



The emerging value of molecular forms of B-type natriuretic peptide in heart failure

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Brain natriuretic peptide (BNP) has an established role in diagnosing heart failure (HF) and has shown to provide independent prognostic information. However, its prognostic value has limitations, leading to the development of other prognostic biomarkers such as ST2 and galectin-3 (1,2). With recent advances, we have gained more understanding into the bioactivity and metabolism of BNP. In different individuals, there are actually many BNP fragments in the circulation as a response to the degradation process. From the success of *angiotensin receptor neprilysin inhibitors* (ARNI) in HF treatment as shown in the PARADIGM-HF trial (3), we have learned that controlling BNP metabolism is associated with better clinical outcome. However, it seems that this is just the tip of the iceberg in the complex world of BNP metabolism. In the article published by Toru Suzuki and colleagues in the *Journal of Clinical Chemistry* (4), it was highlighted that the molecular forms of BNP not only represent the products after degradation, but that they also play a role as prognostic biomarkers. This marks a promising and exciting a new avenue in the evaluation and treatment for patients with cardiovascular diseases.

Paradox

The body's natural response to HF involves activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and the natriuretic peptide system (NPS). NPS is supposed to counteract

the vasoconstrictive effects of the RAAS and SNS by stimulating vasodilatation. However, in advanced HF, the remarkably activated NPS fails to accomplish this important balance. This was previously attributed to an inadequate response to the activated NPS, but now we have gained more understanding into the mechanisms underlying this paradox.

BNP originates from PreproBNP. PreproBNP1-134 is cleaved to form a signal peptide and ProBNP1-108 (Figure 1). ProBNP1-108 is subsequently cleaved by either corin or furin into NT-proBNP1-76 and BNP1-32. However, recent studies have revealed that the commercialized immunoassay for BNP1-32 actually detects any BNPs that express the epitope identified by the immunoassay, rather than specifically measuring the concentration of bioactive BNP1-32 in the circulation (5). This would explain why despite high BNP levels, the beneficial effects on vasodilation, natriuresis etc. are not seen. In fact, the actual bioactive BNP1-32 level could very well be extremely low, however we are not equipped to discuss this issue, as it is not measured as a routine. Furthermore, not only is the real BNP1-32 level overestimated, the degradation of BNP1-32 is also quicker than previously thought. These above circumstances would explain the so-called BNP paradox. The expansion of knowledge on BNP has been further advanced to a new era in which we should consider both the function and quantity of BNP1-32 degraded fragments, the so-called BNP molecular forms.

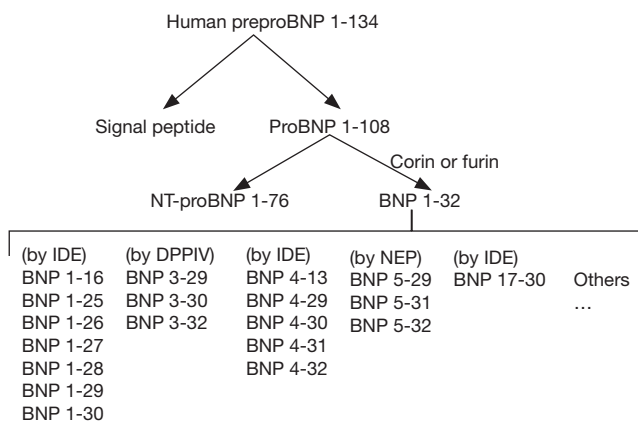


Figure 1 Degradation of human PreproBNP 1-134, and the molecular forms of degraded BNP1-32 by different enzymes. BNP, B-type natriuretic peptide; DPPIV, dipeptidyl peptidase-4; IDE, insulin degrading enzyme; NEP, neutral endopeptidase.

The BNP paradox involves a few critical issues: (I) what is the major form of measured BNP in the circulation? Is it individualized? (II) What is the critical step of producing bioactive BNP1-32 from the inactive BNP1-180 form? Which enzyme is responsible? Is it gene regulated? (III) Are BNP molecular forms bioactive? If so, which has the strongest function and has what effect? (IV) Are the levels manipulated by specific degrading enzymes or their corresponding inhibitors? (V) Which BNP molecular forms are involved in the ARNI effect? And (VI) will a new panel measuring BNP molecular forms be helpful? How are they to be applied in the clinical setting?

