, however, a number of cardiac and noncardiac factors are co-determinants of circulating BNP concentrations, and the variability in BNP and NTproBNP that can be ascribed to left ventricular filling pressures is relatively modest.

Many factors that cause significant interindividual differences in BNP and NTproBNP concentrations in patients with similar hemodynamic status usually remain relatively unaltered in a single patient (e.g., age, gender, and renal function). Accordingly, serial BNP and NTproBNP measurements may be useful tools for monitoring hemodynamic changes in individual patients. In groups of patients, average BNP and NT-proBNP levels clearly drop in parallel with reductions in left ventricular preload (34, 35)(Fig. 4). Still, it has proved difficult to accurately predict the change in a hemodynamic variable, such as PAOP, based on the change in BNP levels. In other words, a given reduction in BNP and in PAOP in one patient may differ substantially from the reduction in BNP level induced by a similar drop in PAOP in another patient. Thus, a significant reduction in BNP during therapy strongly suggests a reduction in PAOP, but the magnitude of the decrease cannot be reliably predicted by the change in BNP in the individual patient. This may be of particular importance in the monitoring of patients in the ICU with sepsis or shock, in whom endogenous or exogenously administered sub-



Figure 4. Effect of reduction in cardiac filling pressures on plasma natriuretic peptide levels. *RAP*, right atrial pressure; *PCWP*, pulmonary artery occlusion pressure; *ANP*, A-type natriuretic peptide; *BNP*, B-type natriuretic peptide; *NT-proANP*, N-terminal fragment of prohormone of ANP. Adapted from Johnson et al (35).

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stances may affect BNP concentrations independently of hemodynamic status.

Can BNP Be Used to Discriminate Between Systolic and Diastolic Heart Failure?

Symptomatic heart failure may be caused by both systolic and diastolic dysfunction, and variable degrees of both systolic and diastolic dysfunction are commonly observed in the same individual (36). Circulating levels of BNP and NT-proBNP can be elevated secondary to both systolic and diastolic dysfunction of the left ventricle, and particularly high levels may be observed in those with combined systolic dysfunction and a restrictive filling pattern (37). As heart failure with preserved systolic ventricular function is prevalent, particularly in the elderly, BNP and NT-proBNP have proved to be less reliable indicators of systolic dysfunction than of clinical heart failure (38). Moreover, BNP and NT-proBNP cannot reliably discriminate between systolic or diastolic dysfunction as the cause of heart failure (17).

What Causes BNP Elevation in Patients Without CHF?

A number of factors other than ventricular function, including advanced patient age and female gender, decreased body mass index, decreased renal function, left ventricular hypertrophy, history of myocardial infarction and ongoing cardiac ischemia, pulmonary embolism, chronic right ventricular failure, and cardiac arrhythmias, have been shown to influence circulating BNP and NTproBNP levels. Clearly, the presence of any of these factors may confound the relationship between elevated BNP and NT-proBNP levels and the diagnosis of acute heart failure and thus impair the diagnostic accuracy of BNP and NTproBNP testing (12, 39-42). Most studies, however, have assessed only the significance of single factors, and until recently their relative and independent importance as confounders had not been evaluated. In a recent analysis based on the Breathing Not Properly multinational study, multivariable modeling was used to identify factors independently associated with elevated BNP levels in the absence of heart failure (43). Five independent predictors of elevated BNP levels in the absence of acute heart failure were identified: low hemoglobin values, low body mass index, a medical history of atrial fibrillation, radiographic cardiomegaly, and advanced age of the patient. Notably, renal function did not emerge as an independent predictor of BNP, possibly because of colinearity with patient age.

