Heart Failure
A Corin-Deficient State?

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Editorial Commentary

Atrial and brain natriuretic peptides (ANP and BNP) possess important regulatory cardiaoreal functions, such as promoting natriuresis, diuresis, vasodilatation, and activation of anti-hypertrophic responses on pathophysiological stress. Release of ANP and BNP is significantly increased in response to atrial and ventricular stretch, respectively. Both ANP and BNP are produced and stored as prohormones and are present in the circulation as a mixture of propeptide and active 28- and 32-amino acid, carboxyl-terminal peptide hormones, respectively.1

Both ANP and BNP bind to the natriuretic peptide receptor-A, which is coupled to particulate guanylate cyclase to generate cGMP, the primary second messenger mediating downstream signaling cascades in target tissues. Despite stimulation of the same receptor, the physiological effects of ANP and BNP are somewhat different: ANP predominantly regulates sodium-water homeostasis and blood pressure, whereas BNP has more antihypertrophic effects, although there is substantial overlap.1

In theory, increases in generation of ANP and BNP in response to myocardial stretch should occur as part of compensatory mechanism(s) to restore homeostatic balance. However, the lusitropic, antihypertrophic, and natriuretic effects of ANP and BNP are significantly attenuated in congestive heart failure despite a considerable apparent increase in plasma concentrations. It is now increasingly accepted that the key reason for this discrepancy is because of variable activation/processing of natriuretic peptides, resulting in much greater proportion of the peptides circulating as prohormones.1 This finding in turn has stimulated closer evaluation of the enzymes and mechanisms responsible for natriuretic peptide activation.

Corin, a recently identified serine protease,2 is generally regarded as a major activator of natriuretic peptides, via cleavage from propeptide to active form of both ANP and BNP (although furin and dipeptidyl peptidase IV have also been shown to process BNP).3 Corin is synthesized as a zymogen, which in turn requires activation by cleavage of a conserved site. The corin activator has not been identified.2 Corin is highly expressed in cardiomyocytes, and its promoter shares many of the same transcription binding sites as ANP and BNP precursors, such as GATA-4.2 Thus, it could be predicted that corin and natriuretic peptides would be upregulated in response to similar stimuli.

To date there has been some interest in abnormalities of corin kinetics/activity in several forms of heart failure. In corin knock-out mice, there was spontaneous development of hypertension and increased left ventricular mass but no differences in left ventricle function.4 Corin-deficient mice have also been shown to develop heart failure rapidly in response to increased afterload.5 However, 2 separate studies have demonstrated significant upregulation of cardiac corin expression, in the setting of heart failure of ischemic origin6 and myotrophin overexpression-induced heart failure,7 respectively. Only 1 of these studies evaluated corin activity and found it unchanged despite the increased corin expression,7 suggesting that relative activity per unit protein expression is reduced. Yet, reduced plasma corin levels have been uniformly reported in heart failure patients, and reduction in plasma corin levels correlated with heart failure severity.8,9 Furthermore, in African Americans, corin variants with impaired natriuretic peptide processing activity have been associated with hypertension, cardiac hypertrophy, and poor clinical outcomes.10 These data suggest that corin defects may be an important contributing factor in hypertension and heart disease.

One of the possible ways of reconciling the discrepancy between observed increased cardiac expression of corin in most studies and reduced soluble corin levels in plasma is to examine what is known about the shedding of corin. It has been suggested that soluble plasma corin reflects the shedding of active cardiac corin to prevent excessive proteolytic activities on cardiomyocytes.2 Ectodomain shedding of corin is not completely understood: however, it has been shown that the metalloproteinase ADAM10 is responsible for cleaving corin producing a fragment that is active in plasma, whereas corin autocleavage produces smaller inactive fragments. If corin is indeed a key element in the pathogenesis of heart failure and a modulator of its severity, it is conceivable that some of the observed effects relate to the dysfunctional ectodomain cleavage of corin.

In this issue of Hypertension, Gladysheva et al11 evaluated effects of corin overexpression in a transgenic model of dilated cardiomyopathy (DCM) resulting from a phosphorylation-resistant cAMP response element-binding protein mutant. Interestingly and unexpectedly, the authors found that corin expression in this model of DCM was reduced. Overexpression of corin in wild-type mice did not produce any noticeable phenotype and was characterized only by increased pro-ANP to ANP cleavage. Crossing corin-overexpressing mice...
(corin-Tg) with DCM mice (DCM, corin-Tg) markedly attenuated heart failure phenotype, as evidenced by reduced myocardial fibrosis, improved contractile function, reduced alveolar edema and congestion, as well as prolonged survival. There was associated increased pro-ANP processing, with reduction in blood pressure and increased cGMP production, although BNP kinetics were not evaluated in detail. Thus it remains unclear what proportion of the observed beneficial effect of corin is secondary to its ANP versus BNP-activating effects. It is entirely possible that some of the improvements in cardiac contractility and reduced fibrosis seen in the DCM, corin-Tg mice are secondary to enhanced BNP processing. The hallmark finding of the study by Gladysheva et al is the demonstration that increasing corin expression (and presumably activity) is sufficient to ameliorate the heart failure phenotype in this model of heart failure. It further suggests that corin deficiency state dictates phenotype more so than the heart failure-inducing mutation.

This study raises important questions regarding mechanisms of action of corin and bases for corin deficiency in this and, perhaps, other models of heart failure. A critical issue is how corin deficiency plays such an important permissive role in the development of heart failure. This may be a phenomenon specific to this model or a more generalized finding applicable to other causes of heart failure. If the latter is true, manipulation of corin activation may indeed be important for the prevention or therapeutics of heart failure. At present, however, there is a lack of understanding how precisely corin is activated and regulated, and hence it is not known whether it is feasible to manipulate corin via nongenetic means.

The findings of the study by Gladysheva et al potentially place corin center-stage in the pathogenesis of heart failure, provided it can be determined that the same relationship between corin activity/expression and heart failure severity phenotype exists in humans. In view of these findings and the intriguing possibility that corin deficiency may be implicated in other disturbances of vascular constrictor tone such as preeclampsia, modulation of corin expression and activity becomes an attractive therapeutic target.

Disclosures
None.

References
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Hypertension. 2013;61:284-285; originally published online December 10, 2012;
doi: 10.1161/HYPERTENSIONAHA.112.196253
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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