Renal denervation for the treatment of resistant hypertension: review and clinical perspective


Department of Physiology, University of Medicine and Pharmacy, "Gr. T. Popa," Iasi, Romania; Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi; and Department of Medicine, ASH Comprehensive Hypertension Center, The University of Chicago Medicine, Chicago, Illinois

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RESISTANT HYPERTENSION is defined as failure to achieve a goal-line-driven blood pressure of less than 140/90 mmHg in patients who are adherent to maximally tolerated doses of at least three antihypertensive drugs, including a diuretic appropriate for kidney function (13). Population-based studies published over the last decade indicate that anywhere from 3 to 12% of hypertensive patients in the United States have resistant hypertension, despite the abundance of efficacious blood pressure-lowering agents belonging to over seven drug classes (11, 20, 68). Moreover, in addition to the cardiovascular mortality risk directly linked to the extent of blood pressure elevation, resistant hypertensive patients frequently have additional risk factors such as obesity, diabetes, chronic kidney disease, and age over 55 and are therefore more likely to die from stroke, myocardial infarction, heart failure, and end-stage renal disease (47, 76).

Since increased sympathetic activity was believed to be present in many patients with resistant hypertension, renal denervation was thought to be the solution for all patients whose blood pressure could not be controlled by medication and was introduced for clinical use 6 years ago. In the open label, uncontrolled SYMPLICITY HTN-1 and SYMPLICITY HTN-2 trials, undertaken in patients with resistant hypertension, reductions in systolic blood pressure as much as 33 mmHg persisted for as long as 3 years after renal denervation (43, 44, 80). These initial denervation studies were really proof of concept studies rather than bona fide clinical outcome trials (10).

SYMPLICITY HTN-3 added a sham procedure, patient blinding, blinding of follow-up assessors, blinding of study management, and mandatory 24-h ambulatory systolic blood pressure >135 mmHg as inclusion criteria (4). It was also more than four times larger than previous studies and 80% powered on a safety end point, >95% powered for efficacy end points. Last, this trial was conducted with greater rigor and oversight than the previous two trials combined (40). SYMPLICITY HTN-3 met the safety end points, just like the previous trials, but failed to achieve the primary end point, as patients with renal denervation had a reduction in systolic BP only 2 mmHg better than sham-operated patients at 6 mo.

While these results initially seemed to portend the demise of renal nerve ablation for resistant hypertension, the striking differences in the efficacy of this procedure in the different trials have spurred numerous explanations. A number of factors were evaluated and published elsewhere (40). More recent speculation about changes in medications and dosing during the trial were not found to be substantiated with similar levels of protocol violations between groups. Additionally, the use of medications such as spironolactone and vasodilators in African Americans may have contributed to differences but they were not confirmed statistically. However, it is becoming clearer that not everyone in the trial had the same level of extensive denervation mandated by the protocol. As discussed latter, more careful examination based on animal studies demonstrated that the extent of denervation, even when the procedure was performed correctly, may have been inadequate. Recent animal studies indicate that all main renal arteries including branches by the hilum need to be denervated to achieve optimal therapy (33, 58). Such extensive denervation has not been routinely achieved in the SYMPLICITY trials (22, 26).

While clinical trial design or procedural issues are the focus of current debate regarding the fate of renal denervation for resistant hypertension, the inquisitive researcher is still intrigued with the question: if all goes well technically, can renal
denervation lower blood pressure in patients with resistant hypertension? This paper aims to bring a physiological perspective to the conditions that influence the blood pressure response to renal denervation. By providing better insight into the mechanisms that account for blood pressure lowering following renal denervation, experimental studies may help identify the subsets of this heterogeneous patient population who stand to benefit the most.

**Overview of Renal Sympathetic Nerve Activity in Resistant Hypertension**

There is now considerable evidence that the sympathetic nervous system plays a major role in the pathogenesis of primary hypertension (21, 22, 26). In addition, recent clinical observations indicate that sympathetic activity is increased in many patients with resistant hypertension (22, 26, 27). This is not surprising as conditions associated with increased sympathetic activity such as obesity, sleep apnea, and use of blood pressure-lowering drugs such as diuretics, dihydropyridine calcium channel blockers, and vasodilators such as hydralazine are common in patients with resistant hypertension (13, 22, 26).

Of particular relevance to this paper, measurements showing increased renal norepinephrine (NE) spillover in many, but not all, patients with primary and resistant hypertension support the hypothesis that the renal nerves provide the critical link between increased central sympathetic outflow and impairment of renal excretory function that leads to chronic hypertension (21, 22, 26). This hypothesis is further supported by studies showing that renomediation attenuates or abolishes many forms of experimentally induced hypertension (17, 41, 65). At the same time, it is clear that renal nerve ablation does not always lower arterial pressure in patients with resistant hypertension, and the conditions for a favorable blood pressure response are largely unknown (4, 43, 79, 80).

