A New Signal From B-Type Natriuretic Peptide in ST-Elevation Myocardial Infarction
What Does It Mean for B-Type Natriuretic Peptide and Innovative Diagnostics?

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B-type natriuretic peptide (BNP) is a cardiac-derived peptide hormone that consists of a 17-AA ring structure created by a disulfide bond joining 2 cysteine residues with distinct N and C terminal extensions. BNP binds to its particulate guanylyl cyclase receptor (GC) -A to activate the second messenger, cyclic GMP. Studies have established widespread pleuripotent actions that result in natriuresis, vasorelaxation, inhibition of renin and aldosterone, enhanced myocardial relaxation, inhibition of fibrosis and hypertrophy, promotion of cell survival, angiogenesis, and inhibition of inflammation.1,2 The clinical therapeutic potential of BNP continues to emerge, with studies demonstrating that it protects against diabetic nephropathy when genetically over-expressed by gene transfer,3 lowers blood pressure when delivered orally in experimental hypertension,4 and is cardioprotective when administered to humans undergoing cardiopulmonary bypass surgery.5

Most recently, studies have focused on the processing of BNP from its production to its degradation. BNP is produced as a preprohormone that subsequently is processed into a prohormone by cleavage of an N-terminal signal peptide (see the Figure). Human preproBNP is a 134-AA peptide that is cleaved to the 108-AA proBNP.6 Processing of proBNP to mature BNP is mediated by corin, and a role for furin has also been implicated.7,8 Human BNP, a 32-AA peptide, is released from the myocardium in response to various physiological and pathophysiological stimuli such as myocardial wall stretch, with evidence that myocardial ischemia releases BNP.9 Once released, BNP is cleared by the natriuretic peptide clearance receptor, which is widely expressed.1 

Importantly, BNP is degraded by neutral endopeptidase 24.1110 but also by dipeptidyl peptidase IV.11,12 The latter resulting in a novel BNP3-32, which possesses altered cardiorenal actions and may uniquely function at the tissue level as a locally acting BNP.

Today, BNP is a widely used worldwide as a biomarker for heart failure (HF). When state-of-the-art transform ion cyclotron resonance mass spectrometry is used in human HF, much of plasma BNP immunoreactivity measured by commonly used assays is due to altered circulating molecular forms with reduced cyclic GMP–activating properties.12 We now know that BNP circulates in various forms—as its precursor proBNP1-108, as mature BNP1-32, as N-terminal peptide proBNP, and as BNP3-32. Importantly, in vitro analysis has reported that only BNP1-32 and BNP3-32 could stimulate cyclic GMP production in human cardiac fibroblasts and cardiomyocytes.13 Thus, patients with HF have low circulating “functional” BNP1-32 levels whereas other non-functional BNP levels, including proBNP levels, are higher than in normal subjects.12,14 This functional deficiency state of active BNP may affect the progression of HF and the remodeling process. The utility of BNP (especially proBNP1-108, mature BNP1-32 and N-terminal proBNP [NTproBNP]) continues to grow with its use now as a prognostic biomarker for future adverse cardiovascular outcomes,15 as a guide for therapy in HF,16 and as a biomarker for myocardial injury.17,18

Of great interest is the report by Siriwardena et al in the current issue of Circulation,19 which advances our knowledge of the biology of BNP as well as of its role as a biomarker for cardiovascular disease. These investigators explored the novel idea that the signal peptide of BNP (BNPsp) is secreted by the human heart and circulates in normal human subjects. They further tested the hypothesis that BNPsp would be a cardiac biomarker for the diagnosis of myocardial ischemia and injury. As noted in the Figure, BNPsp is the N-terminal 26 amino acid sequence of preproBNP1-134. As stated above, proBNP1-108 or other BNP molecular forms, with the exception of BNPsp, have been reported to circulate in humans. In the current report, the authors had the innovative thought that BNPsp is also cleaved into a C-terminal 10 amino acid BNPsp17-26 by proteolysis as signal peptides in general are degraded by a signal peptide peptidase in the endoplasmic reticulum membrane as reported previously for other preprohormones.21 They next generated a specific radioimmunoassay with their own specific antibody, which would recognize human BNPsp17-26. It is also possible that their antibody also recognizes the complete intact 26 amino acid BNPsp, a possibility that will require further studies including peptide isolation and sequence analysis.

In a most comprehensive approach, Siriwardena and co-workers performed a series of studies in human myocardial
tissue, in normal human subjects, and in humans with cardiovascular and renal disease. They first demonstrated that they could detect BNPsp17-26 in the extracts from human heart tissue specifically in both atrial and ventricular myocardium, and they showed that, like mature BNP1-32, BNPsp17-26 was higher in atrial myocardium. The authors then reported that BNPsp17-26 is present in the circulation in normal humans and is secreted from the normal human heart. But surprisingly, they also reported that BNPsp17-26 is secreted from the head, kidney, and lower limbs and is cleared by the liver. This observation is in stark contrast to their data in the article, which included no evidence, as determined with their NT-proBNP assay, for the secretion of mature BNP outside the heart.

