Translational medicine: the antihypertensive effect of renal denervation

Gerald F. DiBona and Murray Esler

1University of Iowa Carver College of Medicine and Veterans Administration Medical Center, Iowa City, Iowa; and 2Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia

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DiBona GF, Esler M. Translational medicine: the antihypertensive effect of renal denervation. Am J Physiol Regul Integr Comp Physiol 298: R245–R253, 2010. First published December 2, 2009; doi:10.1152/ajpregu.00647.2009.—Translational medicine is concerned with the translation of research discoveries into clinical applications for the prevention, diagnosis, and treatment of human diseases. Here we briefly review the research concerning the role of the renal sympathetic nerves (efferent and afferent) in the control of renal function, with particular reference to hypertension. The accumulated evidence is compelling for a primary role of the renal innervation in the pathogenesis of hypertension. These research discoveries led to the development of a catheter-based procedure for renal denervation in human subjects. A proof-of-principle study in patients with hypertension resistant to conventional therapy has demonstrated that the procedure is safe and produces renal denervation with sustained lowering of arterial pressure.

Physiological Effects of Alterations in RSNA

The effects of alterations in RSNA on various renal functions were examined following both increases and decreases in RSNA (11). In acute experimental studies, RSNA could be increased via direct electrical stimulation of renal sympathetic nerves or totally eliminated by renal denervation. Physiological increases or decreases in RSNA could be achieved via actions on a variety of cardiovascular reflexes.

Increased RSNA results in increases in renin secretion rate (RSR), increased renal tubular sodium reabsorption with antinatriuresis, and renal vasoconstriction. These responses are dependent on the level of RSNA (Fig. 1) and effector-specific adrenoceptors (Fig. 2). At the lowest level, there is increased RSR in the absence of changes in urinary sodium excretion, RBF, or glomerular filtration rate (GFR). The RSR response is mediated by $\alpha$-1 adrenoceptors located on renal-containing juxtaglomerular granular cells. At a slightly higher level of RSNA, the increase in RSR is accompanied by an antinatriuresis, still with unchanged RBF and GFR. The increased renal tubular sodium reabsorption and antinatriuresis are mediated by $\beta$-1 receptors located on the basolateral membrane of renal tubular epithelial cells in the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct. At the highest level of RSNA, there is increased RSR, antinatriuresis, and a decrease in both RBF and GFR.

The renal vasoconstriction is mediated by $\alpha$-1a receptors located on the vascular smooth muscle cells of the intrarenal resistance vasculature. These findings establish the important concept that subvasoconstrictor levels of RSNA can produce increased RSR and renal sodium retention (without changes in overall renal hemodynamics), which could contribute to renal sodium retaining disease states such as congestive heart failure and hypertension.

Conversely, decreases in RSNA result in renal functional responses that are opposite to those following increases in RSNA. Acute renal denervation, generally performed during anesthesia and surgery wherein the basal level of RSNA is increased, result in decreases in RSR and renal tubular sodium...
reabsorption with natriuresis and increases in RBF. In conscious animals, reflex decreases in RSNA result in decreases in RSR and renal tubular sodium reabsorption with natriuresis without alterations in RBF or GFR. These data indicate that the basal level of RSNA, while relatively low, has a tonic effect on RSR and renal tubular sodium reabsorption. In addition, decreases in RSNA attenuate the RSR response to other known stimuli for renin secretion, i.e., decreased arterial pressure and diuretic administration. An obligatory requirement for intact renal innervation to achieve sodium balance is observed under conditions of marked dietary sodium restriction.

At the cell signaling level, in the intrarenal resistance vasculature norepinephrine released from renal sympathetic nerve terminals binds to α-1a adrenoceptors with subsequent activation of phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) to inositol trisphosphate (IP3) and diacylglycerol (DAG). In turn, DAG can activate PKC, resulting in vascular smooth muscle cell contraction, and IP3 results in increased intracellular calcium concentration with subsequent activation of myosin light chain kinase resulting in vascular smooth muscle cell contraction.

