REVIEW ARTICLE

Use of Natriuretic Peptide Assay in Dyspnea

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SUMMARY

Introduction: Acute dyspnea is a common symptom in patients admitted to hospital via emergency department. Heart failure is a common cause with high morbidity and mortality, but diagnostically challenging. Improvement in diagnostic techniques is needed.

Methods: Selective search of Medline.

Results: B-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are extremely helpful in the diagnosis of heart failure in patients with acute dyspnea. The use of natriuretic peptide assay has also been shown to be cost-effective. Since plasma levels of natriuretic peptides reflect the extent of systolic and diastolic dysfunction, measurement of natriuretic peptides is helpful in estimating overall risk in patients with heart failure or acute myocardial infarction. They have also been used in the management of patients with valvular disease and in tailoring therapy in patients with heart failure.

Discussion: BNP and NT-proBNP are quantitative markers of heart failure that are helpful for diagnosis, prognosis and treatment monitoring.

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Patients with acute dyspnea have a high mortality risk (1) due principally to cardiac causes such as acute heart failure. Acute heart failure is diagnostically challenging because of the lacking sensitivity and specificity of clinical diagnostic procedures (2). The purpose of this article is to critically review clinically important experiences with natriuretic peptides in the diagnostic and therapeutic settings. The database for B-type natriuretic peptide (BNP) is presented and discussed, including important data relating to the N-terminal fragment of BNP (NT-proBNP).

Methods

A selective literature search was performed in the Medline database (1966 to June 2007) using the search terms "natriuretic peptides", "B-type natriuretic peptide", "NT-proBNP", "heart failure", "acute dyspnea", "outcome", and „mortality“. A search was also conducted in recent review articles. The authors selected relevant manuscripts relating to diagnosis, prognosis, and therapy monitoring.

Natriuretic peptides – important cardiac hormones

BNP is synthesized as a prohormone mainly in the left ventricular myocardium following myocardial extension under volume and pressure stress and is secreted in a pulsatile pattern into the circulation by neurohumoral stimulation (3). Enzymatic cleavage of the prohormone produces the active hormone BNP (C-terminal) and the inactive N-terminal fragment (NT-proBNP). Besides the natriuretic effects from which the hormone derives its name (decrease in tubular reabsorption of sodium), BNP causes peripheral vasodilatation. BNP also inhibits sympathoadrenergic activity and reduces renin release and aldosterone production (3).

Neutral endopeptidase (30%) and receptor mediated endocytosis (70%) cause inactivation of the hormone (3). The half-life of the active hormone is approximately 22 minutes, whereas NT-proBNP has a half-life of about 60 to 120 minutes and exhibits much better stability *ex vivo* (several days) (4). Since NT-proBNP is mainly eliminated via the renal route, the NT-proBNP levels are dependent to a greater extent on the glomerular filtration rate.

An increase in circulating BNP levels principally reflects a decompensated cardiovascular situation and

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FIGURE 1

Algorithm for interpreting BNP/NT-proBNP levels in acute dyspnea patients. The BNP/NT-proBNP levels must always be interpreted in association with other clinical signs and symptoms (modified from [23]). BNP, B-type natriuretic peptide; NT-proBNP, N-terminal fragment of BNP; LV, left ventricular; RV, right ventricular; HF, heart failure

correlates with left ventricular (LV) end-diastolic wall tension (3). BNP is therefore used as a marker of diseases associated with LV or right ventricular (RV) dysfunction (4).

Importance in laboratory diagnosis

Besides automated assays designed for use in large laboratories, point-of-care assays are commercially available that allow the bedside determination of BNP/ NT-proBNP. It is of practical importance to ensure that point-of-care assays are also subjected to standardized quality controls. These comprise firstly the standards integrated in every assay and secondly regular external quality testing.

Many clinical statements are based on examinations performed with a point-of-care BNP assay kit. Numerous results are now also available for NT-proBNP. In patients with acute dyspnea, BNP levels correlate closely with NT-proBNP levels. In other populations, however, this correlation is much lower. Since the values cannot be converted by a simple calculation, specific cut-off values have to be used for BNP and NT-proBNP. It appears important to ensure that once tests have been introduced, they should only be changed after consulting laboratory medicine personnel and clinical physicians, since the clinical experience gathered with one test is difficult to extrapolate to another test. Natriuretic peptide assay is currently

remunerated with about 25 euros (EBM2000plus [standard schedule of fees for medical services], version Q3 2007).

