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Physiology of natriuretic peptides: The volume overload hypothesis revisited

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Abstract

The discovery of the natriuretic peptide system in the early 1980s aroused great interest among clinical cardiologists. The heart was not a mechanical pump alone, but also an endocrine organ that had powerful effects on blood circulation. Natriuretic peptides caused both natriuresis and diuresis, and they responded to a volume overload which caused either stretch or pressure on the heart. As a result, the findings led to the conclusion that the human body had a hormone with effects similar to those of a drug which treats high blood pressure. Later, it became evident that the volume contraction was fortified by extrarenal plasma shift. Here, a hypothesis is presented in which the role of natriuretic peptides is to regulate oxygen transport as the volume contraction leads to hemoconcentration with an increased oxygen-carrying capacity. Wall stress, either chemical or mechanical, changes the oxygen gradient of the myocardium and affects the diffusion of oxygen within a myocyte. In support of this hypothesis, hypoxia-response elements have been found in both the atrial natriuretic peptide and the brain natriuretic peptide genes.

Key words: Natriuretic peptides; Hypoxia; Hemoglobin concentration; Volume overload

Core tip: A new concept is suggested for the understanding of the physiology of natriuretic peptides. Both chemical and physical challenges will ultimately increase the oxygen consumption of the heart which is the factor regulating the release of natriuretic peptides. Diuresis, natriuresis and plasma shift lead to hemoconcentration and the oxygen transport in human body will be enhanced.

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INTRODUCTION

In a recent state-of-the-art review, Mangiafico *et al*[1] discuss the possibility of inhibiting the natriuretic peptide system by neutral endopeptidases as an evolving strategy to treat hypertension and heart failure. The concept behind this review and the related drug trials, such as in the case of Solomon *et al*[2], has been that both atrial natriuretic peptide [ANP (A-type)] and brain natriuretic peptide [BNP (B-type)] are secreted from the heart as a result of direct wall stress, caused either by stretch or pressure affecting cardiocytes, to protect the human body from a volume overload. NT-proBNP especially, the biologically inactive sequence of proBNP with a long half-time and circulating in blood, has been utilized either as an indicator of the metabolism of natriuretic peptides or as a guide of treatment in a wide array of heart diseases. The hypothesis was formulated about thirty years ago when a large and rapid intravascular volume increase resulted in high plasma levels of ANP in rats[3] and since then has prevailed without an alternative interpretation. At that time, it was also shown that an infusion of rat heart atrial extracts into a rat's circulation brought about massive diuresis and natriuresis[4], reaffirming the hypothesis.

These findings were greeted with excitement in cardiology; now we had an endogenous hormone available that could combat all pressure-caused heart diseases, similar to those of the drugs previously developed to treat high blood pressure. The large numbers of articles published on natriuretic peptides, more than 28000 by the end of 2013, reflect the high expectations in clinical cardiology towards these peptides over a broad time frame, but perhaps also that the physiological role of the natriuretic peptide system in healthy humans has not been definitely clarified. As a result, the significance of the natriuretic peptide as a tool in cardiology has remained obscure.

PHYSIOLOGY OF NATRIURETIC PEPTIDES

The conclusion that a direct mechanical load on myocytes is the key factor regulating the synthesis and release of the natriuretic peptide system, occurring across the whole animal kingdom, is rather confusing as it bypasses the function of nervous stretch receptors in the atria and disregards the effects of variable flow conditions in the atrial lumen occurring during physical activity. In addition, terrestrial mammals living in a dry and warm environment do not experience large intravascular volume overloads but, on the contrary, are constantly in danger of becoming dehydrated. In his review on volume and pressure regulation, Guyton, the single author of several textbooks of medical physiology and a specialist in blood pressure regulation, did not refer to the natriuretic peptide system as a pressure controller at all, a role which he gave solely to the kidneys[5]. What was not known in the early 1980s and became evident later, was that a natriuretic peptide has strong extrarenal vascular actions, contributing to contracting the plasma volume by transferring fluid and plasma protein from plasma to interstitial compartments[6].