In renal tubular segments, the activity of various transporters is increased by norepinephrine: Na+/H+ exchanger (NHE)1, NHE3 and sodium bicarbonate cotransporter (NBC) in proximal tubule; Na-K-2Cl cotransporter (NKCC2) in thick ascending limb of Henlé’s loop; and Na-K-ATPase throughout the nephron. In renal tubular epithelial cells, α-1b adrenoceptor stimulation activates multiple signaling pathways. Activation of G\(_{\alpha_i}\) engages PKC-dependent pathways, which increase the activity of basolateral NHE1. Activation of a PKC-independent MAPK pathway increases the activity of apical NHE3. Activation of the PLC-PIP\(_2\)-IP\(_3\) pathway raises intracellular calcium concentration and increases the activity of calcineurin (protein phosphatase 2B), which dephosphorylates and thereby increases the activity of Na-K-ATPase.

In renin-containing juxtaglomerular granular cells, β-1 adrenoceptor stimulation activates G\(_{\beta\gamma}\), which increases adenylate cyclase and cAMP concentration leading to PKA activation and exocytic renin release.

**Role of RSNA in Experimental Hypertension**

A major hypothesis for the development of hypertension is that abnormal renal function is critical for the initiation, development, or maintenance of primary hypertension (8). The maintenance of sodium and water balance by the kidneys is believed to be primary in long-term control of arterial pressure. An increase in arterial pressure leads to an increased urinary sodium and water excretion (pressure natriuresis and diuresis) with consequent reduction of blood volume and cardiac output until arterial pressure is returned to normal. In hypertension, it is hypothesized that factors disrupt the maintenance of sodium and water balance by the kidneys such that an elevated arterial pressure is required to reestablish and maintain normal sodium and water balance.

Several types of renal dysfunction could contribute to the development of hypertension, including increased renal vascular resistance, increased renal retention of sodium and water, and increased release of renin, catecholamines, or other vasoactive substances. Overall, increased RSNA results in increased RSR, increased renal tubular sodium reabsorption and renal sodium retention, and decreased GFR and RBF with increased renal vascular resistance. Thus, increased RSNA was noted to represent an important candidate as a mediator of the abnormal renal function with impaired pressure diuresis and natriuresis deemed essential for the development and maintenance of hypertension.

In this regard, renal denervation was demonstrated to reset the pressure diuresis and natriuresis mechanism such that urinary water and sodium excretion is greater at every level of renal perfusion pressure (arterial pressure) in the denervated vs. the innervated state (Fig. 3, Ref. 44).

There are several important steps linking increased RSNA, the prohypertensive renal actions of increased RSNA and experimental hypertension. Investigators attempted to induce hypertension experimentally by renal nerve stimulation or the surrogate maneuver of renal arterial infusion of norepinephrine.

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**Fig. 1.** The relationship between renal nerve stimulation (RNS) frequency and maximum response of renin secretion rate (RSR) (increase), urinary sodium excretion (decrease) and renal blood flow (RBF) (decrease). [From DiBona GF (10a).]

**Fig. 2.** Effects of increased renal sympathetic nerve activity (RSNA) on the 3 renal neuroeffectors: the juxtaglomerular granular cells (JGGC) with increased RSR via stimulation of β-1 adrenoceptors (β-1-AR), the renal tubular epithelial cells (T) with increased renal tubular sodium reabsorption and decreased urinary sodium excretion (\(U_{Na}\), V) via stimulation of α-1b-AR, and the renal vasculature (V) with decreased RBF via stimulation of α-1a-AR. (From DiBona GF (12a).]
rine. In conscious dogs, chronic stimulation (22 h/day) of renal nerves (33) or the greater splanchnic nerve (35) resulted in hypertension that was sustained for the duration of the stimulation (up to 41 days). Of interest, the renal nerve stimulation parameters were sinusoidal form (4 V amplitude and 2 Hz frequency). While these stimulation parameters decreased RBF in acute experiments, RBF and GFR were not found to be decreased in the chronic stimulation experiments wherein hypertension was produced. In conscious dogs, chronic renal arterial infusion of norepinephrine at a dose adjusted to keep RBF constant produced sustained hypertension for the 28-day duration of the infusion (43). The hypertension was not associated with an increase in plasma renin activity or renal sodium retention. It was suggested that the chronic sustained increase in renal vascular resistance led to an increase in renal vascular reactivity to norepinephrine and possibly other circulating vasoactive factors.

The direct demonstration of increased single-fiber RSNA in genetically spontaneously hypertensive rats compared with the genetically normotensive Wistar-Kyoto rat was a significant step and established increased RSNA as an important feature in experimental hypertension (52).

