Atrial secretion of B-type natriuretic peptide

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In the normal heart, the endocrine capacity resides in the atria. Atrial myocytes express and secrete natriuretic hormones that regulate fluid homeostasis and blood pressure. But in ventricular disease, atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) gene expression is also activated in ventricular myocytes. Plasma concentrations of natriuretic peptides and their biosynthetic precursors are accordingly increased in patients with marked ventricular dysfunction. In contrast, atrial peptide secretion in ventricular disease has received less attention, and our present understanding of the endocrine atria during ventricular dysfunction is still scarce. Although ventricular disease and increased circulating concentrations are associated, it does not entail that the ventricle is the sole or even the main source in all types of heart disease. Clearly, the endocrine atria are also active in heart failure. Plasma measurement of cardiac natriuretic peptides and their molecular precursors can perhaps help us to discriminate when, where and how.

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Although it remains to be established whether a pre-existing inflammatory state promotes atrial fibrillation, these contributors may interrelate in such a way that inflammation is not only a response to the arrhythmic substrate but also an integral part of the process. Rapid atrial activation is also known to cause calcium overload in atrial myocytes and initiation of atrial apoptosis. Such tissue injury may further initiate a low-grade local inflammatory state and be part of the structural remodelling process causing an increased tendency to persistence of atrial fibrillation. Local inflammation causes release of cytokines such as TNF-alpha, interleukin-6beta, and IL-6, which are key stimulants for synthesis of acute-phase proteins such as C-reactive protein. Systemic inflammation with increased levels of circulating C-reactive protein may cause atrial fibrillation in pre-disposed patients with triggering foci in the atria or pulmonary veins. Moreover, C-reactive protein could have a direct role in the development of a local inflammation due to ligand binding and the ability to activate the complement pathway.

Some patients with idiopathic atrial fibrillation have circulating autoantibodies against myosin heavy chain, which highlights the possibility of an autoimmune inflammatory process in these patients.11 Also, patients with atrial fibrillation have higher concentrations of C-reactive protein than patients in sinus rhythm, and if atrial fibrillation persists, the C-reactive protein concentrations are even higher compared to patients with paroxysmal atrial fibrillation. Longer duration of atrial fibrillation is thus associated with both increased C-reactive protein concentrations and larger anatomical size of the atria, which supports a biological relationship between atrial fibrillation and inflammation. So far, a few studies have investigated the relationship between IL-6 and atrial fibrillation, and most have found increased IL-6 levels in patients with atrial fibrillation compared with healthy subjects. In addition, the 174G/C IL-6 promoter gene variant appears to influence the risk of developing post-operative atrial fibrillation.12 Clinical studies employing anti-inflammatory drugs in atrial fibrillation have so far involved treatment with steroids and statins. Administration of glucocorticoids in patients undergoing cardiac surgery has been shown to reduce the risk of early (within 3 days) post-operative atrial fibrillation.13 Another small, randomized study has disclosed that treatment with glucocorticoids in patients with their first episode of persistent atrial fibrillation is followed by a lower incidence of relapse and decreased C-reactive protein concentrations.14

Atrial fibrillation in the absence of left ventricular disease is associated with increased concentrations of BNP,15 and restoration of sinus rhythm can decrease plasma BNP concentrations.16 As mentioned earlier, it has recently been reported that the peripheral concentration of proBNP, but not proANP, is increased in lone atrial fibrillation.7 Taken together with the in vitro findings of selective BNP gene regulation by inflammatory cytokines, it seems reasonable to suggest that BNP concentrations in blood could reflect mostly atrial secretion. A study by Inoue et al.17 has in fact suggested mostly atrial BNP secretion in atrial fibrillation. In extension, it will be interesting to also elucidate the chamber-specific secretion of the precursor peptides, as both proANP and proBNP in plasma are markers of left ventricular dysfunction. Atrial myocytes contain a complex biosynthetic apparatus for peptide storage and maturation, and it may be argued that increased secretion of poorly processed proANP and proBNP could dominantly be a feature of ventricular release.18 According to this hypothesis, the ventricular myocytes may secrete unprocessed precursor peptides in a constitutive manner. In fact, there are data that do suggest such a mechanism.19,20 Moreover, the necessary biochemical tools for examining such molecular differences in the secreted peptides are now emerging.21 Processed, bioactive