Given that there are regional differences in sympathetic outflow and increased renal sympathetic nerve activity (RSNA) is expected in many patients with resistant hypertension (21, 22, 26), it is unfortunate that there are practical limitations to widespread use of the technology for assessing RSNA by measuring renal NE spillover. Therefore, the relationship between basal RSNA and the subsequent blood pressure response to renal nerve ablation is unclear, as are the conditions that might modify a direct correlation if one were to exist.

Proponents of renal denervation for treatment of resistant hypertension often emphasize studies whereby renal denervation attenuates or abolishes hypertension in different experimental models. They also highlight clinical studies conducted many decades ago, before the advent of effective antihypertensive drugs, showing that thoracolumbar splanchicectomy, interrupting sympathetic outflow to the kidneys, reduces the severity of hypertension in patients with severe hypertension. This perspective is often accepted without fully understanding the following relevant issues that provide a more objective viewpoint. First, the predominance of studies where renal denervation is reported to attenuate or abolish different forms of experimental hypertension was conducted in rodents. In these models, blood pressure lowering following renal denervation has not been a consistent finding. That is, in many of the same experimental models of hypertension, lowering of arterial pressure by renal denervation has occurred in some but not in all studies (17, 41, 42). These inconsistencies appear to be related to differences in experimental design, such as method of blood pressure measurement, surgical technique, as well as timing of the intervention.

The most consistent antihypertensive responses to renal denervation in rodent models of hypertension have been reported in the spontaneously hypertensive rat (SHR), a model of hypertension in which increased RSNA has been documented (39, 63, 86). However, even in the SHR, renal denervation has minimal blood pressure-lowering effects in the advanced stages of the hypertension when there is target organ damage (86). In dogs, there is no evidence for sympathetic activation or a contribution of the renal nerves to renal vascular hypertension (Goldblatt hypertension) or hypertension produced by chronic infusion of angiotensin II (ANG II) and aldosterone (25, 48, 50, 51, 55, 66). In contrast, in the sympathetically driven model of obesity hypertension induced by feeding dogs a high-fat diet, renal denervation abolishes the hypertension before the onset of significant target organ damage (54). These experimental studies indicate that the renal nerves do not contribute to all forms of hypertension, but that they do play a critical role in chronically increasing arterial pressure when RSNA is elevated.

The second point often misrepresented by those promoting renal nerve ablation for treatment of resistant hypertension are the surgical sympathectomy studies conducted in hypertensive patients in the middle of the 20th century. While surgical sympathectomy in humans greatly improved mortality and survival rates, Smithwick and Thompson (78) reported that the severity of hypertension was attenuated in only about half of the 1,266 patients analyzed. These studies followed a pioneering report by Irvine Page (67) in 1935 showing that renal denervation did not have antihypertensive effects in a patient in this patient, Page concluded that “renal denervation in cases of essential hypertension is of no therapeutic value.” Taken together, these observations indicate that it is misleading to base the potential merits of renal nerve ablation on only the favorable blood pressure responses to renal denervation and thoracolumbar splanchicectomy. Clearly, there are numerous experimental and clinical observations that are inconsistent with such a superficial argument. Indeed, in recent clinical trials, renal nerve ablation has attenuated the severity of hypertension in some but not in all patients with resistant hypertension (4, 43, 44, 79, 80). Unfortunately, because of technical limitations in determining renal NE spillover, the only method available currently that provides a quantitative assessment of sympathetic outflow to the kidneys, clinicians are unable in routine practice to assess the relationship between the antihypertensive effects of renal denervation and baseline RSNA in patients with resistant hypertension.

**RSNA and Hypertensive Mechanisms**

The relationship between renal perfusion pressure and the rate of sodium excretion by the kidneys plays a major role in the regulation of body fluid volume and blood pressure (16, 28). If this relationship is invariant, alterations in arterial pressure induced by changes in cardiac output and/or peripheral resistance will lead to changes in renal sodium and water excretion that adjust extracellular fluid volume until arterial
pressure returns to the initial baseline level. According to this concept, long-term changes in arterial pressure can only occur through mechanisms that alter renal pressure-natriuresis. Indeed, all forms of human or experimentally induced hypertension are associated with resetting of the pressure-natriuresis mechanism to a higher level of arterial pressure or to a level of renal perfusion pressure necessary for renal excretion of salt and water to precisely match intake. Since the sympathetic nervous system is commonly activated in resistant hypertension, increased RSNA is a likely mechanism that impairs pressure natriuresis and thereby contributes to resistant hypertension (16). As indicated above, this possibility is supported by measurements showing that increased renal NE spillover is prevalent in patients with resistant hypertension. A corollary of this concept is that acute responses to global inhibition of the sympathetic nervous system do not necessarily reveal the quantitative importance of neural mechanisms in mediating hypertension. Acute arterial pressure responses to inhibition of the autonomic nervous system, such as those during ganglionic blockade, are dominated by changes in cardiac output and peripheral resistance, whereas chronic responses to neural inhibition reflect the impact of the nervous system on the more sluggish renal mechanisms for control of body fluid volume and arterial pressure. While acute, global sympathectomy generally lowers arterial pressure within seconds to minutes, pressure reduction is not invariably sustained over the long term unless renal mechanisms are involved. In contrast, steady-state reductions in arterial pressure in response to renal specific sympathectomy, such as after renal denervation, take days to manifest.

