Use of Natriuretic Peptides in the Emergency Department and the ICU

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Introduction

The clinical importance of a specific disease marker is related to the overall importance of the disease or biological signal it quantifies, the availability of alternative methods to reliably diagnose the disease and quantify disease severity, and, of course, the performance of the marker. Natriuretic peptides, as quantitative markers of cardiac stress and heart failure, owe their clinical importance to the fact that heart failure is a major public health problem, the uncertainty in the clinical diagnosis and management of heart failure, and to their excellent diagnostic and prognostic utility [1–5].

Natriuretic Peptides are Quantitative Markers of Cardiac Stress and Heart Failure

Most clinical data on natriuretic peptides have been obtained with assays measuring either B-type natriuretic peptide (BNP) or N-terminal pro BNP (NT-proBNP). Preliminary data suggest that other members of the natriuretic peptide family, including midregional proANP and proANP, may have comparable clinical utility at least in some indications [6–8].

Natriuretic peptides can be seen as quantitative markers of cardiac stress and heart failure summarizing the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction, and right ventricular dysfunction (**Fig. 1**). In general, levels of BNP and NT-proBNP are directly related to the severity of heart failure symptoms and to the severity of the cardiac abnormality. BNP is a 32-amino acid peptide that is secreted with the inactive aminoterminal proBNP (NT-proBNP) and intact proBNP from the left and the right cardiac atria and ventricles in response to ventricular volume expansion and pressure overload [9–15]. Recent data suggest that left ventricular end-diastolic wall stress and wall stiffness may be the predominate triggers of BNP release [13, 14].

Two important principles should underlie the clinical use of natriuretic peptides. First, a natriuretic peptide level is not a stand-alone test. It is always of greatest value when it complements the physician's clinical skills along with other available diagnostic tools. Second, natriuretic peptide levels should be interpreted and used as continuous variables in order to make full use of the biological information provided by the measurement (like, e.g., calculated glomerular filtration rate).

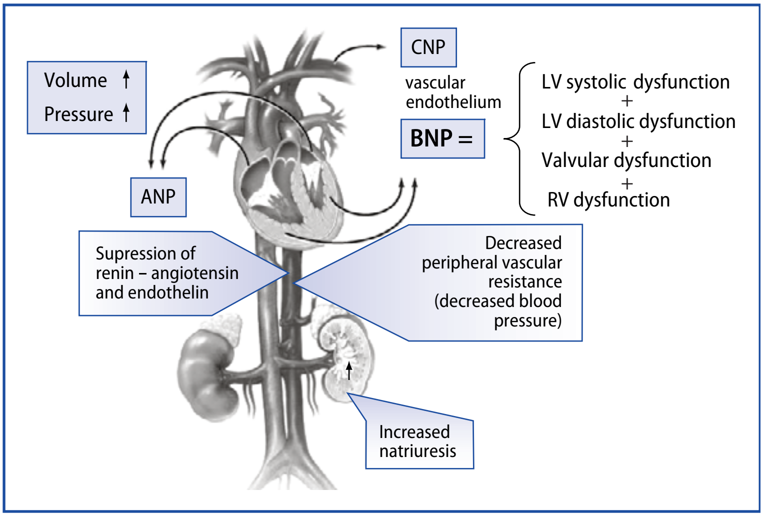

Fig. 1. Natriuretic peptides are quantitative markers of cardiac stress and heart failure. RV: right ventricular; LV: left ventricular; BNP: B-type natriuretic peptide; ANP: A-type natriuretic peptide; CNP: C-type natriuretic peptide

Clinical Indications: Patients with Acute Dyspnea

Current evidence is sufficient to recommend the routine clinical use of natriuretic peptides in only one situation: The diagnosis and management of patients presenting with acute dyspnea. Although other indications in the emergency department (ED) are the subject of intensive investigation and natriuretic peptides have been shown to be powerful tools for risk stratification also, e.g., in patients with acute coronary syndromes, pulmonary embolism, and pneumonia, further research is needed to justify routine clinical use [3].

The rapid and accurate differentiation of heart failure from other causes of acute dyspnea remains a clinical challenge, both in the ED and in the intensive care unit (ICU). After evaluating a patient's symptoms, conducting a physical examination, and performing electrocardiography (EKG) and chest radiography, the clinician is often left with considerable diagnostic uncertainty, which can result in misdiagnosis and delay the initiation of appropriate therapy [1–5].