Cut-off values for diagnosis of heart failure

The concentration of natriuretic peptides is to be understood as a quantitative marker, the level correlating with the severity of heart failure. The use of two cut-off values has proved practicable in routine clinical settings (figure 1):

- At BNP levels <100 pg/mL heart failure in patients with acute dyspnea is very unlikely (high negative predictive value 90%; 95% confidence interval [CI]: 88%–91%) (5).
- At BNP levels >400 pg/mL, however, there is a high probability of heart failure (positive predictive value >90%) (4, 6).

The correct diagnosis can be made in three of four patients using these BNP cut-off values (6, 8). The studies cited involved consecutive patients without further selection attending the emergency department of a hospital due to acute dyspnea. In the BASEL study, about 50% of these patients had dyspnea of cardiac origin (8). The BNP values show an even distribution: 37% of the patients examined had BNP values below 100 pg/mL, whereas 40% of the patients had BNP values above 400 pg/mL (8). With readings between these cut-off levels (gray zone) it is difficult to correctly diagnose the cause of dyspnea based on the BNP values. In the gray zone region, it is also necessary to perform a differential diagnostic evaluation of other medical conditions such as pulmonary edema or pneumonia which can also cause a slight increase in natriuretic peptides.

The diagnostic value of natriuretic peptide assay was evaluated at a time when the complex dependency of BNP/NT-proBNP plasma levels on other factors was not adequately characterized (8, 11). Recent research has shown that impaired renal function leads to an increase in BNP levels, and body weight gain to a decrease in these levels. The diagnostic accuracy of BNP can therefore be further improved by using a cut-off value of 200 pg/mL to rule out heart failure in renal insufficiency patients, while applying lower cut-off values for obese patients (BMI > 35 kg/m²) (for BNP: 50 pg/mL for exclusion and 200 pg/mL for detection) (7). In the BASEL study, 16% and 7% of the patients had a BMI above 30 and 35 kg/m² respectively. On the other hand, neither age nor gender are important factors in this indication. BNP/NT-proBNP values should therefore always be interpreted in the clinical context.

Hospital-based assay

In patients with acute dyspnea the cause of the dyspnea is usually acute heart failure or lung disease (8). Many experienced colleagues will assume that it is easy to distinguish between dyspnea of cardiac and non-cardiac etiology in daily practice using simple diagnostic means. A systematic study, however, revealed that

there are no clinical symptoms which conclusively allow one or the other diagnosis (2).

Value in the diagnosis of heart failure

Heart failure is commonly associated with high morbidity and mortality (*figure 2*). Frequent rehospitalizations for heart failure (1) severely impair the affected patient's quality of life. High downstream costs are generated for the health system. Statistical surveys estimate that the care of heart failure patients in Europe costs more than 50 billion euros annually (9).

The clinical diagnostic challenge presented by dyspnea may be illustrated with one short example: chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are two commonly encountered entities in daily clinical practice. Patients without a history of lung disease who develop increasing dyspnea are referred relatively soon for further cardiological diagnostic evaluations such as echocardiography, followed by initiation of the appropriate procedures and therapies. In COPD patients, progressive dyspnea does not result in the initiation of any cardiologic tests or, if it does, they are significantly delayed (10). Appropriate heart failure treatment is therefore not provided or only after a delay. This must be considered within the context that the risk of developing heart failure is about 4.5 times higher in COPD than in patients without COPD (10). The high mortality among patients with non-cardiac dyspnea (*figure 3*) is possibly due to the fact that the cardiac component of dyspnea is frequently underestimated in patients with pulmonary disease.

In this context, natriuretic peptide assay offers the possibility of eliminating these diagnostic uncertainties. In the "Breathing Not Properly" (BNP) study, Maisel et al. examined 1586 patients admitted to the emergency department with the symptom acute dyspnea. BNP levels >100 pg/mL offered a sensitivity of 90% and specificity of 76% for distinguishing whether dyspnea of cardiac or non-cardiac origin was present (11). The use of BNP in diagnosing heart failure increased the diagnostic accuracy to 81%, whereas it was 74% based on clinical information alone. In one of 14 patients, therefore, additional BNP assay produced the correct diagnosis. The clinical dilemma involved in making the correct diagnosis in dyspnea patients, however, is generally underestimated: if there is a history of lung disease (or a cardinal pulmonary symptom such as radiographic pneumonic infiltrate), cardiac etiology is often insufficiently taken into account (10).