Because increased RSNA shifts the pressure-natriuresis relationship to higher arterial pressure levels (16), the intensity of sympathetic outflow to the kidneys may be a key determinant of the antihypertensive response to renal denervation. In this regard, elucidating the mechanisms whereby increased RSNA promotes hypertension may provide greater insight into the variable responses to renal denervation in resistant hypertension. All parts of the renal vasculature are innervated with the greatest density of innervation along the afferent arterioles (17). Adrenergic neuroeffector junctions are also present throughout the renal tubules with the exception of the inner medulla. Renin-secreting granular cells of the juxtaglomerular apparatus also receive sympathetic innervation. This anatomic distribution of the renal nerves provides multiple mechanisms for control of sodium excretion and modulation of pressure-natriuresis.

Through activation of different subtypes of α-adrenergic receptors on renal tubules and the renal vasculature, increased RSNA has direct effects to decrease sodium excretion by promoting tubular sodium reabsorption and by decreasing glomerular filtration rate (GFR) through constriction of the afferent arterioles (prespiglomerular vessels) (17). Furthermore, activation of β-adrenergic receptors located on the juxtaglomerular cells indirectly promotes sodium retention by increasing renin secretion with subsequent generation of ANG II and concomitant aldosterone secretion from the adrenal glands. These direct and indirect effects of increased RSNA on sodium excretion lead to a reduction in renal excretory capacity, necessitating a chronic increase in arterial pressure to achieve sodium balance (Fig. 1). Despite the established role of increased RSNA in promoting and maintaining hypertension, the relative contribution of the direct and indirect neural pathways for sodium retention has been difficult to assess. Acute experimental approaches that have increased RSNA progressively through electrical stimulation of renal sympathetic nerves showed that the lowest levels of RSNA promote renin secretion, followed by reductions in sodium excretion and ultimately decreases in GFR and renal blood flow at the highest levels of RSNA (17). Because acute studies indicate that the sodium retention associated with physiological and most pathophysiological increases in RSNA is independent of neurally mediated reductions in GFR, it is likely that juxglomerular arteriolar vasconstriction is not a primary mechanism whereby increased sympathetic activity chronically impairs pressure-natriuresis in hypertension. A case in point is that increases in RSNA that enhance tubular sodium reabsorption and impair pressure-natriuresis in obesity hypertension are actually associated with increases in GFR and renal blood flow (29, 52, 54).

Based on findings in acute studies, the antinatriuretic effects of increased RSNA are often attributed primarily to the direct effects of adrenergic stimulation on tubular reabsorption. However, extrapolation from the acute to the chronic state may be especially misleading because in many short-term studies there has been insufficient time to allow the antinatriuretic effects of ANG II to manifest. In contrast, in studies lasting more than an hour and up to several days, reflex and electrical activation of the renal nerves and chronic infusion of NE into the renal artery clearly demonstrate that the indirect effects of renal adrenergic stimulation on sodium excretion, mediated by ANG II through stimulation of renin secretion, play an appreciable role in chronically promoting sodium retention (45, 71, 72, 83). The potential relevance of this indirect ANG II pathway to the variable antihypertensive effects of renal denervation in resistant hypertension is discussed below.

An expedient assessment of the role of the renin-angiotensin system (RAS) in contributing to neurally mediated hypertension is made by measuring plasma renin activity (PRA). However, this measurement can be misleading as even apparently normal levels of PRA may be indicative of ANG II playing a significant role in shifting pressure-natriuresis to a higher arterial pressure. Neurally mediated stimulation of renin secretion is achieved directly by β-adrenergic stimulation of juxtaglomerular cells and indirectly by decreasing sodium delivery to the macula densa as a result of α-adrenergic stimulation of sodium reabsorption in the proximal tubule and loop of Henle (Fig. 1). However, over time as extracellular fluid accumulates and arterial pressure increases, sodium delivery to the macula densa tends to return to control levels, greatly diminishing one of the stimuli for renin secretion, resulting in hypertension with seemingly normal PRA.

This time course is nicely reflected in longitudinal measurements of PRA in the sympathetically mediated obesity model of hypertension in dogs fed a high-fat diet (Fig. 2). Early increases in sympathetic activity associated with weight gain over the initial weeks of fat feeding are paralleled by two- to threefold increases in PRA (49, 54). In subsequent weeks as hypertension progresses, PRA returns toward control levels, resulting in only subtle increases in renin secretion not easily detected by intermittent measurements of PRA (Fig. 3), even in well-controlled longitudinal studies. However, this does not
discount the importance of even small increases in ANG II in mediating the hypertension since, for the prevailing level of volume expansion and hypertension, even normal levels of ANG II would be considered inappropriately elevated. Indeed, abolition of the neural drive to the kidneys by global suppression of central sympathetic outflow through chronic electrical activation of the carotid baroreflex (53) or by renal-specific sympathoinhibition through renal denervation abolishes the hypertension in parallel with reducing PRA (Figs. 2 and 3) (54). Other studies in experimental animals show that ANG II blockade or angiotensin-converting enzyme (ACE) inhibition attenuates sodium retention, volume expansion, and increased arterial pressure in obesity (8, 73). ANG II blockers, renin inhibitors, and ACE inhibitors are also effective in lowering arterial pressure in obese hypertensive patients (18). In summary, the indirect pathway for sodium retention and the concomitant impairment of pressure-natriuresis mediated via stimulation of renin secretion contributes significantly to neurally mediated hypertension in obesity.

