Discovering a new role for the atrial natriuretic peptide: A novel risk factor for cardiovascular diseases

SPERANZA RUBATTU, MASSIMO VOLPE

Division of Cardiology, II Faculty of Medicine, University of Rome “La Sapienza”, Sant’Andrea Hospital, Rome - Italy; IRCCS Neuromed, Pozzilli (Is) - Italy

ABSTRACT: Atrial natriuretic peptide, a diuretic, natriuretic and vasorelaxant hormone, is also involved in the regulation of cardiovascular remodeling and it has been recently shown to be significantly associated with higher occurrence of cardiovascular diseases. In fact, high plasma ANP levels predict higher mortality rate for cardiovascular events. Moreover, ANP gene alterations are associated with higher risk of cardiovascular intermediate phenotypes, such as left ventricular hypertrophy, and of cardiovascular diseases, such as stroke and hypertension. Thus, the characterization of ANP plasma levels, and of ANP genotype for known mutations can be proposed as an informative component of the individual cardiovascular risk profile. (Heart International 2006; 2: 78-81)

KEY WORDS: Atrial natriuretic peptide, Cardiovascular risk, Genetic

INTRODUCTION

The atrial natriuretic peptide (ANP) is a well known component of the natriuretic peptide family, which also includes BNP and CNP, and plays an important role in the regulation of electrolytes and water balance through its diuretic and natriuretic effects, as well as of vasomotor tone through its vasorelaxant effect. Thus, ANP maintains blood pressure homeostasis. Moreover, through the reduction of preload and afterload as a consequence of its hemodynamic effects, ANP is a key regulator of cardiac performance (1).

Since its discovery in 1981 (2), the atrial natriuretic peptide has been largely investigated in the pathophysiology of several cardiovascular diseases, such as hypertension, heart failure, coronary and cerebrovascular disease (3).

Thus, circulating and cardiac levels of ANP are directly correlated with the degree of cardiac dysfunction in heart failure (4). Elevated ANP levels are also a hallmark of arterial hypertension (5, 6).

However, only through the recent introduction of molecular genetic techniques have we had the chance to learn important new information on the direct contribution of ANP to the individual susceptibility to develop cardiovascular diseases (Fig. 1).

ANP and the risk of cerebro-vascular disease

Evidence from an animal model of stroke, the stroke-prone spontaneously hypertensive rat, implicated, for the first time, the gene encoding ANP as a direct contributor to stroke susceptibility. In fact, the ANP gene was found to map at the peak of linkage of a “protective” quantitative trait locus for stroke proneness identified in the SHRsp animal model (7). A subsequent detailed analysis of the rat ANP gene revealed structural
Rubattu et al.

In this regard, **in vitro** studies have previously documented an antiproliferative effect of regular ANP on rat cultured vascular cells (13). In fact, exposure of rat endothelial cells to ANP stimulated the process of apoptosis through the induction of p53 and the inhibition of Bcl2 proteins (14). The proapoptotic effect of ANP was inhibited by specific blockade of the NPR-A receptor. Consistent results were obtained in myocardiocytes (15).

Of interest, parallel epidemiological observations have reinforced the etiopathogenetic contribution of ANP to cardiovascular events. Results from the Framingham population have underscored a predictive role of high circulating levels of natriuretic peptides towards an increased mortality due to cardiovascular causes (16). Moreover, high plasma levels of natriuretic peptides at the time of either a stroke or a myocardial infarction have been correlated with a negative prognostic value for the patient, since they are associated with an increased mortality rate within the following five years (17).

**ANP and hypertension**

Convincing evidence in favour of a contributory role of ANP in the development of hypertension has been provided only recently through genetic approaches in experimental animal models (18-20). In fact, ablation of ANP gene in mice was associated with the development of salt-sensitive hypertension (18), whereas the overexpression of the ANP gene in transgenic mice was associated with reduced blood pressure levels (19). On the other hand, ablation of the ANP receptor (NPR-A) gene caused hypertension as well, although not of the salt-sensitive type (20).

Testing of ANP gene, through the candidate gene approach, in human hypertensive populations has led so far to evidence of a significant association only in certain ethnic groups, such as African Americans (21). Some positive results were also obtained with the characterization of NPR-A gene (22). However, a more direct demonstration of a causal role of both ANP and NPR-A genes in the predisposition to develop hypertension in humans is still lacking. Current studies are trying to clarify this issue (unpublished observations from our group).
ANP and left ventricular hypertrophy

ANP has long been known as a marker of left ventricular hypertrophy, simply as a consequence of a significant induction of ANP gene transcription during the hypertrophic process of cardiac myocytes (23). However, we have recently learned that ANP plays an independent, direct role on cardiac mass regulation in both animal models and in humans (18–20, 24). In fact, ablation of ANP gene was associated with a greater ratio of heart weight/body weight, independently from hypertension (18), whereas the overexpression of ANP was associated with presence of smaller hearts (19). Moreover, mice lacking the NPR-A gene had a marked cardiac hypertrophy (20).

In this regard, studies from our group have recently demonstrated for the first time a direct modulatory role of both ANP and NPR-A genes on cardiac mass development in humans. In fact, an ANP promoter gene variant, associated with significantly lower levels of circulating ANP, was found to associate with increased LVMI, left ventricular posterior wall thickness, left ventricular septum thickness, and relative wall thickening in human essential hypertension. On the other hand, an allelic variant of NPR-A gene was associated with increased LVMI and left ventricular septum thickness in the same human sample (24).

Taken together, these findings support the ANP-NPRA system as a relevant regulatory mechanism antagonizing hypertrophic growth responses within the heart. Thus, the increase of ANP that generally accompanies cardiac hypertrophy should not be interpreted as a marker of a contributory role of ANP to cardiac growth, but rather as the response of an intrinsic “friendly” mechanism that protects myocardiocytes against hypertrophic stimuli (25).

Perspectives

The traditional view of atrial natriuretic peptide as a key regulator of blood pressure and electrolyte homeostasis, as well as a marker of ventricular hypertrophy and cardiac failure has been overcome by the new concept of ANP as a cardiovascular risk factor.

In fact, both experimental and clinical evidence show a role for ANP in the development of all major cardiovascular diseases (Fig. 1).

Therefore, measurement of ANP plasma levels, and, furthermore, assessment of the ANP genotype for the known mutations can be proposed as important elements when assessing the cardiovascular risk profile of an individual subject.

The future research in this exciting field will certainly provide us with more information which, hopefully, we will also be able to apply in better therapeutical strategies.

Address for correspondence:
Speranza Rubattu, MD
IRCCS Neuromed
Località Camerelle-Zona Industriale
86077 Pozzilli (IS) - Italy
rubattu.speranza@neuromed.it

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