In a pooled analysis of four studies that included 1,256 patients with acute dyspnea, 215 patients had an intermediate NT-proBNP concentration, of whom 116 subjects (54%) were classified as having a diagnosis of acute heart failure (44). Multivariable modeling was used to identify predictors of acute heart failure in patients with NT-proBNP levels in the gray zone (defined as 300-450 pg/mL in patients aged <50 yrs, 300-900 pg/mL in patients aged 50-75 yrs, and 300-1800 pg/mL in those >75 yrs of age). The absence of cough, use of loop diuretics on presentation, paroxysmal nocturnal dyspnea, and jugular vein distension were independently associated with a diagnosis of acute heart failure. Importantly, an intermediate (or gray zone) NT-proBNP concentration was associated with increased mortality compared with those with NT-proBNP <300 pg/mL regardless of a diagnosis of acute heart failure or not. Accordingly, a gray-zone BNP or NTproBNP should not be misinterpreted as a false-positive or false-negative result but rather as a result that signifies an intermediate risk of death.

What Causes "Normal" BNP Levels in Patients With CHF?

In patients with documented CHF, BNP and NT-proBNP levels may occasionally be below the decision threshold for heart failure. In stable ambulatory patients with symptomatic systolic CHF, approximately 20% of patients were reported to have BNP levels <100 pg/mL (30). These patients with so-called normal BNP values were more likely to be younger, to be female, to have nonischemic pathogenesis, and to have better preserved renal and ventricular function and less likely to have atrial fibrillation. In acutely dyspneic patients, falsenegative BNP and NT-proBNP results are less common but may be seen in patients with flash pulmonary edema and those with severe obesity (40). Etiology of heart failure at the level of the atrium (e.g., mitral stenosis or acute mitral regurgitation) is another possible cause of unexpectedly low BNP and NT-proBNP levels.

Prognostic Value in Acute CHF

Given the association between both BNP and NT-proBNP and the severity of heart failure, it is not surprising that that these peptides are strongly predictive of the incidence of mortality and heart failure hospitalizations. However, multiple studies have shown that BNP and NTproBNP provide prognostic information above and beyond conventional risk markers, including clinical assessment and indices of ventricular function. This has been documented in large populations of patients with stable CHF (45) as well as in patients with acute decompensation (46, 47) and in patients presenting with acute dyspnea (48, 49). The Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT) evaluated the association between BNP levels, perceived heart failure severity by the emergency department physician, clinical decision making, and outcomes in 464 acutely dyspneic patients with elevated BNP (i.e., >100 pg/mL), of whom 90% were admitted (50). Interestingly, BNP levels did not differ between patients admitted and those discharged, and no correlation was observed between BNP levels and perceived disease severity. By logistic regression analysis, the intention of the emergency department physician to admit or discharge was not related to 90day outcome. Conversely, a single BNP measurement in the emergency department was predictive of the combined end point of mortality and heart failure admissions.

Some studies have suggested that in patients with acute heart failure, BNP levels at discharge are more closely associated with prognosis than concentrations on admission. In one study of 72 patients admitted with decompensated heart failure, those with high levels on presentation and at discharge were most likely to experience death or readmission within 30 days (47). The value of serial testing of NT-proBNP was confirmed in a study of 182 consecutive patients hospitalized with decompensated heart failure who were followed for 6 months. Although several variables were related to outcome, in a multivariate model discharge NT-proBNP emerged as the strongest prognostic indicator (46). These observations suggest that although BNP or NT-proBNP measurements on presentation are helpful for diagnostic purposes, a repeated test on discharge may provide additional prognostic information of conTable 4. Strategy for triage and therapy of patients with acute heart failure using B-type natriuretic peptide (BNP) and clinical evaluation

	No Congestion at Rest	Congestion at Rest
Adequate perfusion at rest	Warm and dry	Warm and wet
	BNP 100–400	$BNP \ge 600$
Low perfusion at rest	Cool and dry	Cool and wet
	BNP 400–1000	$\mathrm{BNP} \geq 1000$

Adapted from Stevenson (53) and Stevenson and Maisel (54).

sequence for the intensity of therapy and the interval between outpatient control visits following discharge. Minor changes in BNP and NT-proBNP should, however, be interpreted cautiously as the intraindividual variability of BNP and NTproBNP levels may be as high as 40% (51, 52).