Although electrical activation of the carotid baroreflex has central actions to globally suppress sympathetic activity (Fig. 3), an impressive response was that abrogating sympathetic drive to the kidneys alone by renal denervation was sufficient to abolish obesity hypertension (Fig. 2). Because the natural activation of the baroreflex in hypertension has sustained effects to inhibit RSNA and promote sodium excretion (50, 51) and because obesity hypertension is associated with increased RSNA (2, 26, 29, 52), these findings emphasize the importance of the renal nerves in providing the critical link between increased central sympathetic outflow and impaired renal function that leads to and sustains obesity hypertension. Once again, as illustrated in Fig. 3, suppression of PRA during both baroreflex activation and renal denervation reflects the contribution of neurally mediated renin secretion to the hypertension.

Additive Blood Pressure-Lowering Effects of Renal Denervation during Antihypertensive Drug Therapy: Influence of the RAS

As obesity is prevalent in patients with resistant hypertension and likely contributes to sympathoexcitation (14, 26, 29, 52), the above interrelationships between increased RSNA and

Fig. 1. Increased renal sympathetic nerve activity (RSNA) leads to chronic increases in blood pressure by decreasing sodium excretion (orange boxes and lines). The 3 major pathways by which changes in RSNA affect sodium excretion are through alterations in activation of the renin-angiotensin system (red boxes and lines), sodium reabsorption (blue box and line), and glomerular hemodynamics (purple boxes and lines). Light blue and light purple lines represent mechanisms indirectly affected by RSNA. Continuous lines represent stimulatory effects; dotted lines reflect inhibitory effects. E.A., efferent arteriole; A.A., afferent arteriole; GFR, glomerular filtration rate.
activation of the RAS provide a physiological basis that may account, at least in part, for the variable antihypertensive response to renal denervation. Because maximally tolerated doses of ACE inhibitors and ANG II blockers are part of the standard therapy for treatment of resistant hypertension, suppression of this indirect pathway for neurally induced sodium retention would be expected to diminish the antihypertensive response to renal denervation. However, pharmacological strategies to inhibit the RAS may be suboptimal in some individuals with resistant hypertension as a result of incomplete blockade due to submaximal drug dosing. Thus, in some individuals, suboptimal RAS blockade may leave this indirect pathway amenable to neural modulation by renal denervation. Counterbalancing this potential mechanism for blood pressure lowering is aldosterone breakthrough, defined as increases in plasma aldosterone concentration compared with baseline levels before blockade of the RAS through mechanisms that are incompletely understood (5, 61).

Because many patients with resistant hypertension have inappropriately high plasma levels of aldosterone, aldosterone excess may oppose blood pressure lowering following renal denervation by contributing to the sodium retention and intravascular volume expansion that are prevalent in these patients, despite concurrent use of diuretics (14, 24). Indeed, the aldosterone antagonist spironolactone produces further reductions in arterial pressure in patients with resistant hypertension on standard antihypertensive drug therapy (14, 15, 24, 70, 74, 82); however, spironolactone is not widely administered in this patient population (68).

Most experimental and clinical studies indicate that mineralocorticoid-induced hypertension is not associated with increased sympathetic activity (9, 46, 55, 57, 59). Additionally,
in aldosterone hypertension, the RAS is likely unresponsive to neural blockade because baseline levels of renin secretion are markedly suppressed. Given this information along with aldosterone excess being common in patients with resistant hypertension, the blood pressure-lowering effects of chronic baroreflex activation and surgical renal denervation were evaluated in dogs with hypertension induced by chronic infusion of aldosterone. Under control conditions before the induction of hypertension, the intensity of electrical carotid sinus stimulation was selected to achieve an approximately 15-mmHg decrease in arterial pressure during the first 24–48 h of baroreflex activation, but no further changes in activation were made after this time period. This initial fall in arterial pressure persisted throughout the 7 days of baroreflex activation (Fig. 4) along with an approximately 40% reduction in plasma NE concentration, indicating sustained suppression of sympathetic activity. In contrast, despite an equivalent intensity of carotid sinus stimulation and suppression of sympathetic activity in these same dogs, the long-term blood pressure-lowering effects of baroreflex activation were diminished ~55% after induction of aldosterone hypertension (Fig. 4). Moreover, following renal denervation, there was no attenuation of aldosterone hypertension (Fig. 4). This study indicates that suppression of sympathetic activity and especially RSNA has negligible effects to offset the powerful antinatriuretic effects of high circulating levels of aldosterone that lead to increased arterial pressure. That is, in the presence of elevated circulating levels of aldosterone (and suppressed PRA), inhibition of α-adrenergic receptor-mediated tubular reabsorption of sodium during suppression of RSNA leads to only modest increases in sodium excretion and lowering of arterial pressure. An implication of this finding is that there may be diminished antihypertensive responses to renal ablation therapy in patients with resistant hypertension not treated with aldosterone antagonists. This supposition is consistent with a recent post hoc analysis from a cohort of patients in the SYMPLICITY HTN-3 trial indicating that use of an aldosterone antagonist at baseline was a positive predictor for a favorable antihypertensive response to renal nerve ablation (40). Unfortunately, many patients with resistant hypertension have reduced GFR, likely intensified further by drug therapy that includes blockers to the RAS, and therefore the use of mineralocorticoid antagonists may be contraindicated because of the risk of life-threatening hyperkalemia and further reductions in renal function (15, 74, 82). However, as patients with impaired kidney function [i.e., estimated GFR (eGFR) <45 ml·min⁻¹·1.73 m⁻²] were excluded from most renal denervation trials, the possibility that these adverse effects of mineralocorticoid antagonists are more likely to manifest in patients with resistant hypertension and reduced GFR has not been established.

