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Review

The Endocrine Heart: Natriuretic Peptides and Oxygen Metabolism in Cardiac Diseases

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ABSTRACT

Circulating natriuretic peptides are widely used as tools in the diagnosis and follow-up of cardiac diseases, and their use has been increasing throughout other medical branches. After 40 years and more than 40,000 publications, their function in healthy human adults of reproductive age appears to remain confusing—with every physiology and pharmacology textbook telling a different story. In cardiology, mechanical load upon the heart is generally regarded as the condition that regulates the synthesis and release of natriuretic peptides. The key issue in cardiology remains how mechanical activity and oxygen consumption are related, and yet no published paper has shown that mechanical load does not increase oxygen consumption, as wall tension is a major determinant of myocardial oxygen consumption. However, this relationship has been largely neglected in studies on natriuretic peptides. Based on published papers, an outline is presented of how oxygen metabolism, related to mechanical stress, could play an important role in the pathophysiology of natriuretic peptides. The natriuretic peptide system might enhance oxygen transport by causing diuresis, natriuresis, and water transfer from the intra- to extravascular space, resulting in volume contraction and hemoconcentration, thus indirectly promoting the transfer of oxygen into tissues and organs. Mechanical stress and oxygen consumption are 2 sides of the same coin. The

RÉSUMÉ

Les formes circulantes de peptides natriurétiques sont des outils très utilisés dans le diagnostic et le suivi des maladies cardiaques, et leur utilisation ne cesse de croître dans toutes les autres branches de la médecine. Après 40 ans et plus de 40 000 publications, leur fonctionnement chez les humains adultes en bonne santé et en âge de reproduire semble encore confus (devant tous ces manuels de physiologie et de pharmacologie qui brossent des tableaux différents). En cardiologie, la charge mécanique sur le cúur est généralement considérée comme la condition qui régule la synthèse et la libération des peptides natriurétiques. L'enjeu principal en cardiologie reste à connaître le lien entre l'activité mécanique et la consommation d'oxygène, mais jusqu'à ce jour, aucun des articles publiés n'a montré que la charge mécanique n'augmentait pas la consommation d'oxygène, alors que la tension sur la paroi est un déterminant majeur de la consommation en oxygène du myocarde. Toutefois, dans les études sur les peptides natriurétiques, on a grandement négligé cette relation. Selon les articles publiés, une ébauche sur la façon dont le métabolisme de l'oxygène, en relation avec le stress mécanique, jouerait un rôle important dans la physiopathologie des peptides natriurétiques est présentée. Le système des peptides natriurétiques pourrait accroître le transport en oxygène en provoquant la diurèse, la

Two extensive reviews have been published recently describing the role of circulating natriuretic peptides (ANP and BNP, or A- and B-type natriuretic peptide) in human physiology and cardiology.[1,2] After 40 years and more than 40,000 publications, their function in healthy human adults of reproductive age appears to remain confusing—with every physiology and pharmacology textbook telling a different story. Without knowing their precise physiological role, it has been and will be difficult to capitalize on natriuretic peptides as tools in clinical settings or targets for drug development. What is undeniably clear is that mammalian heart atria feature large quantities of natriuretic peptides,[3,4] and structurally, natriuretic peptides colocalize in small, paranuclear granules in atrial myocytes, which cannot be found in ventricular myocytes.[5,6]

In these 2 recent reviews, the authors demonstrated that natriuretic peptides are synthesized and released from cardiac myocytes in response to mechanical stress (either stretch or pressure), which contributes to blood pressure regulation. This concept was first introduced in a seminal letter of Lang et al.,[7] published in *Nature* in 1985, in which researchers showed that a large and rapid saline infusion into a rat (8 mL within 1 minute), which more than doubled the intravascular volume and stretched the heart atria, resulted in high plasma levels of ANP; however, the authors did not discuss their results relative to any metabolic parameters. Subsequently, the release of BNP has also been suggested to be mechanosensitive.[8] These findings resulted in creation of the paradigm that terrestrial mammals, including humans, have a powerful regulatory system that counteracts large and rapid intravascular fluid excess through the control of diuresis and natriuresis. However, physiologically large intravascular overloads are rarely experienced. In contrast, like all terrestrial mammals, humans are in constant danger of becoming dehydrated. Both the short half-life and the

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relationship between mechanical stress and oxygen metabolism, in the particular case of natriuretic peptides, represents a new avenue for clinical studies and will better explain the results of studies that have been published previously.

natriurèse et le transfert d'eau de l'espace intravasculaire à l'espace extravasculaire, qui entraînerait une contraction du volume et une hémoconcentration et, par conséquent, favoriserait indirectement le transfert d'oxygène dans les tissus et les organes. Le stress mécanique et la consommation en oxygène sont les deux côtés de la médaille. La relation entre le stress mécanique et le métabolisme de l'oxygène, particulièrement des peptides natriurétiques, représente la nouvelle avenue des études cliniques et permettra de mieux expliquer les résultats des études publiées antérieurement.

large reservoir of natriuretic peptides found in the heart atria[3,4] suggest the involvement of these peptides in an acute physiological response, rather than their being involved in a volume control process that occurs over several hours and is mainly regulated by thirst and antidiuretic hormone.