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Diagnostic Value of Natriuretic Peptides in Patients with Acute Dyspnea

Numerous observational studies including patients presenting with acute dyspnea have validated natriuretic peptides against a gold standard diagnosis of heart failure and shown convincingly that natriuretic peptides have a very high diagnostic accuracy [6, 8, 16–24]. The higher the natriuretic peptide level the higher the probability that acute dyspnea is caused by heart failure. The largest validating study included more than 1500 patients and found that adding BNP to clinical judgment would have enhanced diagnostic accuracy from 74 % to 81 %. The areas under the receiver operating characteristic (ROC) curve were 0.86, 0.90, and 0.93 for clinical judgment, for BNP, and for the two in combination, respectively ($p < 0.0001$ for all pair-wise comparisons) [4, 5].

Prognostic Value of Natriuretic Peptides in Patients with Acute Dyspnea

Natriuretic peptides predict prognosis and help risk stratify patients with dyspnea irrespective of the cause of dyspnea (heart failure or non-cardiac) [20, 25–28]. The natriuretic peptide level quantifies cardiac stress and accurately predicts the risk of death, both in-hospital and long-term. The areas under the ROC curve for the ability of natriuretic peptide to predict death were 0.70 to 0.75. For example, a NT-proBNP value of 5180 pg/ml or higher at presentation to the ED predicted death within 76 days with a sensitivity of 68 %, a specificity of 72 %, and a negative predictive value of 96 % in patients with acute heart failure [20].

Impact of Natriuretic Peptide on the Management of Patients with Acute Dyspnea

Easily applicable algorithms for the interpretation of BNP and NT-proBNP using specific cut-off levels have been developed. In order to make best use of the diagnostic and prognostic information from natriuretic peptide levels, the clinician needs to understand that natriuretic peptides are quantitative markers of cardiac stress and heart failure. The higher the natriuretic peptide level, the higher the likelihood that the dyspnea in the individual patient is caused by heart failure. It has become common to use two cut-off values: A lower one with a high negative predictive value to reliably exclude heart failure as the cause of acute dyspnea, and a second, higher cut-off with a high positive predictive value to 'rule in' heart failure as the cause of dyspnea. For BNP, the two cut-off levels 100 pg/ml and 400 pg/ml should be used. These cut-off values apply irrespective of age and sex [29, 30]. However, these cut-offs do need to be adjusted in the presence of two clinical conditions: Kidney disease and obesity. In patients with kidney disease and an estimated glomerular filtration rate of less than 60 ml/min, 200–225 pg/ml rather than 100 pg/ml is the most appropriate cut-off value to rule out heart failure [31, 32]. In contrast, the presence of obesity requires the use of lower cut-off values. In patients with severe obesity and a body mass index (BMI) above 35, we recommend a BNP cut-off value of 60 pg/ml to rule out and 200 pg/ml to rule in heart failure as the cause of acute dyspnea [33,34].

The International Collaborative for NT-proBNP Study defined the most appropriate cut-off values for NT-proBNP [19, 20]: 300 pg/ml should be used to 'rule out' heart failure. Depending on age (< 50, 50–75, and > 75 years), 450 pg/ml, 900 pg/ml, or 1800 pg/ml should be used to 'rule in' heart failure. As renal function in this population was closely related to age, no further adjustment for renal function was necessary. Obesity is also associated with lower NT-proBNP levels [35]. It is a matter of debate whether NT-proBNP levels should be adjusted for obesity.

Added Value of Using Natriuretic Peptide in the Management of Patients with Acute Dyspnea

The added value of natriuretic peptide in the management of patients with acute dyspnea was examined in two randomized controlled trials including patients presenting to the ED [36, 37] Together, these randomized studies provide a clear answer to the remaining key question: Does the increase in diagnostic accuracy associated with the use of natriuretic peptide translate into improved patient management when used in clinical practice?

The BNP for Acute Shortness of Breath Evaluation (BASEL) study randomized 452 consecutive patients presenting with dyspnea to the ED to either BNP-guided management or standard management without the use of BNP [36]. The use of BNP resulted in a reduction in the time from presentation at the ED to the initiation of the appropriate therapy according to the final discharge, a reduction in hospital admission rate, a reduction in the need for intensive care, and a reduction in the time to discharge. The total cost of treatment was $5,410 in the BNP group compared with $7,264 in the control group, a significant reduction of 26 %. These data support the conclusion that, when used in conjunction with other clinical information, rapid measurement of BNP in the ED improves medical and economic outcome. These findings were recently confirmed by a Canadian multicenter study (IMPROVE-CHF) using NT-proBNP [37]. Five hundred patients presenting with dyspnea to seven EDs were studied. Knowledge of NT-proBNP results reduced the duration of ED visit by 21 %, the number of patients rehospitalized over 60 days by 35 %, and direct medical costs of all ED visits, hospitalizations, and subsequent outpatient services (US $6129 to US $5180 per patient; $p = 0.023$) over 60 days from enrolment. Adding NT-proBNP to clinical judgment enhanced the accuracy of a diagnosis; the area under the ROC curve increased from 0.83 to 0.90 ($p < 0.00001$).