In summary, while incomplete blockade of the RAS may result in a more favorable antihypertensive response to renal denervation in some patients by allowing suppression of the indirect as well as the direct pathway for neurally mediated sodium retention, the sodium-retaining effects of aldosterone excess during blockade of the RAS may limit blood pressure lowering after renal denervation.

The lowering of arterial pressure with some drugs commonly used for hypertension therapy, including diuretics and dihydropyridine calcium antagonists, increases central sympathetic outflow with concomitant activation of the RAS (13, 22, 23, 26, 37). To this point, a canine study showed substantial activation of the sympathetic nervous system and stimulation of the RAS with a dose of amlodipine that chronically lowered mean arterial pressure by 13 mmHg (37). During prolonged carotid baroreflex activation and continued amlodipine administration, suppression of this augmented central sympathetic outflow, and presumably RSNA, further lowered arterial pressure by 11 mmHg along with reducing PRA. This study provides direct evidence that neurohormonal activation ap-

Fig. 4. Effects of prolonged baroreflex activation on mean arterial pressure before and after induction of aldosterone hypertension (HT), and the response of aldosterone hypertension to bilateral renal denervation. Blood pressure lowering in response to global and especially renal-specific sympathoinhibition was diminished in aldosterone hypertension. Values are means ± SE from 24-h recordings of arterial pressure. *P < 0.05 vs. values before either global or renal-specific sympathoinhibition.

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precipitously attenuates the antihypertensive effects of this drug commonly used in the treatment of resistant hypertension and suggests that renal denervation may be especially effective in lowering arterial pressure in patients whose ongoing pharmacological therapy includes dihydropyridine calcium antagonists.

Because many patients with resistant hypertension have inappropriate volume expansion that is managed to varying degrees of success using diuretic therapy and judicious consumption of dietary salt, an important consideration is the impact of salt intake on the therapies for blood pressure lowering. It is well established that the sensitivity of arterial pressure to salt intake is linked to the responsiveness of the RAS. Consequently, chronic increases in salt intake have relatively little influence on arterial pressure as long as renin secretion is adequately suppressed. Because progressive increases in GFR do occur during increases in salt intake (30), it was suggested that a key mechanism for regulation of renin secretion during variations in salt intake may be the filtered load of sodium and the attendant sodium chloride delivery to the macula densa, rather than alterations in renin secretion mediated through neural mechanisms (35). Two studies have directly tested this possibility. In one study, steady-state arterial pressure and neurohormonal responses were determined in dogs on different salt intakes under control conditions and during a constant level of carotid baroreflex activation (35). Although arterial pressure was lower at all salt intakes during baroreflex-mediated suppression of sympathetic activity, changes in arterial pressure, PRA, and plasma aldosterone concentration were similar to those occurring under control conditions. Similarly, in a study in rats, renal denervation did not alter chronic salt-induced changes in arterial pressure (38). Therefore, while the renal nerves do tonically stimulate renin secretion, changes in sympathetic activity do not appear to be primary mediators of the effect of salt on renin secretion and, consequently, arterial pressure. Although patients with resistant hypertension are exquisitely salt sensitive, in part because drug treatment includes blockade of the RAS, these studies suggest that after renal denervation the magnitude of blood pressure lowering may be independent of salt intake. If this hypothesis is true, the antihypertensive effects of renal denervation would be expected to lead to a parallel leftward shift in the relationship between arterial pressure and salt intake and, unlike most drug treatments, provide a therapy that is insensitive to the capricious salt intake in the resistant hypertensive population.