With this background, it logically followed that the investigators examined the effect of renal denervation on the development and maintenance of hypertension. Table 1 shows the various forms of experimental hypertension wherein renal denervation has completely prevented or delayed the onset of or ameliorated the magnitude of the hypertension. While the vast majority of studies did demonstrate favorable effects of renal denervation on blood pressure, there are isolated contrary reports in the DOCA-NaCl and IK-1C Goldblatt models suggesting that intact renal nerves are not necessary for the development or maintenance of hypertension. In the spontaneously hypertensive rat, the hypertension reappeared following the initial renal denervation concurrent with renal reinnervation; repeat renal denervation again attenuated the hypertension documenting that renal reinnervation was the cause of the recurrent hypertension.

That renal denervation has been effective in models of varying etiology, and in multiple species, suggests that the renal nerves are importantly involved in the pathogenesis of hypertension, possibly as a major participant in the final common pathway. Where examined, the beneficial effect of renal denervation on the hypertension was associated with a concurrent decrease in renal sodium retention. These results reinforce the view connecting the requirement for maintenance of external sodium balance with the setting of a level of arterial pressure that enables this to be accomplished via the pressure natriuresis mechanism. Again, this emphasizes that increased RSNA acts to oppose pressure diuresis and natriuresis and this can only be overcome by an increase in arterial pressure, allowing external sodium balance to be achieved at the cost of hypertension (Fig. 3).

To this point, the focus has been on the renal efferent sympathetic nerve fibers: fibers proceeding from the neuraxis to the kidney and containing norepinephrine as the primary effect.

### Table 1. Models of experimental hypertension in which renal denervation prevents or delays the development of hypertension.

<table>
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<tr>
<td>Spontaneously hypertensive rat (SHR)</td>
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<td>Borderline hypertensive rat</td>
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<tr>
<td>Stroke prone SHR</td>
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<tr>
<td>New Zealand SHR</td>
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<td>Goldblatt IK, 1C (rat)</td>
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<td>Goldblatt 2K, 1C (rat)</td>
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<td>Aortic coarctation (dog)</td>
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<td>Aortic nerve transection (rat)</td>
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<td>DOCA-NaCl (rat)</td>
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<td>DOCA (pig)</td>
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<td>Grollman renal wrap (rat)</td>
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<td>Low sodium, 1K hypertension (rat)</td>
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<tr>
<td>Angiotensin II hypertension (rat)</td>
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<tr>
<td>Obesity hypertension (dog)</td>
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<td>NaCl (baroreflex-impaired rabbit)</td>
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Fig. 3. Influence of renal nerves on relationship between urinary flow rate (%H₂O excretion) and renal perfusion pressure (RPP). (From Roman RJ and Cowley AW (44).)
neurotransmitter. However, it is now appreciated that there is abundant renal afferent sensory nerve fibers: fibers proceeding from the kidney to the neuraxis and containing substance P and calcitonin gene-related peptide as primary sensory neurotransmitters (38). These renal afferent sensory nerve fibers are located primarily in the renal pelvic wall where they exhibit mechanosensitive (responding to increases in renal pelvic pressure) or chemosensitive (responding to changes in chemical composition of the urine) properties. Physiological stimulation of afferent renal mechanosensitive nerves by increasing ureteropelvic pressure increases afferent renal nerve activity and decreases efferent RSNA, resulting in a diuresis and natriuresis, a renorenal reflex (31).

However, in addition to this inhibitory reflex (i.e., inhibitory afferent renal nerve fibers), there are also excitatory reflex responses such as increases in sympathetic vasoconstrictor activity and arterial pressure in response to electrical stimulation of afferent renal nerves (50). Renal injury produced by renal tissue injection of phenol increased arterial pressure and both afferent and efferent renal nerve activity (54). These observations focused on the kidney and the afferent renal nerves as the source of signals to the neuraxis, which result in increases in peripheral sympathetic nerve activity and hypertension.