The concept of mechanical stress has been adopted in the field of clinical cardiology, as evidenced by a recent position paper providing practical guidance on the use of natriuretic peptides by the Heart Failure Association.[9] In this review, the authors credited the letter published in *Nature*[7] stating that the most important condition modulating the plasma levels of natriuretic peptides could be understood in the context of volume expansion and/or pressure overload. Despite the fact that the measurement of natriuretic peptides (biologically active BNP, biologically inactive aminoterminal fragment of proBNP, and midregional proANP) is currently utilized in clinical settings, mechanical stress does not explain every aspect of high plasma levels of natriuretic peptides.

Is it possible to interpret the effects of mechanical load on the endocrine heart through the lens of oxygen metabolism?

Hypoxia

In the shadow of the letter published in *Nature*,[7] Baertschi et al.[10] found that hypoxic conditions could reversibly stimulate the release of ANP from the Langendorff isolated heart, which is widely used in both physiological and pharmacologic in vitro studies. Further studies using isolated myocytes, atrial or ventricular muscle strips, and isolated heart blocks consistently showed that a decrease in oxygen tension unequivocally stimulated the release of natriuretic peptides. Prior to these experimental studies, the isolation and characterization of natriuretic peptides were first introduced when de Bold et al.[11] infused heart atrial extracts into a rat's circulatory system and observed a strong diuretic and natriuretic response, which was followed by a decrease in blood pressure. ANP was the first natriuretic peptide discovered in atrial extracts, in the early 1980s. Therefore, during the era that followed this finding, physiological experiments were mostly performed using ANP. In 1988, BNP was discovered, first in the brain—hence the term brain natriuretic peptide[12]—but its main site of synthesis was found to be the heart atria.[4] The earliest physiological experiments using BNP were reported in the 1990s. The observations aroused intensive interest among pharmacologists because mammals appeared to have an endogenous diuretic and natriuretic, contributing to blood pressure regulation. The focus of natriuretic peptide research rapidly moved toward clinical science and drug development, and in vivo physiological studies were neglected, disrupting a bridge between basic science and cardiology. Studies examining oxygen metabolism and natriuretic peptides have been far less common than those examining the mechanical load concept, and thus far, they have been unable to challenge the prevailing paradigm. Additionally, the autocrine and paracrine C-type natriuretic peptide, secreted from endo-

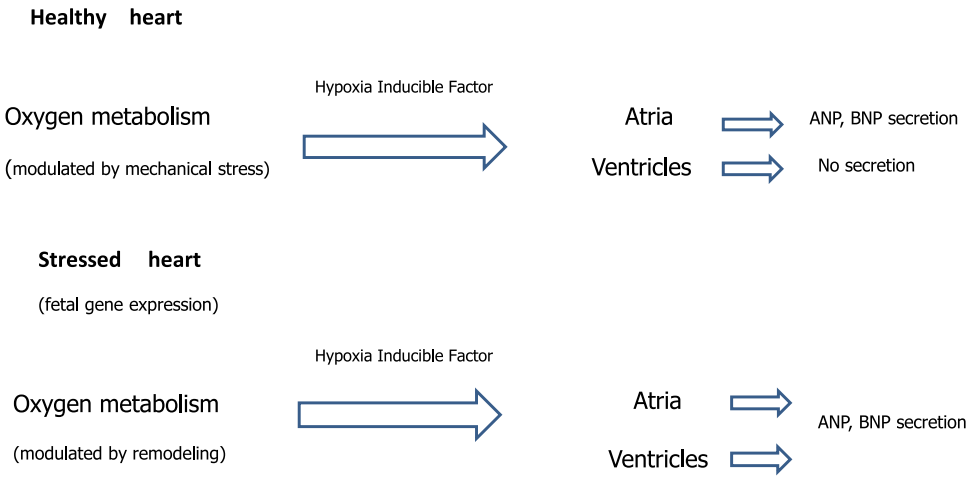

Figure 1. Function of endocrine heart. The natriuretic peptide system of the heart is oxygen sensitive and is modulated by mechanical stress. In healthy heart, the secretion of A- and B-type natriuretic peptide (ANP and BNP) from atria results in hemoconcentration and increased oxygen-carrying capacity of blood. In stressed heart, after remodeling that starts fetal gene expression, ventricles commence secretion of ANP and BNP.