Inhibition of RSNA and Renal Hemodynamics

Most renal imaging and eGFR measurements conducted within the first year after renal denervation in patients with resistant hypertension indicate that the endovascular renal nerve ablation technology does not have adverse functional or structural effects that diminish kidney function (4, 43, 79, 80). Results from the SYMPLICITY trials indicate that GFR is well preserved after 6 mo of renal denervation. In contrast, in the SYMPLICITY HTN-1 registry, eGFR loss at 36 mo was estimated to be 9.3 ml/min1.73 m2 (44), a greater than twofold larger decrease in eGFR than in another recent trial in which hypertensive patients at high cardiovascular risk were treated with drug therapy (3). It is unclear whether the greater fall in GFR reported in the SYMPLICITY HTN-1 registry reflects adverse effects of the technology, impaired ability of the afferent arteriole to dilate in response to a fall in arterial pressure due to persistent functional and/or structural abnormalities caused by sustained hypertension, the natural progression of resistant hypertension, or physiological responses to renal denervation.

Obesity is common in patients with resistant hypertension, and hypertension and glomerular hyperfiltration are precursors of progressive renal injury in obesity. Therefore, the comparative renal hemodynamic responses in the dogs with obesity hypertension during global reflex suppression of sympathetic activity by chronic baroreflex activation and renal specific sympathoinhibition by surgical renal denervation may provide insight into physiological mechanisms that account for reductions in GFR following suppression of RSNA (Fig. 5) (52, 54). In keeping with the likely physiological effects of increased RSNA in obesity, the hyperfiltration has been attributed to both a high rate of neurally mediated sodium reabsorption before the
macula densa and to stimulation of renin secretion (81). More specifically, increased neurally mediated sodium reabsorption in the proximal tubule and loop of Henle decreases sodium delivery to the macula densa (Fig. 1). In turn, this elicits a tubuloglomerular (TGF) signal to dilate the afferent arterioles. In addition, generation of ANG II in response to stimulation of renin secretion exacerbates TGF-mediated hyperfiltration by constricting the efferent arterioles (Fig. 1). Accordingly, suppression of sympathetic activity would be expected to diminish these renal responses. Indeed, the antihypertensive effects of chronic global suppression of central sympathetic outflow by baroreflex activation in this canine model of obesity hypertension are associated with diminished hyperfiltration (Fig. 5). Furthermore, because reductions in fractional sodium reabsorption and PRA occur concomitantly with the antihypertensive effects of BA (Figs. 3 and 5), it is reasonable to suggest that the fall in GFR can be attributed to TGF-mediated consequences of BA (Figs. 3 and 5). Consequently, increased neurally mediated sodium reabsorption, it was surmised that that complete surgical renal denervation may decrease preglomerular resistance as a result of achieving reductions in RSNA that exceed those seen during the more natural reflex suppression of sympathetic activity by baroreflex activation. The decrease in preglomerular resistance in this study is consistent with a reported 56% increase in renal plasma flow immediately following renal nerve ablation in a patient with resistant hypertension (77). Thus, by decreasing preglomerular resistance and increasing glomerular pressure, renal denervation may predispose obese patients with resistant hypertension to glomerular injury due to glomerular hypertension, particularly if the antihypertensive response to renal nerve ablation is modest or absent, as seen in many patients. In this regard, a recent meta-analysis of a European database of 109 patients with resistant hypertension showed that although the overall mean eGFR of this patient population was in the normal range, higher baseline serum creatinine levels were associated with a lower probability of arterial pressure improvement after renal denervation (69). Therefore, in resistant hypertensive patients with significant loss of nephrons or nephrons with declining function, an additional reduction in preglomerular resistance in hyperfiltering remnant nephrons may accelerate the progression of renal injury.

In summary, the findings reported in the SYMPLICITY HTN-1 registry indicating a relatively excessive reduction in eGFR after 36 wk of renal denervation in patients with resistant hypertension emphasize the need for careful long-term determinations of kidney function in this patient population not only with preserved but with impaired baseline GFR as well.

Other Potential Determinants of the Antihypertensive Response to Renal Denervation

Renal afferents. The renal nerves carry not only efferent signals from the central nervous system to the kidneys but afferent information from the kidneys to the brain as well. The renal afferent limb of the sympathetic pathway emanates from both mechanoreceptors and chemoreceptors (17). Stimulation of pressure-sensitive mechanoreceptors by increased renal pelvic pressure inhibits sympathetic activity. In contrast, stimulation of renal chemoreceptors initiates a sympathoexcitatory reflex and is presumably activated in renal disease, seemingly in response to ischemic metabolites and/or uremic toxins.

Activation of this excitatory reflex leads to an increase in central sympathetic outflow that has been postulated to contribute to the hypertension of chronic kidney disease and, more recently, resistant hypertension (21, 26).

There is some indirect evidence that activation of chemoreceptor afferents may play a role in established Goldblatt hypertension in rats (42, 65), but this is not a consistent finding (64). Other rodent studies clearly show that renal afferents do not contribute to the maintenance of hypertension in the DOCA-salt and Grollman models of hypertension or to the hypertension of the SHR (19, 42, 63, 65). While renal denervation abolishes sympathetically mediated obesity-induced hypertension in dogs fed a high-fat diet, findings indicate that this antihypertensive response can be attributed to elimination of efferent sympathetic outflow to the kidneys (54, 87).

