Sympathetic Nervous System and Hypertension

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Recent Advances in Hypertension

With the development and implementation of device-based therapeutic interventions to decrease renal and systemic nerve activity in patients with resistant hypertension, there has been an increase in research dealing with the role of the sympathetic nervous system in hypertension. These interventions have produced substantial decreases in blood pressure in patients wherein pharmacological treatments, including agents which inhibit the effects of the renin–angiotensin–aldosterone system, have failed serves to confirm and reassert the essential role of the sympathetic nervous system in hypertension. This review will encompass recent publications dealing with the sympathetic nervous system and hypertension, focusing on those recently published in Hypertension.

Sympathetic Activation in Animal Models

Obesity-Related Hypertension

Although there has been a debate as to whether sympathetic activation is a cause or consequence of obesity, the studies noted below support the view that it is the obesity that leads to sympathetic activation. The importance of this sympathetic activation for the development of the hypertension is supported by the finding that renal denervation prevents the development of obesity hypertension in the dog.

Studies have now focused on the developmental phase of obesity hypertension regarding the renal sympathoexcitation. In rabbits fed high-fat diets, body weight, plasma insulin and leptin concentrations, mean arterial pressure, heart rate, and renal sympathetic nerve activity were all increased after 1 week. Mean arterial pressure and body weight continued to increase over 3 weeks of high-fat diet, whereas heart rate and renal sympathetic nerve activity did not change further. Arterial baroreflex control of renal sympathetic nerve activity was attenuated from the first week of the high-fat diet. Excitatory responses to air jet stress diminished over 3 weeks of high-fat diet. Resumption of normal diet normalized glucose, insulin, leptin, and heart rate, but body weight, visceral fat content, mean arterial pressure, and renal sympathetic nerve activity remained elevated. Increased renal sympathetic nerve activity and its impaired baroreflex control, which occur with 1 week of high-fat feeding, seem integral to the rapid development of obesity hypertension. Increased plasma leptin and insulin may contribute to the initiation of hypertension but are not required for maintenance of the hypertension, which is related to the sustained increase in renal sympathetic nerve activity. As the air jet stress response is transduced by hypothalamic neurons, the authors speculate that this site is involved in the maintenance phase of the hypertension with a sustained increase in renal sympathetic nerve activity.

The early effects of diet-induced fat accumulation on lumbar sympathetic nerve activity were also examined in rats over 15 days. Increases in brown and white adipose tissue (but not body weight) were accompanied by increases in plasma leptin (but not glucose) concentration and heart rate; however, mean arterial pressure was not significantly changed compared with control rats. Increases in lumbar sympathetic nerve activity became significant at day 12. In relation to other studies of high-fat feeding in rats where increased renal sympathetic nerve activity and mean arterial pressure were observed after 8 to 20 weeks on the diet, it seems likely that sympathetic activation precedes the increase in mean arterial pressure.

Capsaicin-stimulated afferent nerve activity from white adipose tissue increases renal sympathetic nerve activity, mean arterial pressure, and activates the paraventricular nucleus (adipose afferent reflex). Lidocaine inhibition of neurons in the paraventricular nucleus abolishes the adipose afferent reflex. In high-fat diet obese hypertensive rats, basal- and capsaicin-stimulated afferent nerve activity from white adipose tissue were found to be increased as compared with controls. Sensory denervation of white adipose tissue or injection of a leptin antagonist into white adipose tissue decreased renal sympathetic nerve activity and produced a prolonged reduction in mean arterial pressure; these responses were greater in obese hypertensive rats than controls. In obese hypertensive rats, lidocaine inhibition of the paraventricular nucleus decreased renal sympathetic nerve activity and mean arterial pressure. It seems that both tonic and stimulated afferent nerve activity from white adipose tissue serve to increase renal sympathetic nerve activity via a central pathway involving the paraventricular nucleus. This renders visceral fat a potentially treatable candidate for one possible source of increased renal sympathetic nerve activity.