Apart from the pharmacological interest in developing a new class of drugs to treat high blood pressure, based on the volume overload hypothesis, Baertschi *et al*[7] showed that hypoxia was a direct and sufficient stimulus for ANP release from an isolated rodent heart. Later, hypoxia-sensitive elements were found from the promoter sequence of both the *ANP* and the *BNP* genes[8,9]. In line with these findings, there are many studies, performed with isolated myocytes, heart muscle strips and animals, which clearly provide evidence that there is a hypoxia sensitive component in the release mechanism of the natriuretic peptide system. When the blood flow in the coronaries of the pig heart was surgically blocked, the BNP mRNA increased significantly in the wall area that had become hypoxic[10] and the plasma levels of NT-proBNP were associated with the extent of myocardial damage and microvascular obstruction in patients, as assessed by contrast-enhanced cardiac magnetic resonance imaging[11]. Stockmann *et al*[12] studied the effects of oxygenation in the hypertrophied heart ventricular of the rat and showed that when normoxic conditions were restored, the ANP content decreased to control levels despite the persisting hypertrophy. Salmon cardiac peptide, a hormone related to A-, B- and C-type natriuretic peptides[13] and localized in salmon heart ventricle[14], has a hypoxia sensitive component in its release mechanism which is independent of contraction[15].

It is interesting to note that in the clinical studies in which the oxygen delivery into contracting myocytes is impaired, the measurement of natriuretic peptides has shown its strength. A meta-analysis of 2784 patients from sixteen studies identified stress-induced myocardial ischemia as a significant condition linked with high plasma levels of BNP[16]. In a five year prospective longitudinal clinical study with 4775 primary care subjects, a single measurement of NT-proBNP significantly improved the prediction of incident cardiovascular events[17]. The combined endpoint in this study was restricted to the occurrence of myocardial infarction, coronary revascularization and cardiovascular mortality due to a sudden cardiac death or a fatal myocardial infarction. When comparing troponin assays with NT-proBNP assay in an acute coronary syndrome, Gravning *et al*[18] showed that the latter assay was superior to former ones to predict the long-term mortality in a prospective study of 458 patients. NT-proBNP predicted the extent of coronary artery disease and ischemia in the patients with stable angina pectoris, thus contributing to the diagnostic process[19], and was linked to the severity of the aortic valve disease[20]. The recent ACTION Registry-GWTG study[21] reports the measurements of natriuretic peptides from a cohort of almost 30000 patients admitted to hospitals with an acute myocardial infarction. Among these patients without heart failure, natriuretic peptides were strongly and independently associated with the in-hospital mortality, even after adjustments for the severity of presentation. Also, in the patients with paroxysmal, persistent atrial fibrillation, most probably causing elevated oxygen consumption, plasma levels of natriuretic peptides were increased[22]. This accumulating experimental and clinical evidence for a direct role for oxygen has, however, been overshadowed by the wall stress hypothesis which alone has been used as a magnifying glass when looking at clinical results.

CRITICAL DEBATE

What if the wall stress hypothesis has been misleading clinical cardiologists for nearly thirty years? The volume overload hypothesis originates from a rather small number of physiological experiments made in the 1980s. Additionally, as the following decade saw the rundown of physiology departments due to the strong emergence of molecular biology, the focus of natriuretic peptide research was rapidly moved towards clinical applications.

