Rethinking natriuretic peptides: hypoxia and haemoconcentration in atrial fibrillation

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Atrial fibrillation (AF) is the most common supraventricular arrhythmia, with a current global prevalence of 60 million cases. It poses a significant economic burden and is strongly linked to increased all-cause mortality. Mechanical production of thrombi by local laminar and turbulent flows in the left atrial appendage (LAA), possibly feeding clots into the cerebral circulation, is generally considered to be the leading cause of ischaemic stroke. As the LAA is a blind-ended passage with a long and narrow inlet, blood stasis may occur during AF when flow velocity is significantly reduced and the contractility of LAA is concomitantly disturbed. Circulating endocrinological markers of AF, although less studied, have been investigated for the diagnosis and follow-up of the disease. Among them, natriuretic peptides in plasma have been shown to be closely associated with AF; however, their role remains unclear.

Members of the natriuretic peptide family were isolated and characterised in the 1980s; first the atrial natriuretic peptide (ANP) or A-type natriuretic peptide, and then the brain natriuretic peptide (BNP) or B-type natriuretic peptide with strong diuretic and natriuretic effects. The C-type natriuretic peptide with paracrine actions joined the family later. However, there is variation in the inclusion criteria of natriuretic peptides in cardiac diseases.

Although plasma NT-proBNP (the biologically inactive amino terminal fragment of proBNP) and MR-proANP (mid-regional proANP) are commonly used in the clinical management of heart failure, the role of natriuretic peptides in AF is not fully understood. A recent systematic review and meta-analysis of cohort studies identified a strong association between higher NT-proBNP levels and the risk of incident AF; however, the question remains whether this association is the cause or consequence of AF.[1] The prevailing view is that the synthesis and release of natriuretic peptides and their derivatives is due to mechanical stress on cardiac myocytes alone, which regulate the plasma natriuretic peptide levels. This concept stems from a 1980s' *Nature* letter. The authors showed that a large and rapid intravascular volume load in rats caused high plasma levels of ANP from heart atria following stretching. However, these experiments were unphysiological, and the role of intracellular oxygen metabolism, possibly explaining the effects, was not studied.

Linking cell physiological findings with natriuretic peptides to clinical studies on AF may offer another perspective with implications on research and patient management.

Studies have shown that when supraventricular tachycardia (SVT) was induced in humans by programmed cardiac stimulation within the physiological range, plasma levels of ANP increased.[2] Cardiac pacing studies corroborated these findings, showing ANP release without atrial pressure changes—challenging the mechanical-stress-only paradigm. These results were further supported by studies in awake dogs with an experimentally induced complete atrioventricular block (heat cauterisation of His' bundle): when the frequency of atrial contractions was rapidly doubled, the plasma level of ANP was significantly increased and the atrial pressure again remained constant.

Studies using isolated rat atria, which were not spontaneously beating and were perfused with physiological buffer solution, found that incremental increases in the pacing frequency from 120 beats/min to 480 beats/min (normally 350 beats/min) resulted in a continuous rise of ANP in the perfusate.[3] These findings further evidence that the raised frequency of atrial contractions directly increases ANP secretion. Yet the metabolic pathways driving natriuretic peptide secretion during AF remain underexplored and misunderstood.

Oxygen homoeostasis is a critical constraint during biological evolution in all cells, including heart myocytes, and operates in all conditions. One of the basic paradigms in cardiology is that the mechanical load on the heart is the primary determinant of oxygen consumption. Mechanical stress and oxygen metabolism in the heart are inextricably connected; however, clinical studies on AF have not explored this relationship.

To maintain the cellular oxygen concentration within an adequate range, biological evolution has resulted in a common intracellular metabolic pathway which is activated in all cells, including cardiac myocytes, in hypoxic conditions. The key regulator in this pathway is the hypoxia-inducible factor (HIF), a nuclear heterodimeric protein. Its structural components are phylogenetically conserved across the animal kingdom. HIF comprises a labile α subunit (α 1–3), which is regulated, and a stable β subunit, which is constitutively expressed. With normal oxygen tension, hydroxylase enzymes rapidly oxidise HIF-1α. In hypoxic conditions, HIF-1α begins to accumulate, which initiates the expression of thousands of genes involved with cardiac diseases.[4]

Hypoxia directly and sufficiently induces ANP and BNP expression via the HIF pathway.[5 6] When markers for hypoxia (HIF) and angiogenesis (vascular endothelial growth factor, VEGF) were investigated with immunostaining in atrial appendages during open heart surgery in patients with AF, a close association was found between AF and the upregulation of both HIF and VEGF, similarly to that in myocardial infarction.[7]

Following the discovery of natriuretic peptides, clinical studies understandably focused on their endogenous natriuretic and diuretic effects. Their extrarenal effects, not as evident as diuresis or natriuresis, went unnoticed by pharmacologists and cardiologists, although it was shown experimentally that an ANP infusion in rats led to volume contraction due to extrarenal fluid transport and resulted in haemoconcentration. Interestingly, the animals were nephrectomised, suggesting that extrarenal water and plasma shift may be the most important physiological effect of natriuretic peptides.

During programmed cardiac stimulation causing SVT in patients, the haematocrit significantly increased; these findings were later confirmed in patients either with paroxysms of AF or chronic AF (persisting for at least 4 years).[8]

Rapid haemoconcentration increases oxygen-carrying capacity per blood volume unit, significantly contributing to oxygen transport to tissues and organs, which appears to be the biological function of natriuretic peptides. In addition to mechanical flows, haemoconcentration due to AF may present an important element in circulatory pathophysiology, participating in the formation of emboli.

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The established practice in pharmacology and cardiology of treating high blood pressure with diuretics further guided the conceptualisation and execution of clinical studies on natriuretic peptides. However, the role of haemoconcentration in contributing to possible activation of the fibrinocoagulation system during AF was not acknowledged as similarly important. Interestingly, cardiologists, while studying polyuria in patients with paroxysmal atrial arrhythmias which obey the physiological pathway, observed without understanding the biology of natriuretic peptides. Had their biology been clarified alongside their discovery, natriuretic peptides might have merited a Nobel Prize.

As a cardiac disorder, AF offers a model for studying physiological natriuretic peptide release. The release of natriuretic peptides during increased frequency of atrial contractions causes a rapid haemoconcentration (extrarenal plasma shift, diuresis and natriuresis) contributing to oxygen transport in circulation in healthy humans (fight-and-flight response). At the cellular level, a high frequency of contractions unequivocally increases the oxygen consumption of the atria, which is intracellularly mediated through the HIF pathway, a direct and sufficient operator for the synthesis and release of natriuretic peptides, independent of atrial pressures. In AF, natriuretic peptide-induced haemoconcentration may predispose to coagulation disorders. Revisiting natriuretic peptide biology through the lens of oxygen metabolism could reshape our understanding of thromboembolic risk in AF.

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