There is a recurrent theme here of the visceral fat serving as a stimulus for sympathoexcitation. In the rabbit study,1 the continued elevation of mean arterial pressure and renal sympathetic nerve activity was associated with continued increase in visceral fat. The increase in lumbar sympathetic nerve activity occurred together with an increase in brown and white adipose tissue, whereas body weight was not significantly changed.2 The

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adipose afferent reflex study offers direct measurements of tonic sympathoexcitation originating from white adipose tissue.\textsuperscript{3}

**Angiotensin II Hypertension**

The issue of whether angiotensin II infusion increases renal sympathetic nerve activity was clarified in studies in conscious rabbits consuming a high NaCl diet.\textsuperscript{4} Using a low dose of angiotensin II, mean arterial pressure slowly increased to day 7; thereafter, it was relatively stable through day 21. Renal sympathetic nerve activity was unchanged until day 17, after which it increased to a level that became statistically significantly different from the controls on day 21. This protocol, minimizing the effect of arterial baroreflex inhibition of renal sympathetic nerve activity, indicates that angiotensin II does increase renal sympathetic nerve activity but, although speculated, the extent to which this contributes to the maintenance of angiotensin II hypertension requires further clarification.

**Device-Based Reductions in Sympathetic Nerve Activity for the Treatment of Hypertension**

**Selective Catheter-Based Renal Sympathetic Denervation**

Catheter-based renal denervation consists of delivering radiofrequency energy to the renal artery wall from within the vascular lumen. This results in a thermal injury to the renal nerves, which lie within and external to the renal artery wall. Renal denervation is verified by substantial reductions in renal tissue norepinephrine concentration in animal studies and decreases in the spillover of norepinephrine into the renal vein in human studies. This technology proceeded directly from the background knowledge that renal denervation prevents, reverses, or ameliorates the severity of hypertension in diverse models of experimental animal hypertension in many different species\textsuperscript{5} and that renal norepinephrine spillover is increased in human essential hypertension.\textsuperscript{6} Efficacy and safety in resistant hypertensive patients were demonstrated in an initial observational proof of concept study\textsuperscript{7} (Symplicity HTN-1) and verified in a subsequent randomized controlled clinical trial\textsuperscript{8} (Symplicity HTN-2).

As with most therapies, there is concern about the durability of the treatment effect. The Symplicity HTN-1 Investigators enlarged the initial cohort from 45 to 153 resistant hypertensive patients who were followed up for a minimum of 2 years.\textsuperscript{9} Baseline mean office blood pressure was 176/98 mm Hg, while consuming an average of 5 antihypertensive medications. Postrenal denervation office blood pressures were reduced by 20/10, 24/11, 23/11, 26/14, and 32/14 mm Hg, respectively, at 1, 3, 6, 12, 18, and 24 months, respectively. The intervention was free of complications in 97% of patients (149 of 153). Thus, in patients with resistant hypertension, catheter-based renal sympathetic denervation resulted in a substantial reduction in blood pressure, which was sustained for a minimum of 2-year follow-up in the absence of significant adverse events.

In association with the sustained reduction in blood pressure, additional benefit was observed in terms of improvement in health-related quality of life.\textsuperscript{10} There was improvement in several items on the 36-Item Short-Form Health Survey and the Mental Component Summary. However, this improvement was not directly associated with the magnitude of the blood pressure reduction.

Obstructive sleep apnea has a very high prevalence in resistant hypertension, and obstructive sleep apnea-mediated sympathetic activation likely contributes to increased blood pressure and blood pressure resistance to pharmacological treatment. Six months after renal denervation, 8 of 10 patients with resistant hypertension and obstructive sleep apnea showed a decrease in apnea–hypopnea index from 16.3 to 4.5 events/h.\textsuperscript{11} This was accompanied by significant decreases in blood pressure, plasma glucose concentration, and hemoglobin A1c. Given the major effect of increased renal sympathetic nerve activity to increase renal tubular sodium reabsorption throughout the nephron,\textsuperscript{2} the speculated mechanism focusing on regulation of sodium-volume status with greater shifts of fluid from the legs to the neck during overnight recumbency in resistant hypertension patients compared with those with controlled hypertension seems reasonable.\textsuperscript{12}

Obstructive sleep apnea is also associated with large increases in blood pressure and cardiac arrhythmias in relation to the apnea episodes. In a porcine model of obstructive sleep apnea (tracheal occlusion), renal denervation prevented the postapneic increase in blood pressure, attenuated the shortening in atrial effective refractory period, and decreased the ability to induce atrial fibrillation.\textsuperscript{13} The study emphasizes the ability of renal denervation to modulate the autonomic control of the heart leading to a decrease in the generation of atrial arrhythmias during experimental obstructive sleep apnea.