To examine this further, it was realized that traditional renal denervation transects both afferent and efferent renal nerve fibers. While regeneration of efferent renal nerve fibers with reinnervation of the kidney is well established (12), there is little evidence for regeneration of afferent nerve fibers in the kidney or in other transplanted organs (e.g., heart, lungs). Selective interruption of the afferent pathway could be achieved by removal of the kidney (presumed source of the signal) or section of the dorsal roots conveying afferent renal nerve input to the neuraxis (T9-L1). In patients with chronic renal disease and hypertension receiving hemodialysis therapy, muscle sympathetic nerve activity and calf muscle vascular resistance were found to be increased (7). Bilateral nephrectomy abolished the hypertension and normalized both muscle sympathetic nerve activity and calf muscle vascular resistance. This study identified the chronically diseased kidney as the source of afferent information resulting in increased muscle sympathetic nerve activity, calf vascular resistance, and hypertension.

The hypertension in rats with chronic renal disease due to partial renal ablation was abolished by dorsal rhizotomy (T9-L1), a maneuver that selectively and specifically interrupts afferent renal nerve input to the neuraxis (5). These studies indicate that the diseased kidney is the source of afferent information that ascends to the neuraxis via the afferent renal nerves and produces peripheral sympathetic activation and hypertension.

Further insight into this was provided by the observation that rats with dorsal rhizotomy, while normotensive on a normal diet, develop profound hypertension on a high dietary sodium intake (Fig. 4, Ref. 30). This NaCl-sensitive hypertension is associated with a rightward shift of the pressure natriuresis curve such that a higher level of arterial pressure is required to excrete the greater sodium load and achieve sodium balance. The hypertension is associated with increased efferent RSNA, impaired arterial baroreflex regulation of efferent RSNA, and augmented renal sympathoexcitatory responses to environmental stressors (32). Therefore, the normal compensatory and adaptive response to dietary sodium loading is dependent on intact afferent renal nerves conveying information from renal sensory receptors to the neuraxis that are important in the integrated renal sodium excretory response required to achieve sodium balance and avoid hypertension.

**Activation of the Sympathetic Nervous System in Essential Hypertension**

Contemporary methods for studying the human sympathetic nervous system. The development of a sympathetic nerve recording technique applicable to humans (clinical microneurography) in 1968 by Hagbarth and Vallbo (24) and the publication of the first sensitive and specific plasma catecholamine assay, also in 1968, by Engelman et al. (13) were milestones in the field of clinical study of the human sympathetic nervous system. Because human sympathetic nervous system responses are differentiated, with activation in one regional sympathetic outflow typically being accompanied by inhibition or no change in another (17), quantification of individual regional sympathetic nervous outflows was needed. This need was met by the sympathetic nerve recording technique, and by radiotracer-derived measurements of regional norepinephrine spillover to plasma (17).

Microneurography. This technique involves insertion of a fine tungsten electrode through the skin, with positioning of the electrode tip in sympathetic fibers of, most commonly, the common peroneal nerve near the head of the fibula. Multifiber recordings of bursts of sympathetic nerve activity, synchronous with the heart beat, are generated in skeletal muscle vascular efferents (24). More recently, single-fiber sympathetic recordings have been successfully performed in humans (36, 39).

**Regional norepinephrine spillover measurements**. The inapplicability of the neural recording methodology for clinical research on internal organs led to a continuing search for alternative techniques, especially biochemical ones. Measurement of organ-specific norepinephrine release to plasma by isotope dilution (17) became the gold standard. During constant rate infusion of tritiated norepinephrine, outward flux of endogenous norepinephrine from an organ (regional norepinephrine spillover) can be measured by isotope dilution: Regional norepinephrine spillover = \[(C_V - C_A) + C_AE\]PF,
where $C_V$ and $C_A$ are the plasma concentrations of norepinephrine in regional venous and arterial plasma, respectively, $E$ is the fractional extraction of tritiated norepinephrine in transit of blood through the organ, and $PF$ is the organ plasma flow.

Using this technique, typical rates of regional spillover of norepinephrine to plasma in healthy humans at rest are as follows: from the heart 5–25 ng/min, from the kidneys 40–110 ng/min, from the lungs 30–120 ng/min, and from skeletal muscle 50–130 ng/min (17).

**Sympathetic neural pathophysiology of essential hypertension.** For the past three decades, a major focus in high blood pressure research has been the renin-angiotensin system. The proven value of antihypertensive drugs that block this system has led to reduced attention to research on other blood pressure-raising systems, including the sympathetic nervous system. Despite this, there is now general agreement that overactivity of the sympathetic nervous system commonly initiates and sustains the blood pressure elevation in patients with essential hypertension (15, 19, 22).