Natriuretic peptides are interpreted as quantitative markers of heart failure: the higher the value, the greater the likelihood of heart failure (23). To simplify diagnosis, two cut-off values are usually employed in clinical practice: if the values are below the first cut-off, the likelihood of heart failure is very low. If the values are above the second cut-off, the likelihood of heart failure is very high (*table*). A possible algorithm for the clinical use of BNP in diagnosing cardiac dyspnea is presented in *figure 1*.

Prognosis of patients attending the emergency department with acute dyspnea. The figure shows the frequency of different endpoints (mortality and composite endpoint of mortality and rehospitalization due to acute dyspnea) within 90 days of index hospitalization (modified from [1])

The BASEL study was performed to evaluate the diagnostic benefits of natriuretic peptide assay and thus also to reach a conclusion regarding the cost effectiveness of this laboratory diagnostic method. The BASEL study is a prospective, controlled trial in which 452 patients with acute dyspnea were randomized. The management strategy in half of the patients included the use of BNP, while the other half were treated according to international guidelines. BNP assay resulted in a significantly shorter hospital stay (8 versus 11 days, $p = 0.001$) and more infrequent transfer of patients to intensive care (8). These data suggest that single BNP assay allows more effective patient management. The resulting cost savings were demonstrable for up to one year after index hospitalization (12). The use of BNP in the emergency care of dyspnea patients results in more cost effective use of available resources.

Prognostic significance

Besides their diagnostic information value, BNP and NT-proBNP are excellent markers for estimating the prognosis of patients with dyspnea. Almost 30% of

Survival of 452 patients attending the emergency department with acute dyspnea. Although patients with a cardiac etiology of dyspnea have a significantly poorer prognosis than patients with non-cardiac dyspnea ($p = 0.001$), mortality is very high in both populations (follow-up data from BASEL study [24])

TABLE

Patients with dyspnea attending the emergency department; diagnostic significance of BNP and NT-proBNP for whether or not heart failure is present

Variable	Cut-off value (pg/mL)	Sensitivity	Specificity	Positive likelihood	Negative likelihood	PPV	NPV	Ref.
BNP	100	0.96	0.57	2.23	0.07	0.66	0.93	(8)
	400	0.75	0.85	5.00	0.29	0.81	0.80	
	100	0.90	0.76	3.75	0.13	0.79	0.89	(11)
	400	0.63	0.91	7.00	0.41	0.86	0.74	
NT-pro BNP	300	0.99	0.68	3.09	0.01	0.62	0.99	(25)
	450	0.98	0.76	4.08	0.02	0.68	0.99	
	900	0.90	0.85	6.00	0.12	0.76	0.94	

Positive likelihood above 5 and negative likelihood below 0.2 are regarded as proof of high diagnostic value;

PPV, positive predictive value; NPV, negative predictive value; Ref., reference.

patients hospitalized with acute dyspnea die within 90 days of index hospitalization or have to be re-admitted due to symptomatic heart failure (figure 2). Further analyses show that up to 25% of these patients die within the first year after index hospitalization (1).

The prognostic significance of natriuretic peptides has been studied in a variety of scenarios: elevated BNP levels suggest a poor prognosis in patients with dyspnea and in heart failure (13). The higher the BNP or NT-proBNP value, the greater a patient's risk of dying during follow-up or of being hospitalized for treatment of congestive heart failure. The increase in the BNP or NT-proBNP value is associated with a continuous worsening of the prognosis. *Figure 4* shows the prognosis during a 24-month follow-up as a function of the BNP values from the BASEL study (from the data set of [8]). The one-year mortality in the BASEL population was 13.1% in patients with BNP values <100 pg/mL, 29.4% for BNP values of 100 to 400 pg/mL and 37.5% for >400 pg/mL. A rise in BNP by 100 pg/mL is associated with an 11% increase in the relative risk of death (95% CI: 8% to 14%).

Since approximately half the mortality of heart failure patients is due to sudden arrhythmogenic death, Berger et al. studied the association between BNP and sudden cardiac death in 452 patients with an LV ejection fraction below 35%. With a median follow-up of about 1.5 years, sudden heart death occurred in 10% of the patients. Multivariate Cox regression analysis showed that BNP was the only predictor for estimating the risk of sudden heart death. Sudden heart death occurred in only 1% of patients with BNP levels below 130 pg/mL (14). The authors were able to confirm these results in patients with a left ventricular ejection fraction (LV EF) <40% and intracardiac defibrillator (primary and secondary prophylaxis). With low BNP levels, correct antitachycardia therapies of the intracardiac defibrillator system were detectable

significantly more rarely. The composite endpoint of antitachycardia therapies and death was also significantly more rare in patients with BNP values below the median (183 pg/mL). In future, serial natriuretic peptide assays could contribute to achieving better risk stratification for tachyarrhythmic events (15).

