Role of Cardiac Natriuretic Peptide Testing in Heart Failure

The long-predicted natriuretic and endocrine function of the heart was demonstrated more than 20 years ago (1) by the discovery of atrial natriuretic peptide [atrial natriuretic factor, A-type natriuretic peptide (ANP)]. This led to the description of a family of structurally similar but genetically distinct peptides, constituting the natriuretic peptide (NP) family, which contribute to the maintenance of cardiovascular homeostasis. These looped peptides are the naturally occurring antagonists of the renin-angioten-
sin-aldosterone system and of the sympathetic nervous system. They promote natriuresis and diuresis, act as vasodilators, and exert antimitogenic effects on cardiovascular tissues.

Two members of the NP family, ANP and brain natriuretic peptide [B-type natriuretic peptide (BNP)] are secreted by the hemodynamically stressed heart mainly in response to myocardial stretch induced by volume load. ANP and BNP appear to form a dual, integrated NP system with ANP acting as a rapid-response hormone and BNP as a backup hormone activated only after prolonged ventricular overload. The NP system is activated to its highest degree in ventricular dysfunction and has an important role in maintaining the compensated state of asymptomatic heart failure (HF) and delaying disease progression. The increased plasma ANP and BNP seen in HF patients is not unique: NPs are increased in all patients with edematous disorders, such as renal failure or ascitic liver cirrhosis, that lead to increased atrial tension or central blood volume (2).

The NPs are synthesized as preprohormones. The endocrinologically active C-terminal peptides (ANP and BNP) and their N-terminal prohormone fragments are found in plasma. It is uncertain at present whether the proteolytic cleavage of proBNP to N-terminal proBNP (NT-proBNP) 1–76 and BNP (C-terminal 32 amino acids) occurs at the time of secretion or later in the circulation (3). ProBNP is, however, a substrate of the transmembrane serine protease corin, suggesting that proBNP is split mainly within or on the surface of cardiomyocytes (4). The functional role of circulating NT-proBNP is uncertain, as are its biological half-life and metabolism and the concentration and significance of circulating NT-proBNP 1–76–derived peptides. The pathophysiologic basis of NT-proBNP must be further clarified before epitopes to which antibodies of the various assays are directed can be defined to achieve optimal analytical and clinical performance and enable assay standardization.

Currently used assays may differ in their cross-reactivity with circulating NT-proBNP split products, and the assays may also be affected by the breakdown products of NT-proBNP produced after blood collection. To overcome these difficulties, in this issue Goetze et al. (5) describe a simple but effective method to quantify proBNP and its products in human plasma, using an analysis independent of precursor processing that does not require extraction of plasma before analysis. As previously and originally described for progastrin measurement (6), enzymatic treatment of plasma with trypsin was performed before measurement to cleave all proBNP peptides to the 1–21 fragment. Total proBNP was determined by measuring proBNP 1–21 by RIA. Trypsin treatment of plasma samples also served as a suitable alternative to extraction of samples before analysis by abolishing nonspecific interferences with the assay.

The new method uses the competitive immunoassay format to measure the small peptide and, thus, suffers from characteristics of such immunoassays, e.g., a long incubation period (several days) and marginal (although acceptable) precision at low concentrations. The need for sample pretreatment, which involves mixing with a trypsin-containing buffer and termination of the enzymatic reaction by boiling, hampers the adaptation of the procedure to automated analyzers. A fully automated version of the assay would be needed for widespread routine use of the marker. Noncompetitive immunoassays offer advantages of better speed, sensitivity, precision, and probably specificity over competitive immunoassays (7). Recently, a noncompetitive immunometric assay has been developed for NT-proBNP measurement without the need for plasma extraction (8). A fully automated version of this assay will soon be commercially available. The potential advantages of processing-independent analysis of NT-proBNP in respect to this and other immunoassays remain to be demonstrated in side-by-side comparison studies. However, before deciding on the best approach to measure NT-proBNP, we need a better understanding of the molecular heterogeneity and significance of the circulating proBNP fragments.

