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EDITORIAL COMMENT

Neprilysin and Heart Failure

A "Sympathetic" Relationship?*

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Understanding various neurohormonal pathways involved in the pathophysiology and progression of heart failure (HF) has led to development of proven strategies to reduce such complications of this morbid disease. Overactivation of the sympathetic nervous system is one such deleterious process in patients with HF and reduced ejection fraction (HFrEF); in this regard, beta-adrenergic blocking agents are the cornerstone for neuromodulation management of affected patients. Besides the pharmacologic blockade of catecholamine receptors, neuromodulation has been tried in other forms, such as renal sympathetic denervation, baroreflex activating therapy, vagal nerve stimulation, spinal cord stimulation, and left cardiac sympathetic denervation (1). Among these interventions, radiofrequency renal denervation (RDN) has received most attention.

RDN was initially designed as a therapy for resistant hypertension, but studies have been mixed relative to clinical benefit in this setting (2). As often happens in all fields of medicine, after failure comes the search for alternative opportunities, such is the case with RDN in HF. RDN reduces efferent and afferent signals, both of which are augmented and detrimental in HFrEF: the efferent signal, from the central nervous system to the kidney, leads to salt and water retention along with stimulation of angiotensin release, while increase in venous pressure and reduced kidney perfusion increase renal afferent nerve flow from the kidney to the central nervous system, resulting in harmful sympathetic overflow to the end organs, including the heart. Thus, RDN appeared a potential option to manage patients with HFrEF.

After the first "safety" experiment of RDN with 7 HFrEF patients (3), clinical data have remained limited to small studies; however, results of RDN in HFrEF suggest potential improvement in cardiac systolic function and remodeling parameters (4). Assumptions were that these cardiac benefits related to suppression of cardiac sympathetic activity and the inhibition of the renin-angiotensin-aldosterone system, as well as the decrease in preload and afterload resulting from amelioration of fluid retention and peripheral vasoconstriction.

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Until recently, little overlap between sympathetic nervous system tone and other deleterious pathways in HFrEF was suspected. However, in the current issue of the *Journal*, Polhemus et al. (5) suggest a new relationship between the sympathetic nervous system, RDN, and neprilysin function. In an experimental model of HFrEF due to myocardial infarction, Polhemus et al. found RDN improves left ventricular systolic function and myocardial fibrosis, which is not a novelty. However, their mechanistic findings are very provocative because they link sympathetic activity with neprilysin activity.

Neprilysin is a ubiquitous enzyme involved in degradation of numerous vasoactive peptides, notably including natriuretic peptides (NP). The readership is well aware of the recent data indicating substantial mortality reduction associated with use of neprilysin inhibition in patients with HFrEF (6).

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Use of sacubitril-valsartan in the PARADIGM-HF (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure) trial was superior to enalapril, yet the mechanism of benefit from the drug remains unclear. The most probable hypothesis is inhibiting neprilysin reduces clearance of favorable biologically active NP such as B-type natriuretic peptide (BNP) along with other vasoactive peptides, leading to their increase, with concomitant reduction in the inactive amino-terminal portion of the peptide (N-terminal pro-B-type natriuretic peptide [NT-proBNP]) (7). The response of BNP to sacubitril-valsartan therapy is similar to that observed by Polhemus et al. (5): following RDN, circulating noradrenaline and neprilysin activity in kidney were reduced, whereas BNP concentrations increased and NT-proBNP did not, with no change in the myocardial expression of NP; these results suggest RDN had a "sacubitril-like effect," leading to reduced clearance of biologically active BNP after release.

Polhemus et al. (5) extended their findings, examining effects of bisoprolol, a selective beta-1 receptor blocker, administered orally in the same model. Curiously, bisoprolol mimicked effects of RDN, which indirectly suggests that the benefits of beta-blockers might, at least in part, lie in their inhibition of neprilysin activity. This surprising finding becomes somewhat more plausible when examining seemingly contradictory findings with respect to effects of beta blockade on cardiovascular peptide production (8,9). Although other evidence-based therapies in HFrEF cause BNP concentrations to fall, beta-blockers may initially increase NP concentrations, which typically do not reflect clinical decompensation (8). Much as chronic sacubitril-valsartan leads to gradual reduction in BNP concentrations (presumably due to reduced release), sustained beta-blocker therapy also reduces BNP chronically (9). In hypertensive rats, carvedilol was associated with increased levels of plasma atrial natriuretic peptide (ANP) despite decreased cardiac overload and no change in the myocardial RNA expression levels (10). When exogenous ANP was administered, the biological half-life was prolonged in the carvedilol group compared with that in the control group. Last, an early increase in BNP has been described more frequently with non-vasodilating beta-blockers and among patients with lower baseline BNP values, which could in fact be a reflection of higher neprilysin activity (11,12). For example, in HFrEF patients after metoprolol administration, ANP and BNP concentrations rose sharply (at 5 and 24 h) with no evident relationship with hemodynamic changes (13).

Although these contradictory increases in NP had been related to down-regulation of the NP receptor-C (one of the clearance pathways), a role for neprilysin was not evaluated or considered. The data from Polhemus et al. (5) open a new path of investigation regarding benefits of beta blockade and RDN as well as a therapeutic strategy for HFrEF.

It is necessary to point out in the model by Polhemus et al. (5) RDN had effects well beyond simple neprilysin inhibition. RDN was also associated with a reduction in angiotensin II concentration, which makes neprilysin inhibition unlikely to be the sole benefit of this procedure, as angiotensin II is a substrate for neprilysin and should have risen if inhibition of this pathway was the only benefit. Additionally, improved vasodilatory response in the aorta was noted. Therefore, RDN was closer to the balanced effects seen during combined sacubitril-valsartan therapy. Indeed, oral administration of sacubitril leads to higher BNP concentrations, but also augmented circulating angiotensin II, impaired vascular relaxation, and led to no improvement in left ventricular ejection fraction. It is well accepted that neprilysin inhibition must, therefore, be combined with an agent to block the angiotensin II receptor type 1 receptor while the angiotensin II receptor type 2 is free to favorably interact with the excess of angiotensin II (14).

The mechanistic findings presented by Polhemus et al. (5) are relevant, not only for supporting RDN as a promising therapy in HFrEF, but also in that they reveal a relationship between the sympathetic system and neprilysin activity might have been "hidden" within the pathophysiology of HF. Of course questions remain. The study does not explain the pathophysiology of this regulation. Regulatory feedback involving beta receptors is the most plausible explanation, but further studies are necessary to clarify this remaining question. Additionally, based on the findings of Polhemus et al., it would be expected that RDN therapy for HFrEF would lead to higher BNP concentrations, similar to the observed response in the experimental model. However, this is not the case: the few studies published evaluating RDN in HFrEF reported significant acute decrease in plasma concentrations of BNP (15,16).

Therefore, the study of Polhemus et al. (5) represents an outstanding hypothesis-driven study, that invite us to look forward to the results of ongoing randomized studies evaluating RDN in patients with HFrEF, as well as being aware that

neprilysin might be at the middle of all well-known players in HFrEF. While waiting for the results of such ongoing clinical trials, we encourage researchers to look on neprilysin with "sympathy" and to search for new mechanistic links within the pathophysiology of HF.

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