The concept that decreased input from afferent renal sensory nerves to the brain following renal denervation contributes to blood pressure lowering by decreasing central sympathetic outflow was advanced from a report in one patient with resistant hypertension showing a 64% reduction in muscle sympathetic nerve activity (MSNA) 1 yr after renal nerve ablation (77). In a follow-up study in 25 obese patients with resistant hypertension, these same SYMPLICITY trial investigators reported that after 3 mo of renal nerve ablation, blood pressure lowering was associated with a much smaller 7–8% decrease in multiunit MSNA (34). In contrast, others have reported that reductions in MSNA and arterial pressure are not consistent responses to renal nerve ablation in patients with resistant hypertension, and, when blood pressure lowering is achieved, there has been no correlation between reductions in arterial pressure and MSNA (12, 31, 85).

Chronic activation of the sympathetic nervous system is also common in metabolic syndrome (36, 56). Although producing a modest fall in arterial pressure in 29 obese patients with metabolic syndrome treated with a maximum of one antihypertensive drug, renal nerve ablation failed to decrease MSNA at a 6 mo follow-up (84). In an ovine model of heart failure, catheter-based renal denervation did not reduce elevated levels of cardiac sympathetic nerve activity when measured 24 h after renal denervation (7).

There is a conceptual issue that is seemingly incompatible with the notion that renal afferents contribute to the sympathetic activation and increased arterial pressure of resistant hypertension. Impaired renal function has been an exclusion criterion for the renal denervation clinical trials in resistant
hypertension. Therefore, because experimental data suggest that renal afferent signaling results in a sympa-thoexcitatory response only if the kidneys are diseased, it is questionable whether a renal injury signal is present in most resistant hypertensive patients studied to date.

Thus, while there is solid evidence that changes in eff-erent RSNA impact the severity of resistant hypertension, at present the data in support of a role for renal afferents in contributing to the sympathoexcitation of resistant hypertension is equivocal and, therefore, this possibility is not resolved. Thus, based on current evidence, the major antihypertensive effects of renal denervation can most likely be attributed to removal of renal sympathetic efferent fibers rather than to disruption of central input from renal sensory nerves.

Renal denervation and reinnervation. One factor that likely influences the magnitude of the antihypertensive response to renal nerve ablation is the extent of denervation, which has not been determined in most clinical studies. In the SYMPLICITY HTN-1 trial, the extent of renal denervation was determined in 10 patients by measurement of renal NE spillover. In this study, renal NE spillover was reduced ~47% when measured 15–30 days after renal denervation (43). Although a quantitative relationship between reductions in NE spillover and blood pressure lowering has not been established, based on the impressive reductions in arterial pressure reported in this study, these investigators concluded that the degree of renal denervation was sufficient to achieve therapeutic efficacy. To this point, in a study conducted in dogs with obesity hypertension, radiofrequency renal denervation lowered renal cortical NE levels 42% or to about the same level as the reduction in renal NE spillover in the above clinical study (32). In response to the 42% reduction in renal tissue levels of NE, mean arterial pressure decreased 9 mmHg. However, this decrease in arterial pressure is only ~50% of the decrease that occurs with surgical renal denervation, which achieves >95% reduction in cortical NE concentration along with abolishing the hypertension (Fig. 3) (54). Based on the heterogeneity in the reduction in renal NE spillover achieved in a group of patients subjected to endovascular renal nerve ablation, with denervation being <25% in several instances, it is likely that suboptimal denervation has contributed to the inconsistent blood pressure lowering in past clinical trials (26). Determinations of renal histology and renal tissue levels of NE in experimental studies indicate that effective therapy may require delivery of ablatice energy to the distal sections of the renal artery, near the bifurcation, rather than to just the more proximal regions of the main renal artery (33, 58). As the renal nerves in the branches are closer to the renal artery lumen than they are in the more proximal regions of the renal artery, this puts the distal location closer to the ablative energy. Unfortunately, although denervation is most complete when it includes the initial branches of the renal artery, this may be technically challenging to achieve and may increase the risk of damaging the arteries.

Other than procedural issues resulting in incomplete denervation, long-term blood pressure lowering after renal nerve ablation may also be limited by renal reinnervation. In a recent study, the Simplicity renal ablation system was used to investigate chronological changes in the renal arteries after radiofrequency renal denervation in the swine model (75). A total of 49 renal arteries from 28 animals with 4 different time points (7, 30, 60, and 180 days) were examined. Semiquantitative histological assessment of the arterial medial circumferential injury was greatest at 7 days and least at 180 days. The nerve injury score was significantly greater at 7 days compared with the other time points. Focal nerve regeneration at the sites of radiofrequency ablation was observed in 17% of renal arteries at 60 days and 71% at 180 days. Studies in rats, dogs, and sheep have demonstrated anatomic and functional reinnervation of both sympathetic and sensory fibers within months after renal denervation (6, 60, 62). While experimental studies in several animal species show renal reinnervation within weeks to months after renal denervation, there is limited data regarding nerve regeneration in humans following renal nerve ablation. Therefore, the time course of functional reinnervation in patients with resistant hypertension and the temporal importance of this mechanism in diminishing the antihypertensive effects of device-based renal nerve ablation are unclear at the present time.

