Sympathetic Signatures of Cardiovascular Disease
A Blueprint for Development of Targeted Sympathetic Ablation Therapies

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Sympathetic nervous system activity is increased in several cardiovascular diseases, including hypertension and heart failure (HF). Indeed, one classification of the severity of HF is based on the direct relationship between the plasma concentration of the sympathetic neurotransmitter, norepinephrine, and impaired cardiac function. Although the role of increased sympathetic nerve activity (SNA) in the pathogenesis of cardiovascular disease is still debated, it is now accepted that many of the pathologies common to several of these diseases, such as endothelial dysfunction, vascular and cardiac remodeling, and dysregulation of glucose metabolism, are linked to excessive activity of the sympathetic nervous system.

Pharmacological treatments for the deleterious effects of increased sympathetic nervous system activity have been in use for >50 years. These strategies have progressed from sympatholytic drugs used in the 1950s (eg, reserpine), which act peripherally to prevent the synthesis and release of norepinephrine from sympathetic nerve terminals, to α- and β-adrenergic receptor antagonists (eg, prazosin and atenolol, respectively), to centrally acting drugs (eg, clonidine), which reduce sympathetic nerve discharge by their actions in the brain. Although these drugs are effective to varying degrees in the treatment of cardiovascular diseases, such as hypertension and HF, they all act in a “global” manner and, therefore, are associated with unwanted adverse effects related to their cardiovascular and noncardiovascular actions.

Over the last 20 years it has become clear that the idea that sympathetic activity is either increased or decreased in various physiological and pathophysiological states is an oversimplification. Rather, the pattern of SNA to individual targets, such as the heart, kidneys, splanchnic organs, and skeletal muscle, is differentially controlled such that SNA to one target may increase, whereas SNA to another may be decreased or unchanged. This was first suggested by studies in anesthetized animals in which the response of SNA to acute stimuli was directly recorded using electrodes implanted on sympathetic nerves innervating different end organs. These experiments initiated the concept of state-specific “sympathetic signatures” in that the pattern of SNA to various organs under one condition, such as hypoglycemia, was different than that observed under another condition, such as hemorrhage.

The extent to which a sympathetic signature exists under chronic conditions has been nearly impossible to establish by direct SNA recordings because of the difficulty of maintaining high-fidelity nerve signals in conscious chronically instrumented animals over long periods of time. Until recently, the strongest support for the sympathetic signature concept in disease states came from studies in humans by Esler and others in which they measured renal and cardiac norepinephrine spillover as a surrogate for SNA in HF subjects. These indirect measures suggested a preferential activation of SNA to the heart, whereas SNA to the kidneys and skeletal muscle (measured by microneurography) were normal (see Figure).

In this issue of Hypertension, Ramchandra et al report the findings of their study in which they directly measured cardiac and renal SNA simultaneously in conscious chronically instrumented sheep with HF induced by rapid ventricular pacing. At the present time, this is the only laboratory capable of conducting these critical but technically challenging experiments. As described in their report, previous studies from their group have shown that, in this ovine model of HF, there is a profound increase in cardiac SNA in contrast to renal SNA, which does not increase (see Figure). These findings are extended in the present study in which they test the hypothesis that cardiac SNA is elevated secondary to activation of angiotensin type 1 receptors in the brain. Consistent with this hypothesis, intracerebroventricular administration of the angiotensin type 1 receptor antagonist losartan, reduced both cardiac SNA and heart rate in HF sheep but had no effect on renal SNA in HF sheep. Moreover, ICV losartan had no effect on cardiac or renal SNA in normal sheep. Overall, the findings of Ramchandra et al clearly show that the sympathetic signature of the ovine model of pacing-induced HF is characterized by increased cardiac, but not renal, SNA, and this is because of activation of brain angiotensin type 1 receptors. Thus, in addition to providing indisputable direct evidence for increased SNA to the heart, but not the kidneys, in a model of HF, this study also provides insight into the brain mechanisms that may determine this particular sympathetic signature. More importantly, they also demonstrate that it is feasible to specifically block cardiac SNA in this HF model by central administration of losartan.

The significance of these findings is that new therapies designed to treat the adverse effects of increased sympathetic activity in HF may be directed to cardiac SNA specifically. Although β-blockers are one pharmacological therapy that is
prescribed to block sympathetic actions on the heart, they are not cardiac specific, because they block renin release from the kidney and may also act centrally to inhibit global sympathetic outflow. These noncardiac-specific effects of β-blockers may result in unwanted adverse effects, such as orthostatic hypotension.

Other cardiovascular diseases may not exhibit a sympathetic signature in which SNA to the heart is the primary feature. For example, recent studies using direct and indirect measures of organ-specific SNA in a rodent model of salt-sensitive hypertension, the Ang II-salt model, also suggest a disease-specific sympathetic signature (see Figure). However, this model of neurogenic hypertension exhibits a selective activation of SNA to the splanchnic resistance and capacitance vessels. In contrast, hypertension in this model is not associated with increased SNA to the kidneys, skeletal muscle, or heart. Similar to developing a targeted sympathetic blockade strategy for the ovine HF model aimed at cardiac SNA, this model of hypertension suggests that targeting the SNA to the splanchnic vascular bed would be an effective therapeutic strategy.

The ability to selectively ablate SNA to a single vascular bed or region of the body is now feasible using a device-based approach, as demonstrated by recent reports of renal nerve ablation for the treatment of drug-resistant hypertension in humans. Interestingly, in addition to the kidney, this procedure appears to reduce SNA to nonrenal targets, as suggested by a case report in which skeletal muscle SNA was reduced after renal nerve ablation and a recent study demonstrating decreases in both plasma glucose and insulin levels after the procedure. Although the mechanisms mediating what appear to be “nonrenal” effects of renal nerve ablation in humans with drug-resistant hypertension are not clear, these observations demonstrate that targeted sympathetic ablation therapies have enormous potential in the treatment of several disorders associated with excessive sympathetic activity.

The emergence of the “disease-specific sympathetic signature” concept, combined with the ability to use a device-based approach to perform targeted sympathetic ablation in humans, has opened a new door for the treatment of cardiovascular and metabolic diseases in which the deleterious effects of increased activity of the sympathetic nervous system are a contributing factor. The elegant studies by Ramchandra et al reported in this issue of Hypertension have firmly established the concept that a sympathetic signature provides an ideal blueprint for the development of novel targeted sympathetic ablation therapies. Their studies strongly suggest that, in addition to renal nerve ablation, novel therapies for cardiac-specific sympathetic ablation may be an important new area of discovery (Figure).

**Sources of Funding**

This work was supported by National Heart, Lung, and Blood Institute grant R01 HL64176 (to J.W.O.).
Disclosures

J.W.O. is a consultant for Medtronic CardioVascular.

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Hypertension. 2012;59:545-547; originally published online February 6, 2012; doi: 10.1161/HYPERTENSIONAHA.111.182899
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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