EDITORIAL COMMENT
Natriuretic Peptides and Cardiac Hypertrophy*

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Cardiac hypertrophy, an increase in the size and/or thickness of the ventricles in the heart, is an important compensatory mechanism for pathophysiological states and an independent predictor of cardiovascular morbidity and mortality (1,2). Several studies have shown that left ventricular mass in healthy populations and athletes is at least partially genetically determined (3–5). At the cellular level, cardiac hypertrophy results largely from an increase in the size of individual cardiac myocytes. A number of molecular pathways related to hypertrophy have been studied in vitro and in animal models, including the alpha- and beta-adrenergic nervous systems, the renin-angiotensin-aldosterone system, endothelin–1, and calcineurin (6,7). Pharmacological blockade of these pathways, to varying degrees, has proven beneficial in the treatment of cardiovascular disorders, including heart failure. Polymorphisms in the adrenergic nervous system and the renin-angiotensin-aldosterone system have been reported to affect ventricular mass and/or hypertrophy, although the findings remain controversial (3,8,9).

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Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are produced by and stored in atrial and ventricular myocytes, respectively (10,11). Both peptides are released in response to stretch and cleaved into an N-terminal peptide fragment (N-terminal proANP, N-terminal pro-BNP) and the active peptide. The peptides bind to their receptors (mainly natriuretic peptide receptor A [NPRA], but also NPRB and NPRC), lead to vasodilation and natriuresis, and are degraded by neutral endopeptidase (NEP). Measurements of serum levels of the natriuretic peptides and their N-terminal cleavage fragments have diagnostic and prognostic value in patients with known or suspected heart failure. Infusions of nesiritide, a recombinant human BNP, improve hemodynamics and functional status in patients with decompensated heart failure, although the long-term safety and efficacy have been questioned (12,13).

The natriuretic peptides prevent cardiac myocyte hypertrophy in vitro (14). They also affect cardiac mass and left ventricular hypertrophy in animal models. In the spontaneously hypertensive rat, a strong correlation was observed between blood pressure and a marker in Nppa, the gene that encodes for the ANP precursor peptide (15). No correlation was found for Nppb, the gene that encodes for the BNP precursor peptide. Targeted disruption of the proANP gene in mice led to hypertension and hypertrophy in homozygous knockouts and salt-sensitive hypertension in heterozygotes (16). Transgenic overexpression of ANP, on the other hand, tended to protect against hypertrophic stimuli (17). Targeted disruption of NprI, the gene encoding NPRA, also caused hypertension and hypertrophy (18). Of note, cardiac-specific overexpression of NPRA in NPRA knockout mice decreased myocyte size without a decrease in blood pressure, and in mice with a cardiac-restricted knockout of NprI, hypertrophy developed without hypertension (19,20). This shows that NPRA receptors are present in the heart and transduce local antihypertrophic stimuli, analogous to the renin-angiotensin system that is present in cardiac tissue and causes hypertrophy and fibrosis (21).

Several polymorphisms in the gene encoding for proANP have been reported, including the C–664G promoter variant, the G1837A intronic variant, and the T2238C exon 3 coding variant (22). The rare C–664G promoter polymorphism has been associated with hypertension in a Japanese population (23). The T2238C polymorphism disrupts the stop codon, extends ANP by two arginine residues, and has been associated with an increased risk of stroke and recurrent stroke (22). The ANP polymorphisms have also been associated with a lower risk of proteinuria (24). Of note, the three ANP polymorphisms are in linkage disequilibrium. In addition, a deletion in the 5′-flanking region of the gene encoding NPRA has been associated with hypertension and hypertrophy (25).

In this issue of the Journal, Rubattu et al. (26) show an association between the −664G promoter polymorphism and left ventricular hypertrophy using echocardiography in a cohort of 203 Italian patients with hypertension. The findings were not explained by differences in blood pressure or by use of medications. Importantly, individuals in this cohort and in a separate group of normotensive patients who carried a copy of the variant allele had markedly decreased proANP levels, providing a potential physiological basis for the effect. An association was also found between a microsatellite marker genotype in the NPRA promoter and left ventricular mass. No associations were found with the other polymorphisms in ANP or with a microsatellite marker at the 3′ end of the BNP gene.

These findings are potentially important for a number of reasons. They provide direct evidence of a role for the natriuretic peptide system in the control of cardiac hypertrophy in humans. This could lead to a novel screen for the genetic risk of hypertrophy, and potentially to trials of early pharmacological treatment in those patients with the hypertrophic genotype. There are also potential pharmacoge-

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netic implications for the use of recombinant natriuretic peptides in heart failure patients.

A number of factors limit the scope and impact of the present study. As pointed out by the investigators, another causal allele in linkage disequilibrium with the −664G allele cannot be excluded. The −664G allele frequency is low, which limits any potential subgroup analysis and decreases the clinical relevance of the polymorphism. The ethnic homogeneity of the subjects reduces genetic and environmental confounding variables, but makes generalization to other populations difficult. The study population was largely male, and it is not clear whether the findings are applicable to women.

Even less can be said about the NPRA polynucleotide repeat, for which no physiological support is presented and which may well be a marker for the causative polymorphism. The findings presented here do not exclude variants in BNP as determinants of hypertrophy. It is not known whether polymorphisms in other genes related to the natriuretic peptide degradation, such as NEP and NPRC, affect hypertrophy (27). It is also not known whether modulating hypertrophy via the natriuretic peptide system will decrease the additional morbidity and mortality associated with hypertrophy.

The study by Rubattu et al. (26) clearly highlights the strengths and weaknesses of this type of association study. Although preliminary, the findings do suggest a potentially causal relationship between the promoter polymorphism and hypertrophy. To prove causality, additional studies on the polymorphism need to be performed in vitro and/or in animal models. In addition, the human studies should be repeated in larger populations both to confirm the association and to exclude other genes. Logically, one would anticipate interactions between functional polymorphisms in several genes in the natriuretic peptide pathways. Unfortunately, the number of subjects required for a complete analysis of interactions among the natriuretic system genes may be prohibitive.

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