Application of the norepinephrine spillover methodology has demonstrated activation of the sympathetic nervous outflows to the kidneys and heart (15, 19). Renal norepinephrine spillover, on average, is elevated two- to threefold in both normal weight patients with essential hypertension and in obesity-related hypertension (Fig. 5) (15, 16, 45). Obesity hypertension is remarkable in that, despite the presence of renal sympathetic activation, surprisingly there is minimal involvement of the sympathetic outflow to the heart; in many obese hypertensive patients, cardiac norepinephrine is actually reduced (45). Multunit recordings from sympathetic nerve fibers directed to the skeletal muscle vasculature similarly show a doubling or trebling of sympathetic outflow (22). Single-fiber sympathetic recordings demonstrate increased fiber firing frequencies and multiple firings within a cardiac cycle (firing salvoes) not seen in health (36).

The syndrome of neurogenic essential hypertension appears to account for no less than 50% of all cases of high blood pressure. This estimate is based on multiple facts: the proportion of untreated patients with essential hypertension who have demonstrable sympathetic excitation, the number in whom substantial blood pressure lowering is achieved, and the extent of this lowering with antiaadrenergic interventions. The application of sympathetic nerve recording and norepinephrine spillover methodologies, in multiple studies from different research groups (15, 16, 21–23, 27, 36, 45), identifies activated sympathetic outflow to the skeletal muscle vasculature and kidneys in 40–65% of patients with the caveat that in those aged more than 60 years, although MSNA is increased, cardiac and renal norepinephrine spillover is typically normal. Sympathetic nervous system activation is evident in both normal weight and obese hypertensive patients; sympathetic activation demonstrable with microneurography is particularly prominent in obesity-related hypertension (23, 27).

Does this sympathetic activation initiate and maintain the blood pressure elevation, as has been suggested (19)? There is strong evidence to support this claim. Combined α- and β-adrenergic blockade markedly reduces blood pressure in patients with essential hypertension, an effect particularly prominent in obese hypertensive patients (4, 53). Ganglionic blockade lowers blood pressure nearly to normal in obesity-related hypertension (53). In patients with resistant hypertension, responding inadequately to concurrent treatment with multiple antihypertensive drug classes, including ACE inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, and diuretics, radiofrequency ablation of the renal sympathetic nerves lowers blood pressure remarkably (34, 46). This new, currently experimental treatment modality is described below.

**The Human Renal Sympathetic Nerves**

Influences on sodium excretion, renal renin release, GFR, and renal blood flow. The evidence for renal sympathetic neural effects in humans is unavoidably less direct and definitive than that arising from experimental studies in animals (see above). Sodium retention from reduced urinary sodium excretion accompanies the sympathetic activation accompanying standing and laboratory mental stress (14). Patients with pure autonomic failure, who have degeneration of postganglionic sympathetic fibers, including those to the kidneys (40), have reversal of the 24-h diurnal urinary sodium excretion pattern and sodium depletion. The relation between renal sympathetic activity and sodium balance is bidirectional; sodium depletion produced by a low-sodium diet markedly activates the renal sympathetic outflow, an adaptive, sodium-retaining response (21). Renal renin release is lowered by β-adrenergic blockade and central sympathetic inhibition with imidazoline drugs (29). GFR falls with the sympathetic activation accompanying standing (14) and with laboratory mental stress (26), and is elevated with renal sympathetic inhibition produced by clonidine administration (18). Renal vascular resistance increases with the sympathetic nervous system activation accompanying laboratory mental stress (26), is reduced by α-adrenergic blockade (25) and with clonidine (18), but does not invariably rise with activation of the renal sympathetic outflow, an example being when this is produced by dietary sodium restriction (21). Perhaps this particular stimulus preferentially activates sympathetic nerve fibers passing to renal tubules and the juxtaglomerular apparatus compared with renal arterioles.

