Post-transcriptional modification of pro-BNP in heart failure: Is glycosylation and circulating furin key for cardiovascular homeostasis?

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This editorial refers to ‘Post-translational modifications enhance NT-proBNP and BNP production in acute decompensated heart failure’, by N. Vodovar et al., on page doi:10.1093/eurheartj/ehu314.

With the discovery that the heart is an endocrine organ, we now know that the heart produces and releases hormones, including the natriuretic peptides (NPs). NPs are thought to be produced and released mainly in response to mechanical stretching, due to increased intravascular volume or under pathophysiological conditions, especially in heart failure (HF). B-type NP (BNP) molecular forms, especially BNP and NT-proBNP, are currently in widespread use as biomarkers in HF. Human BNP is produced as a 134-amino acid preproBNP which is subsequently processed to proBNP1-108 by cleavage of its signal peptide. ProBNP 1-108 is then processed into inactive NT-proBNP 1-76 and the GC-A receptor activator BNP 1-32 by proprotein convertases corin or furin. The processing of BNP molecular forms is therefore critical for its bioavailability.

Critical regulators in proBNP processing have been revealed, including the proteases corin and furin and the role of glycosylation of proBNP. Corin—a cardiac transmembrane serine protease that is abundantly expressed in the heart and kidneys, with a functional soluble form that is shed into the circulation—cleaves both proANP and proBNP into active hormones. It has been reported that the levels of soluble corin (i.e. circulating corin) differ significantly between males and females (it is higher in males) and is decreased in HF. In contrast, furin is thought to be an intracellular endoprotease, present in various organs, which processes not only proBNP, but several proproteins including proCNP, proTGF-beta 1 and proendothelin 1. Furin expression is increased in atrial myocardium in experimental HF, however, to date there have been no studies on functional circulating furin.

Glycosylation plays an important role in the regulation of enzymatic cleavage. Seven O-glycosylated sites have been reported within proBNP, all in the NT-proBNP (aa 1-76) region. Tonne and colleagues reported that proBNP predominantly exists as a non-glycosylated form intracellularly, however, only glycosylated proBNP was detected in supernatant from cardiomyocytes in vitro. Additionally, they found that O-glycosylation of T71 residue in proBNP attenuates its processing into active BNP. Peng and colleagues further reported that proBNP glycosylation differed in HEK cells and cardiomyocytes, with T71 O-glycosylation being essential for proBNP processing by both corin and furin in HEK cells, but not in cardiomyocytes. Clinically, Nishikimi and colleagues studied circulating glycosylated or non-glycosylated NT-proBNP and found that circulating levels of BNP, non-glycosylated NT-proBNP, and glycosylated NT-proBNP all increased with the severity of HF, although the molar ratios remaining unchanged (BNP:non-glycosylated NT-proBNP and BNP:glycosylated NT-proBNP = 1:2.4 and 1:9.6, respectively). Therefore, more glycosylated proBNP may be secreted into the circulation than non-glycosylated proBNP, but the relationship between corin and furin and the glycosylation status of proBNP in its processing and circulating levels in HF remains unclear.

In the current issue of this journal, Vodovar and colleagues focus on proBNP glycosylation and its processing by corin and furin in the circulation in human acute decompensated heart failure (ADHF), non-ADHF (dyspnea but no HF) and chronic HF (CHF). Utilizing plasma samples from patients from these groups, their findings are similar to what has previously been shown, that as the highest percentage of glycosylated BNP is present in CHF, suggesting that proBNP processing is altered more in CHF than in ADHF or non-ADHF. In contrast, the percentages of glycosylated proBNP in ADHF and non-ADHF patients were similar to each other. The significantly increased production and rapid release and processing of proBNP in ADHF may represent an attempt by the heart to rescue itself from volume overload by stimulating GC-A in kidney through the circulating BNP. Further, the authors tell us, for the first time, that furin activity—but not its concentration—is greater in ADHF
than in CHF, thus providing a differential mechanism of proBNP processing in disease progression in HF.