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**Figure 1** proBNP in human atrium visualized by confocal microscopy. Transmural biopsies (~400 mg) from the left atrial appendage were obtained from a patient with severely reduced left ventricular systolic function undergoing cardiac surgery. Paraformaldehyde-fixed tissue sections (7 μm) were prepared and incubated with rabbit proBNP antiserum (1:100), raised against the N-terminal decapeptide of human proBNP, or preimmune rabbit antiserum (control). Bound antibodies were visualized with swine antirabbit antiserum conjugated with fluorescein isothiocyanate (Dako, Denmark) and a confocal laser scanning microscope (Zeiss LSM510, Switzerland). The fluorescent image shows proBNP staining in the atrial myocytes extending along the contractile apparatus, and the adjacent grey panel shows the underlying anatomy of the tissue sample (Normarsi).
precursors may perhaps help us to discriminate when, of cardiac natriuretic peptides and their molecular atria are also active in heart failure. Plasma measurement degree of ventricular disease. Clearly, the endocrine plasma concentrations in patients with otherwise similar ventricular dysfunction may be further classified according where echocardiography and peptide measurements are peptide response could be an integral part of an algorithm, more problem-orientated use of the markers. The local sources of natriuretic peptides could perhaps lead to a focus more on ‘the grey zone’ patient, which means patients their left ventricular function. There is a clear need to concentrations between patients with otherwise similar tion. However, major troubles still haunt the markers, which are used as rule-out markers of severe left ventricular dysfunc-

Another open issue is regional peptide secretion within the cardiac chambers. In the atria, the appendages seem to be the logical sources for natriuretic peptide release, as they represent anatomical ‘overload sensors’. But in the much larger ventricles, the site of ANP and BNP expression may be more difficult to identify. Hypertrophic ventricular myocardium may cope differently with increased end-diastolic pressure than normal myocardium, which could be subjected to more stretch. Moreover, local expression of factors from either the cardiac myocytes or the vascula-
ture could stimulate ANP and BNP gene expression in a par-
ticular region within the ventricle. Finally, some reports have suggested the endocardium as the dominant site of ANP and BNP gene expression in failing hearts. Taken together, there seems to be ample evidence that all myocytes within the ventricle will not respond equally to pathophysiological changes.

But why should physicians bother with the cardiac sources of proANP- and proBNP-derived peptides? Measurement of natriuretic peptides and their precursors in plasma can be used as rule-out markers of severe left ventricular dysfunction. However, major troubles still haunt the markers, which in particular relates to the spectacular variation in plasma concentrations between patients with otherwise similar degree of cardiac disease often classified according to their left ventricular function. There is a clear need to focus more on ‘the grey zone’ patient, which means patients with increased BNP and/or proBNP concentrations but under certain cutoff values. Notably, these patients will be common and could easily be a patient with paroxysmal atrial fibrillation. A better understanding of the local sources of natriuretic peptides could perhaps lead to a more problem-orientated use of the markers. The local peptide response could be an integral part of an algorithm, where echocardiography and peptide measurements are used together rather than as complementary tests (this is most likely already being implemented). Patients with ventricular dysfunction may be further classified according to different atrial and ventricular peptide forms, which in turn could help explain the troublesome variation in plasma concentrations in patients with otherwise similar degree of ventricular disease. Clearly, the endocardic atria are also active in heart failure. Plasma measurement of cardiac natriuretic peptides and their molecular precursors may perhaps help us to discriminate when, where, and how.

Conflict of interest: none declared.

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