Increased renal resistive index and urinary albumin excretion are indicators of renal vasoconstriction via increased renal sympathetic nerve activity and hypertensive renal (glomerular) damage. The effects of renal denervation on renal hemodynamics, renal function, and urinary albumin excretion were examined in 100 consecutive resistant hypertensive patients.\textsuperscript{14} Renal denervation decreased blood pressure, renal resistive index, and incidence of albuminuria without adversely affecting glomerular filtration rate or renal artery structure over 6 months and seems to be a safe and effective therapeutic approach to reduce blood pressure in patients with resistant hypertension. The results support the importance of increased sympathetic nervous system activity, in this case likely involving both afferent and efferent renal nerves, in hypertension and associated renal disease.

Sympathetic activation seems ubiquitous in chronic kidney disease, contributes to progression of chronic kidney disease, and is associated with adverse cardiovascular outcomes. To demonstrate that renal denervation is effective and safe in patients with chronic kidney disease, renal denervation was performed in 15 chronic kidney disease patients (stages 3–4) with resistant hypertension whose average estimated glomerular filtration rate was 31 mL/min (range, 15–43) and blood pressure 174/91 mm Hg at baseline.\textsuperscript{15} At 3 and 6 months, there was no change in estimated glomerular filtration rate, 33 and 29, respectively, whereas blood pressure was significantly decreased, 147/77 and 145/77, respectively. Given the added difficulty of managing resistant hypertension in chronic kidney disease patients and the critical importance of doing so,
the demonstration of both efficacy and safety in this population is most promising.

Given the relationship between increased sympathetic nervous system activity and insulin resistance, the effect of renal denervation on glucose metabolism was examined in resistant hypertensive patients. At both 3 and 6 months, the renal denervated patients exhibited significant decreases in systolic and diastolic blood pressure and fasting concentrations of glucose, insulin, and C-peptide. In addition, the homeostasis model assessment–insulin resistance index was significantly decreased. It was suggested that sympathoinhibition with decreased norepinephrine release has a beneficial effect on both regional hemodynamics (blood flow dependency of glucose uptake) and cellular glucose transport. In this regard, it is known that sympathetic activation shifts blood from more insulin-sensitive striated skeletal muscle to less insulin-sensitive visceral tissue and increases glucagon secretion.

Therefore, reductions in sympathetic nervous system activity would be expected to improve glucose homeostasis. This view is supported by the findings that moxonidine, a centrally acting sympathoinhibitory agent, improves glucose homeostasis.

The polycystic ovary syndrome is associated with hypertension, insulin resistance, and increased activity of the sympathetic nervous system. Two patients with polycystic ovary syndrome presented with hypertension markedly increased muscle sympathetic nerve activity and total body norepinephrine spillover. Renal denervation lowered blood pressure, muscle sympathetic nerve activity and total body norepinephrine spillover and improved insulin sensitivity. In 1 patient who had been amenorrheic for 3 years, regular menses returned 6 weeks after renal denervation. That renal denervation elicited favorable responses in diverse aspects of the polycystic ovary syndrome underscore the importance of increased sympathetic nervous system activity in the pathophysiology of the syndrome.

The earlier observations that renal denervation led to decreased generalized sympathetic nerve activity have been confirmed. In 25 patients with resistant hypertension, renal denervation decreased blood pressure, multi-unit and single unit muscle sympathetic nerve activity at 3 months. All features of single unit muscle sympathetic nerve activity were decreased: firing rate, firing probability, and incidence of multiple spikes. These findings emphasize the importance of interrupting excitatory afferent renal nerve pathways to the brain in mediating the generalized sympathoinhibition and blood pressure reduction.

Reduction in hypertension target organ damage is an important goal in the long-term management of hypertensive patients. Renal denervation, in addition to decreasing blood pressure in patients with resistant hypertension, significantly decreased left ventricular mass index and mean interventricular septum thickness. There were improvements in markers of both systolic function (left ventricular end systolic volume and left ventricular ejection fraction) and diastolic function (left ventricular filling pressures and isovolumic relaxation time).