Conclusions and Clinical Perspective

The renal nerves provide the critical link between increased central sympathetic outflow and impairment of renal excretory function that leads to chronic hypertension. Based on a single report in a small patient population showing that renal NE spillover is elevated in the majority of patients with resistant hypertension (21, 22, 26), renal denervation would be expected to attenuate the severity of hypertension in many patients with resistant hypertension. However, if resistant hypertension is not associated with increased renal sympathetic outflow, renal denervation may not be effective. The above considerations are supported by studies showing substantial antihypertensive effects of global and renal-specific sympathoinhibition in experimental models of hypertension that are neurally mediated (obesity) and lack of effect in those that are not (aldosterone). Both obesity and aldosterone excess are common in patients with resistant hypertension and may have opposing effects on sympathetic activity.

The renal nerves do have direct tubular effects to promote sodium reabsorption by stimulation of α-adrenergic receptors. However, experimental studies indicate that the indirect effects on sodium excretion, mediated via the generation of ANG II, are especially important in mediating neurogenic hypertension. Therefore, the greatest antihypertensive effects of renal denervation may occur under conditions in which there is heightened renal sympathoexcitation and a RAS that can respond to neural inhibition, such as in obesity, which is common in resistant hypertension. In contrast, the antihypertensive effects of neurally induced suppression of α-adrenergic receptor-mediated tubular reabsorption are minimal in the presence of aldosterone excess, which is characterized by a suppressed RAS that is invariant during alterations in renal sympathetic outflow.

Some drugs commonly used in the treatment of resistant hypertension such as diuretics and dihydroxypridine calcium antagonists may increase renal sympathetic outflow and activate the RAS. By extension of the above concept, renal denervation would be expected to appreciably enhance their antihypertensive effects.

Changes in activity of the RAS play a critical role in minimizing alterations in arterial pressure during variations in salt intake. Because changes in neural activity do not appear to play an essential role in this renin response to long-term
variations in salt intake, the lowering of arterial pressure following renal denervation is salt insensitive. Some studies indicate that resistance to therapy is associated with progressive renal damage. By decreasing preglomerular resistance and increasing glomerular pressure and GFR, renal denervation may predispose patients with resistant hypertension to further glomerular injury, particularly if the initial antihypertensive response is modest or absent. Careful long-term follow-up studies of greater duration than those previously conducted are needed to test whether this physiological mechanism may contribute to loss of renal function.

At present, there is only equivocal evidence from patients with resistant hypertension in support of the hypothesis that decreased input from renal afferents contributes to the antihypertensive effects of renal denervation by diminishing central sympathetic outflow. Because this concept is based on a renal injury signal from diseased kidneys, some uncertainty may occur because impaired renal function has been an exclusion criterion in most studies using renal denervation. Clarifying this concept will likely require studies including patients with reduced baseline GFR.

Given the information now gathered about uncertainties related to the extent of renal denervation and the mechanisms that both favor and diminish blood pressure lowering following renal denervation, new technologies and standardized clinical trials will need to be carefully designed to validate this procedure as useful in the treatment of resistant hypertension. It is clear based on the current state of the procedure and other confounders noted in clinical trials, it is time to “start over.” This is, in fact, the approach endorsed by both the Food and Drug Administration and industry. There will soon be at least three different proof-of-concept studies by different companies and different catheters using the now appreciated more extensive denervation approach. Additionally, another company is using an external ultrasound device in ongoing studies in Europe that denervates the area at the hilum of the kidney including branches of the renal artery. Moreover, at least one study will be against placebo and another will include sham control on medication. The authors of this paper anticipate that a definitive answer regarding the role of denervation as an alternative to medication for blood pressure management will be available by 2017.

DISCLOSURES

T. E. Lohmeier is a consultant for CVRx, Inc. G. L. Bakris is a consultant for Medtronic, Kona, Vascular Dynamics, and CVRx, Inc.

AUTHOR CONTRIBUTIONS


REFERENCES


RENAL NERVES IN RESISTANT HYPERTENSION

Perspective

Persell SD.

Page IH, Heuer GJ.

Page IH.

Persu A, Jin Y, Baelen M, Vink E, Verloop WL, Schmidt B, Blicher

Reinhart GA, Lohmeier TE, Hord CE Jr.


Persu A, Jin Y, Baelen M, Vink E, Verloop WL, Schmidt B, Blicher


Reinhart GA, Lohmeier TE.


Reinhart GA, Lohmeier TE, Hord CE Jr.


Sarafidis PA, Georgianos P, Bakris GL.


Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD.


Smithwick RH, Thompson JE.


Symplicity HTN Investigators.


Symplicity HTN Investigators, Esler MD, Krum H, Sobotka PA, Schlaich MP, Schneider RE, Bohm M.


Thomson SC, Vallon V, Blantz RC.


Van Vliet BN, Smith MJ, Guyton AC.


Verloop WL, Spiering W, Vink EE, Beetzink MM, Blankestijn PJ, Doevendans PA, Voskuil M.


Winternitz SR, Katholi RE, Persell S.


Zappe DH, Capel WT, Keen HL, Shek EW, Brands MW, Hall JE.