What does this all mean from a physiological and clinical perspective? We believe that ADHF may function as an exaggerated model of BNP, in terms of production and secretion (Figure 1). Importantly, atrial cardiomyocytes have secretory granules holding NPs under physiologic conditions, and mechanical stretching may increase the secretion of both non-glycosylated and glycosylated NPs. The current study also suggests that circulating non-glycosylated proBNP in ADHF is processed by furin, not corin. Therefore, further supplementation with a mature peptide, such as nesiritide (recombinant BNP), may not be necessary in ADHF, since the endogenous proBNP–BNP system is still effective.

In contrast, the endogenous proBNP–BNP system may be damaged and/or impaired in the setting of CHF. With chronically increased production of BNP in the heart and with release of more glycosylated proBNP 1-108 into the circulation, there will be a defect with processing to mature BNP (Figure 1). This may lead to a ‘mature BNP deficiency state’, even though higher levels of proBNP 1-108 are secreted by the failing heart. Therefore, CHF patients could benefit from chronic BNP protein therapeutic strategies to optimally stimulate GC-A. Indeed, in patients with stable CHF, chronic subcutaneous injection of nesiritide for eight weeks resulted in a reduction in LV mass, improvement in LV function, decrease in LV systolic volume, and improvement in functional symptoms. Thus, the current study by Vodovar provides us with information, not only on the pathophysiology of BNP metabolism, but also on differential NPs therapeutic strategies in ADHF and CHF.

It should be noted that there are some limitations to the present study. First, it lacks a true control group, normal age or gender-matched subjects, from which we can clearly identify the magnitude of circulating glycosylated proBNP and convertases. Without a control group we cannot be certain that the non-ADHF group might not also have relatively impaired processing by increased proBNP glycosylation. Also, it is well known that levels of circulating corin differs with gender, but age- and gender differences of circulating furin are unknown. As we stated previously, corin may cleave multiple sites within proBNP, which may contribute to the lack of statistical significance with proBNP processing, as only the T71 glycosylation site was examined in this study. Further, the CHF group was small and younger, with mild-to-moderate failure in terms of NT-proBNP levels when compared with other reports, and may suggest a less-severe CHF. Finally, the ADHF group was a mixture of those with new-onset ADHF and those with recurrent ADHF after stable CHF, which may have different pathophysiology and BNP metabolism.

Vodovar and colleagues are to be congratulated for tackling this complex question and providing new insights into the overall processing of proBNP into its biologically active state in HF. Specifically, the important role of glycosylation together with proprotein convertases such as furin enhance our understanding of this fascinating system which may ultimately lead to enhanced diagnostics and therapeutics.

References


CARDIOVASCULAR FLASHLIGHT

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Rare case of left ventricular haemangioma: multi-modal approach to diagnosis

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A 59-year-old female with a history of permanent pacemaker implantation for a high-grade AV block presented with lightheadedness. EKG showed LABB. Pacemaker interrogation was unremarkable. A transthoracic echocardiogram (see Supplementary material online, Video S1) revealed an ejection fraction of 40%, apical hypokinesis and septal dyskinesis. Additionally, an echodensity 1.4 × 1.1 cm located in the mid-distal anteroseptal wall was seen and confirmed on a transoesophageal echocardiogram (see Panel B and Supplementary material online, Video S2).

This mass was suspected to be a thrombus and anticoagulation was commenced. After 3 months of anticoagulation, the mass remained stable in size. At this point, the patient underwent a CT angiogram of the chest (Panel A), which raised the possibility of this mass (attached to the septum via a thin stalk) being a neoplasm, however, possibility of thrombus could not be ruled out. MRI was not performed because of pacemaker. Hence, a coronary angiogram was performed to evaluate the vascularity of this mass. Angiograms (see Supplementary material online, Video S3) clearly showed that this mass (arrows in Panels C and D) to be richly supplied by septal perforators arising from the mid-left anterior descending artery (Panels C and D). Hence, the patient underwent surgical resection of tumour (Panel E), 1.0 × 0.9 × 0.6 cm in size, which was initially reported to be myxoma on histopathological examination. However, after correlation of CTA appearance, rich vascular supply seen on angiograms and histopathological findings (showing dilated cavernous vessels, small capillary channels, scattered pericytes and fibroblasts in a myxoid background), this mass was established to be haemangioma. Left ventricular haemangiommas are rare tumours which often are misdiagnosed as thrombus or myxoma.

Supplementary material is available at European Heart Journal online.

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