Not unexpectedly, variable results with renal denervation have come forth. In 13 resistant hypertensive patients, renal denervation did not result in any change in blood pressure or muscle sympathetic nerve activity. It seems likely that an important issue is the variability among patients with resistant hypertension which, unavoidably in studies of few patients, is reflected in patient selection. In these patients, both the baseline levels of blood pressure and muscle sympathetic nerve activity were lower than in several other studies, wherein renal denervation successfully decreased both blood pressure and muscle sympathetic nerve activity. This is further complicated by the fact that the exact pathogenetic coupling between the level of muscle sympathetic nerve activity and the level of blood pressure is not known. Will resistant hypertensive patients with lower (or even normal) levels of muscle sympathetic nerve activity be less responsive to renal denervation? In patients with resistant hypertension and increased muscle sympathetic nerve activity, will renal denervation produce concordant changes in muscle sympathetic nerve activity and blood pressure? The issue of adequate renal denervation is always problematic. The lack of an immediate readout (eg, servo-feedback) to confirm the success and extent of the renal denervation procedure has plagued biotechnological development in this area. Currently, renal tissue norepinephrine concentration stands as the gold standard; however, this is not immediate and, although straightforward in animal studies, is not clinically applicable. Renal vein norepinephrine spillover is the gold standard for human investigation but is complex (involving radioisotope), invasive (renal vein catheterization), and not immediate.

The therapeutic response to renal denervation, which involves interruption of both efferent and afferent renal nerves, has led to a growing interest in the function of the afferent renal nerves. It is known that there is an interaction between afferent and efferent renal nerve activity whereby increased afferent renal sympathetic nerve activity increases efferent renal nerve activity which, in turn, via a renorenal reflex (negative feedback) decreases efferent renal sympathetic nerve activity. The overall goal is to maintain efferent renal sympathetic nerve activity at a low level so as to facilitate renal sodium excretion.

The renorenal reflex response is impaired in spontaneously hypertensive rats, likely contributing to their increased basal level of efferent renal sympathetic nerve activity. This impairment was found to be dependent on increased activation of renal α-2 adrenoceptors and angiotensin II type 1 receptors.

The afferent renal nerve fibers express TRPV1 receptors and release substance P. Systemic administration of a neurokinin 1 receptor antagonist increased efferent renal sympathetic nerve activity in the basal state and after it had been suppressed by renal arterial administration of the TRPV1 receptor agonist capsaicin. Whereas it was proposed that the afferent renal nerves mediate a tonic inhibition of renal sympathetic nerve activity, the systemic administration of the neurokinin 1 antagonist does not allow precise identification of either the site of release of neuropeptide or the site of the neurokinin 1 receptor being blocked.

With renal denervation both efferent renal sympathetic nerve activity and afferent renal nerve activity are decreased. The effects of decreasing efferent renal sympathetic nerve activity on the kidney are decreased activity of the renin–angiotensin–aldosterone system, decreased renal vasoconstriction supporting normal levels of renal blood flow and glomerular filtration.
rate, and decreased renal tubular sodium reabsorption with a favorable leftward shift of the pressure natriuresis relationship. All of these are capable of contributing to a decrease in blood pressure. The effect of decreasing afferent renal nerve activity is a reduction in afferent excitatory input to the neuraxis with the consequence of decreased peripheral sympathetic nerve activity to the resistance vasculature (decreased total peripheral resistance), the heart (decreased cardiac output), and to the kidneys (with favorable effects as noted above). As will be noted below, carotid baroreflex activation decreases peripheral sympathetic nerve activity, which is under the control of the carotid sinus baroreceptor, likely achieving similar effects on the resistance vasculature, the heart, and the kidneys.

Regarding clinical usage, renal denervation is being widely performed in virtually all countries outside the United States. Symplicity HTN-3 is multi-center, prospective, single-blind, randomized controlled study of the safety and effectiveness of bilateral renal denervation in subjects with uncontrolled hypertension. Estimated enrollment is 530 patients with 87 centers in the United States, and estimated primary completion date is March 2013 (NCT01418261 at http://clinicaltrials.gov). The results of this study will be influential about the decision of the United States Food and Drug Administration on clearance/approval for use in the United States.