The meaning of these data is unclear at the moment and will require further studies. However, the data change our thinking about BNP, especially relative to its processing and possibly to where it may be produced. First, to our surprise, BNP's signal peptide (BNPsp17-26) is secreted into the circulation. Conventional wisdom is that a signal peptide functions only intracellularly to translocate a preprohormone from site of production into the endoplasmic reticulum for processing to its prohormone and then ultimately to its release from the cell. Importantly, with rare exceptions, the signal peptide remains in the cell and is degraded and then resynthesized and used. The current article changes our thinking and suggests that a signal peptide like BNPsp17-26 is actually released and circulates. At this point, one can conclude that this secretion/release could be a nonspecific cellular release or overflow of this peptide with no specific biological meaning. Alternatively, one could ask the speculative question of where BNPsp or BNPsp17-26 has an intrinsic function. The second part of this biological BNP conundrum from the current human studies is now the possibility that BNP is synthesized outside of the heart on the basis of a step up of BNPsp17-26 levels across the head, kidney, and lower limbs in addition to the heart. This touches on the compelling concept recently advanced by Kuhn et al that BNP may be synthesized locally in ischemic tissue outside of the heart in satellite cells to induce local angiogenesis. Studies clearly are needed to explore possible production of BNP in these important regions of the body outside the heart and to address the new BNP biology that is provided by the findings of this important article by Siriwardena and colleagues.

Most relevant from a clinical perspective is the report in the current article of circulating BNPsp17-26 levels in human ST-elevation myocardial infarction (STEMI). Specifically, the level of BNPsp17-26 is increased in human STEMI. Further, this elevation is highly specific in terms of when BNPsp17-26 levels increase relative to the phase of STEMI. The authors have found that the level of BNPsp17-26 increases only during the acute phase of STEMI (4 to 6 hours), after which it normalizes, whereas the level of NT-proBNP does not increase during this initial acute phase but only after 12 hours. Furthermore, the BNPsp17-26 level is increased before either myoglobin C or troponin I. Indeed, receiver-operating-characteristic analysis of BNPsp17-26 at 5 hours gave high sensitivity and specificity equivalent to Troponin I. The authors concluded that BNPsp17-26 might be a new and robust biomarker for early-stage myocardial infarction.

Again, these most interesting observations of BNPsp17-26 in STEMI raise important questions. Why did the BNPsp17-26 level increase so rapidly with the onset of myocardial injury, preceding even other well-established biomarkers for injury such as troponin? One could speculate that BNPsp and/or BNPsp17-26 is abundant in the cardiomyocyte and with any leakiness in the cell membrane BNPsp17-26 is leaked and then normalizes as it is depleted. A more risky speculation to explain the current findings is that ischemia induces a novel secretory pathway. It should be noted that BNPsp17-26 was not elevated when first measured in patients with STEMI but increased at 4 hours after STEMI elevation, so one still cannot say that BNPsp17-26 is acutely
released at the very onset of myocardial ischemia and/or injury.

From the clinical perspective of biomarkers for STEMI, the current findings lay the foundation for more extensive human trials. As the authors emphasize, the current studies, with only 25 subjects, are small. A larger trial of STEMI and also acute coronary syndrome is required. Not only do we need reconfirmation of the early activation of BNPs17-26 but we also need to define its relationship to reperfusion, to infarct size, to outcomes, and to mature BNP, NT-proBNP, proBNP, and other cardiac biomarkers. If the current findings are confirmed, then BNPs17-26 may significantly increase our armamentarium of cardiac biomarkers for myocardial ischemia and injury.

It should be stated that, surprisingly, BNPs17-26 was not increased in the circulation in HF in contrast to NT-proBNP, BNP, or proBNP. Again, such an observation has biological and clinical relevance as well as implications for BNPs17-26 as a biomarker. The lack of increase suggests the absence of regulated release and/or depletion of BNPs17-26 with high rates of BNP synthesis. This lack of increase therefore excludes BNPs17-26 as a biomarker for HF, but more studies are needed in terms of the pathogenesis of HF (ischemic versus nonischemic), severity of HF, and systolic versus diastolic HF. The elevation of plasma BNPs17-26 in chronic kidney disease requires one statement, which is that the mechanism could be related to decreased renal clearance or more intriguingly increased renal production. Again, further studies are needed to address this interesting issue.

The authors are to be congratulated for such a comprehensive study from biology to biomarkers, which significantly advances the fields of BNP and cardiac biomarkers. Conventionally, preproproteins including signal peptides, are first synthesized, and the signal peptide is recognized and decyphered by cellular sorting and translocation machinery. Preproproteins are then transported to numerous destinations, such as the nucleus, the endoplasmic reticulum, the Golgi apparatus, and the plasma membrane. Once the signal peptide is recognized, it is removed by specialized signal peptidases, and the mature part of the protein is thereby released and the divided signal peptide is then degraded by signal peptide peptidases.21 Siriwardena and coworkers provide evidence that this may not be entirely the case for preproBNP. Specifically in humans, BNPs (or BNPs17-26), the signal peptide for human preproBNP, is released from the cardiomyocyte (presumably both atrial and ventricular) and circulates. The full biological significance of this seminal observation (ie, regulation and function) remains to be defined. Of most clinical relevance is the plasma elevation of BNPs17-26, with the acute phase of STEMI preceding standard biomarkers of myocardial injury. This key observation offers a rare opportunity for a new and novel biomarker for myocardial injury, which has the potential to enhance the care of patients with STEMI and reduce the burden of human cardiovascular disease. Thus, once again, the field of natriuretic peptides has just gotten more interesting.

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References


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