Practical Recommendations for BNP Testing

Adapting a strategy originally proposed by Stevenson (53), Maisel (54) proposed a conceptual model concerning circulating concentrations of BNP and NTproBNP in patients with decompensated CHF (Table 4). According to this model, plasma BNP comprises two components: a basal or "dry" BNP level observed in the euvolemic state and the additional BNP production caused by volume overload. The sum of basal and the volume overload-induced concentrations will determine the "wet" BNP levels observed during acute decompensation. The dry BNP level is the more important determinant of repeated episodes of decompensation and readmission. Moreover, knowledge of the dry BNP concentration is likely to be useful for monitoring clinically stable patients. An increase from the baseline dry BNP level may indicate the need for intensified diuretic or other vasodilator therapy. Failure of BNP to fall during treatment may have different explanations. Some patients may have very advanced heart failure with high BNP levels in the dry state, a condition associated with a poor prognosis. Other patients may have increasing plasma concentrations of BNP and NT-proBNP because of increasing renal dysfunction.

Cardiac Dysfunction in the ICU

By definition, most patients in the ICU are critically ill and at high risk for complications and death. Cardiac dysfunction, transient or permanent, is relatively common in certain groups of patients in

the ICU. The prevalence of cardiac dysfunction, however, depends critically on the characteristics of the study population and the criteria and methods used to diagnose cardiac abnormalities. In a general intensive care unit sample of 121 consecutive patients included during a 9-wk period, approximately 30% were identified as having a cardiac abnormality, as evaluated by history, electrocardiogram, chest radiograph, and echocardiography (55). In patients with severe sepsis and septic shock, about half of the patients were reported to have some degree of myocardial dysfunction (56). Echocardiographic findings of right or left ventricular dysfunction may have important consequences for evaluation and management of critically ill patients. However, transthoracic echocardiography in this population may be technically challenging, and image quality is frequently suboptimal. Moreover, experienced echocardiographers may not be available on a 24-hr basis. In patients with shock, additional hemodynamic information may be required, particularly concerning cardiac filling pressures and peripheral and pulmonary vascular resistance. Invasive hemodynamic monitoring with pulmonary artery catheters is one approach to patients with shock in the ICU, but the clinical efficacy of such monitoring is unproven (57, 58). Information concerning cardiac performance and hemodynamic status is, however, often desirable in the critically ill, and recently circulating biomarkers, including BNP and NT-proBNP, have been proposed as useful diagnostic and prognostic tools in this setting.

BNP Measurements in the ICU

Given that preexisting cardiovascular disease, critical illness-associated transient myocardial impairment, and renal impairment, alone or in combination, are common phenomena in ICU patients, it is not surprising that many patients have some degree of BNP and NT-proBNP elevation. In one analysis, the presence of preexisting cardiac disease was the single most important determinant of BNP elevation in a general ICU, accounting for nearly 50% of BNP variability (55). However, numerous other factors may cause BNP and NT-proBNP elevation in critically ill patients. Because ICU patients comprise a heterogeneous group and because mechanisms responsible for increased BNP production or decreased clearance may differ according to the index diagnosis of the patient, broad diagnostic categories are discussed briefly next.

Sepsis and Shock. Several studies have examined whether BNP and NT-proBNP can be used to replace invasive hemodynamic monitoring for guidance of fluid resuscitation and vasopressor therapy in patients with sepsis or septic shock (59). One study that included 17 patients with septic shock showed higher levels in patients with septic shock than in agematched control subjects, but absolute concentrations were very low and did not correlate with filling pressures (60). In another study of 40 patients in the ICU requiring hemodynamic monitoring, of whom 12 had a diagnosis of sepsis or acute respiratory distress syndrome, both BNP and NT-proBNP were markedly elevated but only weakly correlated with PAOP (61). Renal function was an important determinant of both BNP and NTproBNP. Moreover, renal impairment modulated the association between natriuretic peptides and PAOP. In another study of 49 patients with shock, of whom 42 were classified as noncardiogenic, no correlation with PAOP was observed, but a low BNP level effectively ruled out a diagnosis of cardiogenic shock (62). In a recent study, 249 consecutive patients were screened for the presence of severe sepsis or septic shock and for acute heart failure (63). Patients with sepsis (n = 24)and heart failure (n = 51) did not have significantly different BNP or NT-proBNP levels, despite markedly different hemodynamic patterns (sepsis vs. heart failure: mean pulmonary artery pressure 16 ± 4.2 vs. 22 \pm 5.3 mm Hg, and cardiac index 4.6 \pm 2.8 vs. 2.2 \pm 0.6 L/min/m²). In summary, although some studies report significant correlations between BNP and PAOP, the association is generally weak. This is probably due to the major contribution of other stimuli for natriuretic peptide production and reduced clearance in ICU patients. Consequently, BNP and NT-proBNP determination should not be employed as a