The role of the natriuretic peptide system is perhaps not to counterbalance pressure changes in circulation, but to regulate oxygen transport, both locally and systemically, by causing volume contraction (diuresis, natriuresis and *plasma shift*) leading to hemoconcentration and an increased oxygen-carrying capacity per unit volume of blood[23-25]. All the conditions that will increase the oxygen consumption or change the oxygen diffusion of

Table 1 Established facts

Already known fact 1	Volume overload (stretch or pressure) stimulates the synthesis and release of natriuretic peptides
Already known fact 2	Natriuretic peptides cause natriuresis, diuresis, vasodilatation and plasma shift

Table 2 Novel insights

New information 1	Natriuretic peptide system responds to oxygen tension (hypoxia-response elements in the promoter sequence of *ANP* and *BNP* genes). Volume overload causes wall stress and changes the consumption or diffusion of oxygen in heart
New information 2	The result of natriuresis, diuresis and plasma shift is volume contraction and increased oxygen-carrying capacity per unit volume of blood. Oxygen transport will be enhanced

ANP: Atrial natriuretic peptide; BNP: Brain natriuretic peptide.

myocytes, such as stretch, pressure or metabolic challenges, will ultimately initiate the synthesis and enhance the release of natriuretic peptides from intracellular locations. Although these conclusions can be partly deduced from existing experimental and clinical results, more precise evidence can be obtained with the following sophisticated methods to support cardiologists in reanalyzing and reinterpreting their previous findings and to bring the natriuretic peptide associated drug development back onto a biologically correct basis.

To initiate a paradigm shift, the following methods should be introduced for the studies of the pathophysiology of natriuretic peptides. A method that is able to reveal perfusion defects in patients suffering from ischemia is positron emission tomography. Although the method has been available for several years, the properties of the tracers used have limited the interpretation of results. By means of newer tracers with a better defect contrast than the previous ones, it is or will be possible to quantify the perfusion of the myocardium during an exercise test or under a pharmacological challenge in patients with ischemia[26].

Further evidence on the role of oxygenation can be obtained during congenital heart surgery with open chest cavity when an optical probe can be placed directly onto the free wall of the right ventricle, measuring the myoglobin saturation of myocytes[27].

Experimentally, the Langendorff perfusion system is the method of choice if the effects of hypoxic conditions on the natriuretic peptide system are to be studied *in vitro*[28]. The isolated rodent heart can be perfused with different types of buffer solution, containing molecules with oxygen-carrying capacity, under appropriate left ventricular preload and afterload pressures. Imaging the fluorescence of NADH (the reduced form of nicotinamide adenine dinucleotide) from a local hypoxic ventricular area provides a measure of the mitochondrial redox state and the method has revealed that in the isolated biventricular working rabbit heart, different pacing rates produce hypoxic conditions[29]. In addition, the gene targeting technology of natriuretic peptides may provide us with new insights into their diverse functions and especially into the role of hypoxia in the physiology of natriuretic peptides[30]. Even the assessing the oxidative metabolism of a single myocyte with NADH fluorescence is possible[31].

In all the methods mentioned above, natriuretic peptides can be measured either from the circulating plasma or from the perfusate and the concentration can be compared with the state of tissue oxygenation.

NEW CONCEPT

According to the hypothesis outlined here, any chemical or mechanical challenge directed towards myocytes will eventually affect the diffusion or consumption of oxygen within a myocyte[32], producing functional and regional heterogeneity of the oxygen supply-consumption ratio in the heart. During large and rapid changes in wall tension, as have occurred in volume overload experiments *in vivo* and pressure increase experiments with the Langendorff preparation *in vitro*, these manipulations have necessarily affected the oxygen metabolism of the heart. Interpreting the results from studies with single myocytes, isolated perfused hearts and with patients suffering from ischemia from a new angle will provide us with a new concept of the physiology of the natriuretic peptide system in healthy humans. To sum up, the role of the natriuretic peptide system is to increase oxygen transport in healthy humans to counteract hypoxic conditions and the stimulus to which the synthesis and release of natriuretic peptides responds is the oxygen gradient among cardiocytes (Tables 1 and 2).

It is worth noting that, in seal pups, able to experience a physiological eupnea-apnea cycle while sleeping, the plasma ANP was significantly higher when they were holding their breath than during the periods of eupnea[33]. Also, blood from seals showed an increase in hematocrit from 55.6% to 63.1% with a peak occurring within 1 min of the end of apnea[34], reflecting an increased hemoglobin concentration.

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