A multimarker approach in which different biomarkers reflect various pathophysiological aspects of heart failure may possibly further improve predictive value in future. Horwich et al. studied the importance of simultaneous assay of troponin I and BNP in 98 patients with ischemic and non-ischemic cardiopathy. During an 18-month follow-up, the mortality of patients in whom neither troponin I nor BNP was elevated was approximately 4%. When both markers were increased, 45% of the patients died (16). In the BASEL study, BNP, troponin I, and C-reactive protein were assayed simultaneously in 333 patients with acute dyspnea. If none of the markers was elevated, the two-year mortality was about 7%. If one marker was elevated, mortality was increased to 20%, and with two or three elevated markers mortality was increased to 50% and 60%, respectively (17). To what extent a change in the therapeutic procedure, e.g., with revascularization and intensified medicinal therapy, improves survival has not yet been systematically studied.

Use in therapy monitoring

A factor of particular importance for the use of natriuretic peptides in therapy monitoring is the observation that a decrease in the BNP or NT-proBNP value during adequate treatment is associated with a reduction in mortality. It therefore appears logical that assaying these markers should be helpful in the practical management of heart failure patients.

Encouraging results in this area are currently emerging from a small number of relevant randomized

studies. In the world's first study devoted to this topic, 69 patients with symptomatic heart failure (New York Heart Association [NYHA] classification II–IV; left ventricular ejection fraction <40%) were randomized and treated according to either NT-proBNP values or clinical aspects. Within 10 months, significantly fewer events such as death or hospitalization due to heart failure or renewed decompensation occurred in patients with therapy optimization including natriuretic peptides (19 versus 54, $p = 0.02$) (18). Similar results were obtained by the authors of the STARS-BNP study who treated 220 patients with chronic heart failure and systolic left ventricular dysfunction in accordance with current ESC guidelines (ESC, European Society of Cardiology) (19). In the BNP group it was attempted to achieve values below 100 pg/mL by optimizing therapy. During a median follow-up of 15 months the primary endpoint, i.e. unscheduled hospitalization or death from heart failure, occurred significantly less frequently in the BNP group (24%) than in the reference group (52%; $p < 0.001$). Results of studies that have produced different results in this context are not currently available.

Basing patient management on natriuretic peptide values appears above all to lead to higher-dose medicinal therapy involving the use of ACE inhibitors, beta blockers, loop diuretics and, when appropriate, spironolactone. Since most of the studies cited enrolled patients with systolic dysfunction, the significance of this approach in patients with preserved LV function has not yet been adequately elucidated. Adverse effects such as orthostatic dysregulation and resulting falls, especially in elderly patients, must be taken into account as potential consequences of overly aggressive afterload reducing therapy. Although these research results are very encouraging, the outcomes of further studies especially in elderly patients, such as TIMECHF (Trial of Intensified versus Standard Medical Therapy in Elderly Patients with Congestive Heart Failure), will have to be awaited.

Other diseases

This discussion has so far focused mainly on the use of natriuretic peptides for diagnosis, estimation of prognosis, and therapy optimization in patients with heart failure and/or acute dyspnea. It has now been shown that the assay of BNP/ NT-proBNP also occupies an important place in other situations: the increase in BNP levels seen in patients with acute coronary syndrome (20) or pulmonary embolism is associated with increased mortality. In these situations, BNP elevations are thought to indicate the presence of cardiac decompensation. Natriuretic peptide assay may also contribute to determining the optimal timing of surgery in patients with acquired valve defects. Relevant results have already been published for patients with mitral insufficiency, aortic insufficiency, and aortic stenosis (21, 22).

Elevated natriuretic peptide values are also associated with an unfavorable prognosis in sepsis.

Whether an increase in these levels is attributable to subtle changes in myocardial function or to endotoxin-mediated synthesis of BNP-mRNA remains uncertain.

Conclusion

Natriuretic peptide assay is an important element in the management of heart failure patients. While the significance of BNP and NT-proBNP values for diagnostic and prognostic purposes is now very well understood, individual changes in plasma levels and their association with specific therapeutic consequences have not yet been conclusively evaluated. Whenever possible, the algorithms used in the randomized studies should be applied.

Conflict of interest statement

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FIGURE 4

Kaplan-Meier curves of 452 patients attending the emergency department with acute dyspnea, stratified for plasma BNP levels measured on admission. BNP, B-type natriuretic peptide

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