![Fig. 5. Renal sympathetic activity, assessed with renal norepinephrine spillover measurements in patients with untreated essential hypertension, expressed in relation to age. Mean values are indicated by the column height, and standard error bars are shown. Renal norepinephrine spillover was elevated in patients aged 20–59 years. **P < 0.01, *P < 0.05](http://ajpregu.physiology.org/pdf/10.1152/ajpren.00554.2009.pdf)
How might renal sympathetic activation cause essential hypertension? Experimental studies, reviewed above, demonstrate the importance of the renal sympathetic nerves in the development of hypertension in various animal models of hypertension, including experimental obesity-related hypertension. Stimulation of renin release and promotion of the renal tubular reabsorption of sodium are likely mediating mechanisms. From the inception of pharmacological treatment of hypertension more than 50 years ago, the full range of antihypertensive drugs employed, including ganglionic blockers, guanethidine, methyldopa, β-adrenergic blockers, α-adrenergic blockers, and imidazoline no doubt had efficacy, in part, via antagonism of these sympathetically mediated renal processes. Particularly telling in this context also is the highly selective inhibition of the human renal sympathetic outflow produced by aerobic exercise training (41); physical conditioning by exercise is a proven, and valuable, form of nonpharmacological antihypertensive therapy.

Can anything more specific than this be said concerning the contribution to blood pressure elevation in essential hypertension of renal neural influences on tubular sodium reabsorption, renin release, reduction in GFR, and renal blood flow? Increased release of renin by the kidneys in patients with essential hypertension is tightly linked to activation of the renal sympathetic outflow (Fig. 6). In those younger patients with the phenotype of high renin-essential hypertension, characterized by an elevated plasma renin activity, it is high renal sympathetic activity that is driving the increased renal release of renin (16). Relationships of renal sympathetic activity to GFR and to renal vascular resistance in essential hypertension, however, are not always as anticipated. Activation of the renal sympathetic outflow in mild obesity-related hypertension paradoxically is associated with glomerular hyperfiltration and normal or increased RBF(45).

Origins of Sympathetic Nervous Activation in Essential Hypertension

The specific causes of the increased sympathetic activity in essential hypertension remain largely unknown, although genetic influences are evident and behavioral and lifestyle factors appear to be involved. Of prime importance, no doubt, is obesity. Obesity activates the sympathetic nervous system, including the renal sympathetic outflow (23, 45), although through uncertain mechanisms.

Epidemiological evidence also indicates an importance for chronic mental stress, including in the workplace (6, 51, 55). A new strand of supporting evidence involves the presence of biological markers of stress exposure, in which parallels are drawn with panic disorder, which provides an explicit clinical model of recurring stress responses (20): 1) there is clinical comorbidity as panic disorder prevalence is increased threefold in essential hypertension (9); 2) plasma cortisol is elevated in both panic disorder and essential hypertension; 3) in panic disorder and essential hypertension, but not in health, single sympathetic nerve fibers commonly fire repeatedly within an individual cardiac cycle; such salvos of single-fiber firing have come to be seen as a “signature” of mental stress exposure; 4) for both, adrenaline cotransmission is present in sympathetic nerves; 5) there is induction of the adrenaline synthesizing enzyme, PNMT, in sympathetic nerves (contained within a subcutaneous vein biopsy), an explicit indicator of mental stress exposure.

Physical inactivity also appears to be important. Habitual levels of exercise have progressively fallen worldwide. Changed work life patterns now favor physical inactivity, as do replacement of walking by other transport options and the widespread adoption of labor-saving devices in the home. The observation that aerobic exercise training in sedentary people reduces sympathetic nervous activity, and preferentially, the renal sympathetic outflow, supports this concept (41).
**Endovascular Catheter-Based Renal Nerve Ablation as a Treatment for Resistant Essential Hypertension**

The sympathetic nervous system in recent years has been the “under appreciated pathway” in the treatment of hypertension. Despite the importance of neural pathophysiological mechanisms in pathogenesis, in the present era in which drugs antagonizing the renin-angiotensin system are the dominant therapeutic mode, therapy specifically targeting the sympathetic nervous system is currently underutilized. However, a revolutionary treatment principle has recently been successfully tested in patients with resistant (uncontrolled) hypertension. This involves ablation of the renal sympathetic nerves with a radiofrequency-emitting catheter inserted percutaneously into the femoral artery in the groin and advanced to lie, in turn, in the lumen of both renal arteries (34). Sympathetic nerves enter the human kidneys in the walls of the renal arteries and lie within reach of ablative energy delivery.