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substitute for invasive hemodynamic monitoring in the ICU.

Realizing the limitations of BNP and NT-proBNP measurements as a surrogate for pulmonary artery catheterization, a possible alternative approach proposed by Januzzi et al. (64) could be to use these peptides to identify patients who may not require insertion of a pulmonary artery catheter. The rationale for this approach is based on the high negative predictive value of BNP and NT-proBNP (64). In the study by Januzzi et al., NT-proBNP <1200 pg/mL had a negative predictive value of 92% for the combination of a cardiac index <2.2 L/min/m² and PAOP >18 mm Hg.

Limited and conflicting data exist concerning the effect of fluid loading and catecholamine therapy on BNP and NTproBNP levels. In one study, fluid loading was found not to be an independent predictor of NT-proBNP levels (65). Another study reported that patients with left ventricular fractional area contraction <0.5, as assessed by transesophageal echocardiography, had higher BNP levels and had received more intravenous fluids than those with left ventricular fractional area contraction >0.5.

Despite important limitations as a diagnostic tool for acute heart failure in ICU patients, both BNP and NT-proBNP may provide useful prognostic information. In one study of patients with severe sepsis or septic shock, high BNP levels correlated with ventricular dysfunction and mortality (56). Similarly, in a cohort of 49 patients with mainly noncardiogenic shock, high levels of both BNP and NT-proBNP were associated with increased mortality (62, 64) (Fig. 5). Importantly, BNP and NT-proBNP predicted mortality independently of conventional risk markers, including Acute Physiology and Chronic Health Evaluation II scores. However, not all studies report an association with prognosis. In a study of 78 patients admitted to a general ICU, patients with sepsis (n = 35) had higher BNP levels than patients without sepsis, but BNP did not predict in-hospital survival (66).

BNP in Pulmonary Disease. The usefulness of BNP and NT-proBNP as indicators of heart failure in acutely dyspneic patients depends critically on the premise that patients with dyspnea due to pulmonary causes, of whom chronic obstructive pulmonary disease is the most common. have low circulating concentrations of these peptides. A considerable proportion of patients with respiratory failure may, however, have levels that exceed the conventional cutoff for heart failure (67). The interpretation of this observation is complicated by the fact that coronary artery disease and chronic obstructive pulmonary share risk factors and often coexist in the same individual. Underdiagnosis of heart failure in chronic obstructive pulmonary disease may not be uncommon. Unfortunately, in patients with respiratory failure, neither BNP nor NT-proBNP appears to differentiate between a low vs. high PAOP state (68). One reason for this may be that a significant proportion of patients with chronic obstructive pulmonary disease and respiratory failure will have evidence of right heart failure, a stimulus for BNP production.

The majority of patients with acute respiratory distress syndrome without concomitant shock or acute cor pulmonale have BNP and NT-proBNP levels below the threshold used for heart failure diagnosis. However, a considerable pro-



Figure 5. Mortality by N-terminal fragment of prohormone of B-type natriuretic peptide (*NT-proBNP*) quartile in intensive care unit patients with shock. Reprinted with permission from Januzzi et al (64).

portion of patients will develop these complications (69) and may have moderately elevated peptide levels (70), although usually not in the acute decompensated heart failure range. Accordingly, BNP and NT-proBNP may still have some utility to identify left-sided heart failure in these patients, but conventional decision limits are probably suboptimal.