thelial cells, cardiomyocytes, and fibroblasts, is a critical regulator of angiogenesis and vascular remodeling in ischemia.[13]

Interestingly, Almeida et al.[14] showed as early as in the mid-1980s that in nephrectomized rats, an infusion of ANP could increase hematocrit levels and decrease plasma volumes due to the efflux of fluid from capillaries. These changes could be interpreted as ultimately resulting in an increased oxygen-carrying capacity in the bloodstream. At the cellular level, for both ANP and BNP genes, hypoxia was found to be a direct and sufficient stimulus for natriuretic peptide expressions through the immediate actions of hypoxia-inducible factor-1 (HIF-1α),[15,16] which is the master switch for oxygen-sensing mechanisms across the animal kingdom. The researchers who discovered the HIF pathway were awarded a Nobel Prize in 2019.

Mechanical Load and Oxygen

The key issue in cardiology remains how mechanical activity and oxygen consumption are related, and yet no published paper has shown that mechanical load does not increase oxygen consumption. When summarizing the results of all papers published on this relationship, Gutterman and Cowley[17] concluded that "wall tension is a major determinant of myocardial oxygen consumption." Based on this relationship, oxygen metabolism can be hypothesized to have been affected by the large mechanical load used in the *Nature* letter.[7] The vast and rapid stretching of the atria following volume expansion increased oxygen consumption, which directly triggered the synthesis and release of ANP, both in vivo and in vitro. How oxygen metabolism in either atrial or ventricular myocytes regulates the synthesis and release of natriuretic peptides in cardiac diseases remains to be determined. For example, oxygen tension is substantially lower in mitochondria than in coronary arteries, producing varying oxygen gradients across chamber walls. Additionally, if direct mechanical stress alone was the physiological stimulus, bypassing the existing stretch receptors as has been suggested, then this release mechanism should be able to sense specific signals among the turbulent and laminar flows caused by physical activity, and the signal-to-noise ratio would be very low.

At the systemic level in healthy individuals, these results can be summarized and explained as follows: the role of the natriuretic peptide system might be to enhance oxygen transport by causing diuresis, natriuresis, and water transfer from the intra- to extravascular space, resulting in volume contraction and hemoconcentration, indirectly promoting the transfer of oxygen into tissues and organs. The decrease in blood pressure is secondary to these phenomena. Large quantities of natriuretic peptides can be immediately released by the atria, which serve as oxygenation sensors and effectors along gas-exchanging surfaces.

Cardiac Diseases

How can we explain the high concentrations of natriuretic peptides, in both plasma and tissue, in terms of oxygen metabolism and in the context of cardiac diseases, such as in supraventricular tachycardias (SVTs; such as atrial fibrillation, paroxysmal SVT, atrial flutter, and Wolff-Parkinson-White syndrome), coronary artery disease, hypertrophic heart, and failing heart conditions?

In all of these diseases, oxygen metabolism appears to play a crucial role. However, we must also consider the source of natriuretic peptides.

By definition, SVT originates in the atria, above the ventricles. The sudden onset of mechanical work performed by excessively beating atria increases oxygen consumption markedly, or otherwise shifts oxygen metabolism from its normal range. Although SVT is clearly a pathophysiological condition, it functions similarly to a physiological rhythm resulting in high levels of a natriuretic peptide without elevated atrial pressure.[18] Several studies have examined the volume parameters during tachycardias, which have corresponded well with the ideas presented here. A well known but less-studied phenomenon is the occurrence of polyuria during an SVT attack.[19] According to some fragmentary findings, both plasma ANP levels and hematocrit were increased in humans during SVT.[20]

Coronary artery disease, hypertrophic heart, and failing heart are clearly pathophysiological conditions in which regulatory systems become activated that are not typically functional in healthy humans. Patients who suffer from these diseases have high levels of natriuretic peptides in their blood circulation, and the ventricular gene expression of natriuretic peptides is also high. A common feature during a stressful condition is extensive remodeling, during which a hemodynamically stressed heart might respond by returning to a pattern of fetal metabolism.[21] Among other effects, this results in the activation of the embryonic gene program in ventricles and the expression of high levels of natriuretic peptides. Fetal gene expression is typically observed under conditions of hypoxia, ischemia, hypertrophy, and atrophy.[21] A remaining open question is why high plasma levels of natriuretic peptides due to ventricular diseases do not initiate diuresis or natriuresis. To better understand this phenomenon, the fetal gene expression of the heart must be further explored. A summary of the ideas presented above is shown in Figure 1.

For example, plasma measurements of natriuretic-proBNP provide us with direct information regarding the oxygenation status of heart ventricles. Thus, what matters more in the synthesis and release of natriuretic peptides appears to be oxygen metabolism; mechanical stress and oxygen consumption are 2 sides of the same coin.

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