**Carotid Baroreflex Activation**

Carotid baroreflex activation affects peripheral sympathetic nerve activity that is under the control of the carotid sinus baroreceptor. Decreases in systemic sympathetic nervous system activity have been achieved by placement of stimulating electrodes around the carotid sinus baroreceptors. Chronic baroreflex activation produces sustained decreases in blood pressure and peripheral sympathetic nerve activity.\(^2\) Obesity-induced hypertension in dogs is completely prevented by prior renal denervation.\(^2\) The effects of chronic baroreflex activation and bilateral surgical renal denervation were compared in obesity-induced hypertension.\(^2\) Both chronic baroreflex activation and bilateral surgical renal denervation decreased blood pressure and plasma renin activity. However, chronic baroreflex activation also decreased plasma norepinephrine concentration, tachycardia, and glomerular hyperfiltration, while increasing fractional sodium excretion. In contrast, glomerular filtration rate increased further after renal denervation. Thus, the additional effects of chronic baroreflex activation on heart rate and glomerular filtration may provide additional benefits in obesity-induced hypertension. The explanation offered for the decrease in glomerular filtration rate during chronic baroreflex activation was increased activity of the tubuloglomerular feedback system via increased macula densa sodium delivery derived from decreased neurogenically regulated proximal tubular sodium reabsorption. The increase in glomerular filtrate rate after renal denervation was speculated to be owing to a greater decrease in preglomerular arteriolar resistance secondary to a larger reduction in renal sympathetic nerve activity with renal denervation than with chronic baroreflex activation. Although properly performed renal denervation should reduce efferent renal sympathetic nerve activity to zero, measurements of efferent renal sympathetic nerve activity during chronic baroreflex activation will be required to support this conjecture. Whereas the decrease in plasma norepinephrine concentration was taken to represent a decrease in systemic sympathetic nerve activity, it must be remembered that plasma norepinephrine concentration is dependent on both norepinephrine release and norepinephrine plasma clearance. There are a variety of circumstances that change the rate at which norepinephrine is removed from plasma, rendering the measurement of plasma norepinephrine concentration unsuitable as an index of norepinephrine release and systemic sympathetic nerve activity.

The cardiovascular effects of chronic baroreflex activation alone and in combination with amlodipine were compared under normotensive conditions.\(^2\) Chronic baroreflex activation alone decreased blood pressure, plasma renin activity, and glomerular filtration rate. Amlodipine alone decreased blood pressure and increased plasma renin activity, but glomerular filtration rate was unchanged. During amlodipine administration, chronic baroreflex activation no longer decreased glomerular filtration rate. Thus, the blood pressure–lowering effects of chronic baroreflex activation are related to decreased renal sympathetic nerve activity, which, in turn, decreases sodium reabsorption in all renal tubular segments before the macula densa with resultant tubuloglomerular feedback mediated afferent arteriolar constriction and reduced glomerular filtration rate. Amlodipine, by dilating the preglomerular vasculature, prevented the decrease in glomerular filtration rate.

**Carotid Body Modulation**

As the main peripheral chemoreceptor, the carotid body senses hypoxia and hypercapnia with resultant hyperventilation, sympathetic activation, and increased arterial pressure. The peripheral chemoreceptor reflex has been found to be enhanced in spontaneously hypertensive rats and hypertensive patients. Carotid sinus denervation (denervation of both carotid body and carotid sinus baroreceptors) prevented the development of hypertension in young prehypertensive spontaneously hypertensive rats and significantly decreased arterial pressure in adult hypertensive spontaneously hypertensive rats. With denervation of the carotid sinus baroreceptors, an increase in arterial pressure might have been expected. However, the aortic baroreceptors were intact, and the arterial pressure decrease supports the view that the peripheral chemoreceptor reflex is hypersensitive in spontaneously hypertensive rats. The decrease in arterial pressure was accompanied by a decrease in sympathetic vasomotor tone (blood pressure response to ganglionic blockade). Carotid body modulation in the form of carotid body excision is being evaluated for treatment of patients with cardiac failure (NCT01653821 at http://clinicaltrials.gov) and hypertension (NCT01729988 at http://clinicaltrials.gov).

**Disclosures**

Dr DiBona has served as a consultant for Medtronic, Cardiosonic, Kona, Ablative Solutions, Abbott Vascular, CVRx, and NeuroAblation.

**References**


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