The inaccurate quantification of BNP1-32 in circulation has led to confusion in the interpretation of BNP values in current publications. Derived from BNP1-108 cleaved by corin, BNP1-32 can be degraded to BNP3-32 by Dipeptidyl peptidase-4 (DPPIV), to BNP5-32 by neutral endopeptidase (neprilysin, NEP), to BNP8-32 by meprin (not present in humans), and to smaller degradation peptides by insulin degrading enzyme (IDE) (*Figure 1*) (6). To confuse matters, BNP1-32 immunoassays also detect proBNP1-108, and BNP3-32, but not NT-proBNP1-76.

In patient plasma, the concentration of proBNP1-108 is almost 6.3 times that of BNP1-32, suggesting proBNP1-108 circulates in much higher concentrations than BNP1-32, and is the major BNP form in HF patients (5,7). Other mechanisms associated with this disproportional ratio include rapid degradation of BNP1-32, impaired production of BNP1-32 from proBNP1-108 (8), and inactivated

convertases seen in HF, such as corin. For example, it has been shown that expression of the corin alleles cause impairment in the processing of proBNP1-108. More clinically relevant, survival free from death or first HF-related hospitalization was significantly worse in carriers of the corin allele compared to non-carriers (9).

Which BNP is bioactive?

Not all processed and degraded forms of BNP have ability to bind to the receptor and show activity. So far, we know that the functioning bioactive BNP is BNP1-32, whereas proBNP1-108 and NT pro-BNP1-76 are not. However, the position is not well established for other BNP fragments. There has been some data on BNP1-32, BNP3-32, BNP8-32, proBNP1-108 (in decreasing order of activity). Mature BNP1-32 is most active; BNP3-32 shows reduced natriuresis, diuresis and lack vasodilating actions (10). Compared to BNP1-32, several BNP forms generated by IDE degradation have been shown to activate bioactive reactions 7-fold greater in some *in vitro* experiments (11). However, information is not adequate for other molecular forms such as BNP5-32 and data regarding functional capacity have not all been consistent. Jessica O'Rear *et al.* investigated the bioactivity of a few proteolysed BNP peptides, including BNP4-32, BNP5-32, BNP5-31, BNP1-25, and BNP1-26, and found no differences compared with BNP1-32 (unpublished data).

In the era of ARNI

In the PARADIGM-HF trial, when compared with enalapril, sacubitril (a neprilysin inhibitor)/valsartan treatment resulted in decreased mortality and hospitalizations for HF along with sustained reductions in circulating troponin-T levels (3). These findings have recently drawn great attention to the role of ARNI. In the era of ARNI, BNP levels are significantly increased with blockage of its degradation. However, the true bioactive BNP level is not well explored. The neprilysin inhibitor component in ARNI is supposed to decrease the degradation of BNP1-32 to BNP5-32, thus leading to increased levels of BNP1-32. However without measuring the different BNP fragments in patients on ARNI, we won't know the actual events. Studies elucidating the changes in concentration of these BNP fragments will shed light on how they exert their beneficial effects in HF patients.

This will be important since not all patients have the same response to ARNI.

Better prognostic value of BNP fragments

Although the methodology of quantitating BNP molecular forms based on mass spectrometry is established, it is not commercialized and popular at the present time. Accordingly, their clinical value is not yet well explored. The article published by Toru Suzuki demonstrated the prognostic value of BNP5-32 in HF patients, comparable to NT-proBNP. Furthermore, the low interference of BNP5-32 with kidney function may contribute to the superior prognostic value of BNP fragments than the traditional NT-proBNP (4). This really opens an avenue of a better outcome assessment based on quantifying the molecular forms of BNP1-32. Siriwardena *et al.* reported the potential of using BNP signal peptide as a biomarker of myocardial ischemia (12). Others have demonstrated that some BNP fragments are valuable in identifying restenosis post-coronary intervention (13). These fragments exhibit a very promising role in various situations and their applications should be further explored and verified.

Clinical applications

It seems reasonable to set up a commercialized panel to measure BNP fragments. With this approach, we can definitely explore the multifaceted details of using BNP fragments for clinical purposes beyond identifying coronary artery restenosis, myocardial ischemia/infarction and assessing prognosis. It is plausible that the utilization of this panel can allow us to better understand the mechanisms underlying the interaction of multiple drug effects, or even develop better pharmaceutical interventions via manipulation of blood BNP fragment levels. The use of mass spectrometry as the primary quantification facility actually broadens how we view the complexity of treating patients with HF. For example, metabolomics is an emerging science in providing big data information on metabolism in HF; studies have shown the promising diagnostic and prognostic value of metabolomics in HF (14). It is likely that a systemic approach based on a platform integrating all these molecules will be the way forward, providing informative assessments of different HF situations and determining response to a variety of medications.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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