Very recently, the usefulness of NTproBNP as a tool to identify acute heart failure during weaning failure in difficultto-wean patients with chronic obstructive pulmonary disease was assessed (71). Plasma levels of NT-proBNP increased significantly at the end of the spontaneous breathing trial only in patients with acute cardiac dysfunction. Moreover, NTproBNP levels at the end of the weaning trial appeared to perform well in detecting acute cardiac dysfunction, although study power was limited and receiver operating characteristic area confidence intervals were wide.

BNP in Pulmonary Vascular Disease. Pulmonary hypertension is associated with increased right ventricular wall stretch and increased production of BNP and NT-proBNP from the right heart. In addition, hypoxia is associated with increased expression of the BNP gene. Accordingly, circulating concentrations of BNP and NT-proBNP are increased in primary pulmonary hypertension (72), persistent pulmonary hypertension of the newborn (73), acute cor pulmonale following pulmonary embolism (74) or acute respiratory distress syndrome (70), and right ventricular failure secondary to congenital heart disease (75). The plasma BNP and NT-proBNP concentrations observed in these conditions are usually only moderately elevated and typically not in the range observed in acute left ventricular failure. In general, concentrations are increased in proportion to disease severity and are predictive of outcome (72). BNP and NT-proBNP levels decrease following successful therapy, for example, after thromboendarterectomy for pulmonary hypertension secondary to chronic pulmonary embolism (76). These findings indicate that BNP and NTproBNP may provide information of potential clinical utility concerning the effect of intervention. The diagnostic and prognostic utility of BNP and NT-proBNP in patients with acute pulmonary embolism has also been examined (77, 78). In patients without right ventricular dysfunction, levels are generally low and cannot be used as a diagnostic tool (79).

However, BNP and NT-proBNP increase in proportion to hemodynamic compromise, and elevation of BNP and NTproBNP has been proposed as a criterion for thrombolytic therapy because of its strong prognostic merit (79). Other investigators, however, argue that the positive predictive value is too low to be clinically useful for this purpose (80).

Other Critical Illnesses. Plasma concentrations of BNP and NT-proBNP also increase in other critical illness. As mentioned previously, both BNP and NTproBNP are elevated in chronic renal failure, but the diagnostic accuracy for heart failure is not markedly reduced if renalfunction-adjusted decision limits are used (12, 81, 82). Sparse data are available concerning the effect of acute renal failure on natriuretic peptide levels in ICU patients, although available evidence suggests that an inverse relation exists (61, 68). As changes in renal function can occur rapidly in the ICU, these observations are important. Natriuretic peptides are also elevated in patients with ischemic stroke (83) and those with subarachnoid hemorrhage (84, 85). Elevation of BNP and NT-proBNP in these conditions has been attributed to high sympathetic outflow or damage of brain areas with regulatory functions for BNP production and may not have prognostic implications. However, plasma levels in subarachnoid hemorrhage also correlate with cardiac dysfunction (85).

CONCLUSIONS

BNP and NT-proBNP provide valuable and well-documented biochemical guidance for the diagnosis of acute heart failure in patients presenting with acute dyspnea. These peptides also provide powerful prognostic information in patients with acute heart failure. Circulating levels of BNP and NT-proBNP are, however, influenced by numerous cardiac and noncardiac factors, including myocardial ischemia, hypoxia, patient age, gender, and renal function. Consequently, BNP and NT-proBNP are sensitive but unspecific markers of cardiac structural and functional abnormalities but can generally not be used as a surrogate for a single hemodynamic index (e.g., PAOP or ejection fraction). In the ICU, many patients may have moderately elevated natriuretic peptide levels without the presence of left ventricular failure. Conditions other than left ventricular failure commonly associated with increased BNP and NT-proBNP levels in the ICU include shock, hypoxia, renal failure, and pulmonary hypertension. As the diagnostic accuracy of BNP and NTproBNP for left ventricular failure is reduced in the ICU, BNP and NT-proBNP measurements in the ICU should be interpreted cautiously and in most cases may augment but cannot replace information obtained from invasive hemodynamic monitoring and echocardiography.

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