As noted earlier in this review, in some experimental models of hypertension the sympathetic outflow to the kidneys is activated, and renal denervation typically prevents the development of the hypertension. In earlier times, prior to the availability of antihypertensive drugs, extensive surgical sympathectomy was used as a treatment for severe hypertension (48); survival benefit was demonstrated but complication rates were high, as was morbidity from the extensive denervation, which did not specifically target the kidneys.

Initiation of the new treatment strategy for hypertension was based on these observations and the demonstration that the renal sympathetic outflow is activated in essential hypertension (15, 17, 19, 45). For entry into the recently published trial, patients had to meet international criteria of uncontrolled essential hypertension (clinic blood pressure in excess of 160/90 mmHg on three drugs, including a diuretic). In participating hypertensive patients, radiofrequency energy in 90-degree quadrants was delivered in stepwise fashion to the full circumference of the renal artery wall.

The initial aims were to establish that the procedure does produce renal denervation in humans that it is safe and that blood pressure is lowered. All seem to have been confirmed (34). To establish whether the catheter ablates renal sympathetic nerves, measurements of renal norepinephrine spillover were made at baseline and at follow up; results to date indicate that sympathetic denervation does, in fact, occur in most patients, although this was often incomplete, the mean fall in renal norepinephrine spillover being 47.5% (P < 0.05) (34). In earlier studies in pigs, 80–90% reduction in renal norepinephrine content was achieved with application of the denervation procedure. The level of blood pressure reduction achieved, a mean fall of 24/10 mmHg at 3 mo and 29/16 mmHg at 12 mo (P < 0.001) (34) was perhaps greater than anticipated, but it should be emphasized that this proof of principle trial is not a random controlled clinical trial including blinded experimental design. At this point (with the longest follow-up in participants being 2 yr), blood pressure reduction is sustained, suggesting that renal sympathetic reinnervation, if it has occurred, is insufficient to cancel out the blood pressure benefit (Fig. 7).

**Importance of renal deafferentation to the antihypertensive response?** Uncertain at present is the importance of destruction of renal afferent nerves in the antihypertensive effect achieved by the radiofrequency ablation procedure. An unexpected observation with the procedure was that sympathetic outflow from the central nervous system was reduced (45). Whole body norepinephrine spillover, a measure of total sympathetic activity, fell by 28% subsequent to the renal nerve ablation procedure (P < 0.05) (34). Since the renal sympathetic nerves contribute materially to the overall influx of norepinephrine to plasma, approximately one third of this fall was directly attributable to the renal efferent sympathetic denervation. Sympathetic nerve traffic to the skeletal muscle vasculature, measured by microneurography, was also substantially reduced by the procedure (46).

There is conclusive evidence that renal afferent nerves projecting to the hypothalamus can stimulate sympathetic outflow (5). This central nervous system input from renal afferent nerves is critical in producing both the sympathetic activation and hypertension found in patients with end stage renal disease (7, 34). It is probable that radiofrequency deafferentation of the kidney in the patients with previously resistant hypertension studied in the reported trial, by inhibiting systemic sympathetic outflow, contributed to the blood pressure lowering observed. The same presumably applies to renal release of renin, which fell with interference to the renal sympathetic input to its release (46).

**A Cure For Essential Hypertension?**

It has been suggested that renal artery catheter-based renal denervation might, perhaps, provide a cure for essential hypertension in selected patients, those with milder hypertension than treated in the recent study. This speculation remains untested. For the procedure to be applied in milder forms of essential hypertension, a very high level of safety would be mandatory. It should be noted that in one of the ~100 patients...
studied to date, insertion of the catheter did cause a renal artery dissection, which was treated by stenting (34). Although no short-term (up to two years) renal artery complications, other than this procedural mishap, have been detected, specifically there have been no instances of renal artery stenosis or aneurysm. Undetected endothelial damage, if it occurred, might possibly contribute to delayed atherogenesis in the renal artery. Effenter sympathetic nerve regrowth is possible, although the degree to which this would fully restore sympathetically mediated function in the kidneys, and perhaps cancel out the observed antihypertensive effect, is unknown. With transplantation of the heart, in which the sympathetic nerves of the heart are severed, some degree of reinnervation commences 2–3 years after the surgery, but this is incomplete (28). Regeneration of renal afferent nerves is unlikely. Any blood pressure reduction attributable to renal deafferentation is likely to be permanent.

DISCLOSURES

G. F. DiBona is a consultant with Ardian, Inc. and CVRx, Inc.

REFERENCES