NP determination is a useful addition to the standard clinical investigation of patients with ventricular dysfunction. During the last 20 years, substantial work, mainly generated with research assays, demonstrated that NPs are the biochemical markers of choice for diagnosis and risk stratification of patients with HF. In side-by-side comparisons, NPs were superior to other neurohormones, such as catecholamines, renin, angiotensin, aldosterone, or endothelin. The preliminary clinical data generated by processing-independent proBNP analysis confirm the presence of NT-proBNP in apparently healthy individuals, with a minor but significant increase noted in the elderly. As expected, the assay discriminated very well between controls and patients with stable end-stage HF referred for consideration for cardiac transplantation. BNP measurement appears to be accurate for diagnosing HF in emergency department patients presenting with acute dyspnea (9). Increased NP plasma concentrations are, however, also frequently found in asymptomatic patients with left ventricular dysfunction. Therefore, these peptides have also been suggested as potentially useful early HF markers.

Questions remain, however, regarding which NP should be measured in HF. According to preliminary data...
from side-by-side comparison studies, BNP and NT-proBNP appear to be equivalent diagnostic and prognostic markers, and both appear to be superior markers over ANP and N-terminal proANP (NT-proANP) for diagnosis and risk stratification in HF patients. Although high ANP and BNP concentrations are associated with increased concentrations of the corresponding N-terminal prohormones, from a pathophysiologic point of view, it certainly makes a difference whether the physiologically active hormones ANP and BNP or their NT-proNP split products are measured; much less is known about the pathophysiologic significance of circulating NT-proANP and NT-proBNP. Differences in pathophysiology and/or elimination rates may lead to subtle differences in the distribution of NP types in plasma. BNP and NT-proBNP correlate more closely with left ventricular functional indicators than do ANP and NT-proANP. Thus, ANP and BNP do not provide identical, but rather complementary indicators than do ANP and NT-proANP. Differences in pathophysiology and/or elimination rates may lead to subtle differences in the distribution of NP types in plasma. BNP and NT-proBNP correlate more closely with left ventricular functional indicators than do ANP and NT-proANP. Thus, ANP and BNP do not provide identical, but rather complementary pathophysiologic information, with ANP as a primary marker of atrial overload and BNP of ventricular overload.

Comparative clinical studies [reviewed in Ref. (2)] demonstrated that BNP was superior to ANP and its N-terminal prohormone fragments for diagnosis of left ventricular systolic (emptying) and/or diastolic (filling) dysfunction or for left ventricular hypertrophy and risk assessment in patients with HF as well as myocardial infarction. BNP is also a prognostic marker in patients with acute coronary syndromes (10).

Standardized conditions for elective blood sampling (as used in the majority of clinical studies on NP) are recommended (e.g., in the morning after an overnight fast and supine after 10 min of rest). ANP is poorly stable in vitro and thus appears suitable only for point-of-care measurement under routine conditions. By contrast, BNP, NT-proANP, and NT-proBNP are sufficiently stable in EDTA-containing plastic tubes to be sent to the laboratory without special care. The larger N-terminal prohormone fragments are more stable and have a longer biological half-life, and the requirements for blood sampling are less critical.

N-Terminal prohormones or NPs are less sensitive to the rapid fluctuations caused by short-term stimuli of secretion, such as change in body posture, exercise, or acute volume load, which particularly affect ANP and, to a much lesser extent, BNP concentrations. Because of their impact on HF diagnosis and management, NPs will make the transition from routine application, as did cardiac troponins. HF is an important clinical problem with significant morbidity, mortality, and socioeconomic impact. Early identification is important to initiate appropriate treatment, which can delay disease progression. A diagnostic test would be of obvious clinical benefit. Indeed, a BNP assay for point-of-care determination has recently received approval from the Food and Drug Administration for the diagnosis of HF. In contrast to studies of myocardial damage, there is currently no generally accepted standard laboratory marker for detection of left ventricular dysfunction against which to test NPs. The considerable clinical data generated during the last two decades with research methodologies should make it easier for newly developed NP assays to be readily accepted by clinical chemists and clinicians for routine use.

For primary care physicians, NP measurement is useful to decide which patient with suspected HF warrants further investigation, particularly when assessment of left ventricular function is not readily available. NPs have an excellent negative predictive value, particularly in high-risk patients (e.g., individuals with coronary artery disease, hypertension, or diabetes or patients over 60 years of age), but NPs cannot replace imaging techniques in HF diagnosis because the underlying cause of HF has to be clarified and these methods provide different information.

An initial increased NP has limited specificity for HF but sufficient positive predictive value to warrant follow-up examinations to determine its etiology. NPs are helpful for monitoring disease course and risk stratification in HF patients because they are independent prognostic markers in HF and myocardial infarction patients. According to preliminary data, NPs are potentially useful for guiding therapy in HF patients (11), and NPs may provide a bridge between the hemodynamic and neurohormonal approaches to the management of HF.

References

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