The BASEL study also assessed the cost-effectiveness of BNP testing during long-term follow-up [38, 39]. To address the fact that tailoring of resources may well be cost-effective initially, but may result in large secondary costs due to recurrent symptoms, cost-effectiveness analyses were performed at 180 and 360 days follow-up. BNP testing was found to be cost-effective also at these time points. The use of BNP levels significantly reduced total treatment cost. This reduction was driven by significantly fewer days spent in-hospital in the BNP group. A large part of this reduction occurred during the initial presentation and was fully maintained throughout 360 days.

The importance of obtaining the natriuretic peptide level immediately at presentation to the ED was further highlighted by a recent analysis from a large registry indicating that delayed measurement of natriuretic peptide levels and delay in treatment for acute heart failure were strongly associated. These delays were linked with modestly increased in-hospital mortality, independent of other prognostic variables. The adverse impact of delay was most notable in patients with greater natriuretic peptide levels [40].

Based on these data it seems appropriate to recommend the measurement of natriuretic peptides at presentation in all patients presenting with acute dyspnea as their main complaint.

ICU Perspective

As diagnostic dilemmas in the ICU are often as challenging as in the ED, recent studies have begun to evaluate whether the use of natriuretic peptides may also be helpful in the ICU. The value of a biomarker to detect heart failure in the ICU is based on the observation that heart failure is common in the ICU and on the assumption that the detection of heart failure in the ICU allows the early initiation of specific heart failure therapy in order to improve morbidity and mortality. However, there are major differences in patient characteristics, disease severity, co-morbidity, resources available for the individual patient, and therapies between the ICU and the ED, so that the role of natriuretic peptides should be specifically assessed in critically ill patients.

The number of patients included in recent ICU studies has been small. Therefore, most recent studies may be considered hypothesis generating rather than confirmatory. Overall, current evidence does not seem strong enough to recommend the routine clinical use of natriuretic peptides in the ICU. However, in some situations, very exciting initial data have recently been reported [41]. As one example, the diagnostic use of natriuretic peptide in patients with hypoxemic respiratory failure and bilateral infiltrates on chest radiograph has been briefly described. This setting often requires the evaluation of cardiac function using pulmonary artery catheterization or echocardiography. These techniques help to differentiate between cardiogenic pulmonary edema from an acute lung injury (ALI). Natriuretic peptides have also been proposed to help in the differentiation between cardiogenic and non-cardiogenic pulmonary edema. Jefic et al. [42] performed a prospective study on 41 consecutive patients with hypoxic respiratory failure undergoing pulmonary artery catheterization to evaluate whether BNP or NT-proBNP or both could be used to differentiate high pulmonary artery occlusion pressure (PAOP) versus low PAOP pulmonary edema. In this study, BNP and NT-proBNP failed to reliably differentiate between patients with high and low PAOP. Additional work by Bal et al. [43] and Forfia et al. [44] underlines the recognition that natriuretic peptide and PAOP provide different windows on the heart. More recently, Karmpaliotis et al. [45] reported data from 81 ICU patients suffering from acute pulmonary edema. BNP offered good discriminatory performance for the final diagnosis established by two independent intensivists. In this study, the median BNP was 1260 pg/ml in patients with heart failure (cardiogenic pulmonary edema) and 325 pg/ml in those with acute respiratory distress syndrome (ARDS). A BNP level below 200 pg/ml offered a specificity of 91 % for the final diagnosis of ARDS, whereas a BNP of at least 1200 pg/ml offered a specificity of 92 % for the final diagnosis of cardiogenic pulmonary edema. Obviously, further evidence from larger studies is needed to appropriately define the potential clinical use of natriuretic peptide for differentiating cardiogenic pulmonary edema from ALI.

Conclusion

Natriuretic peptides have been shown to be very helpful in the diagnosis and management of patients presenting with acute dyspnea. Natriuretic peptides can be seen as quantitative markers of cardiac stress and heart failure, summarizing the extent of systolic and diastolic left ventricular dysfunction, valvular dysfunction, and right ventricular dysfunction. Current evidence supports the routine use of natriuretic peptides in patients with acute dyspnea. As cardiac stress also determines prognosis in other common cardiac and non-cardiac disorders in the ED and in the ICU, the use of natriuretic peptide may also be helpful in many additional disorders including patients with acute coronary syndromes, pulmonary embolism, severe sepsis and septic shock [46].

Acknowledgement: Dr. Mueller was supported by research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the Novartis Foundation, the Krokus Foundation, Abbott, Biosite, Brahms, Roche, Siemens, and the University of Basel.

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