Renal denervation

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Abstract

Severe hypertension, resistant to conventional antihypertensive medications, is associated with major adverse cardiovascular and cerebrovascular events and renal insufficiency. Renal sympathetic nerve over-activity frequently accompanies essential hypertension. Catheter-based renal sympathetic denervation leads to a reduction in renal and overall sympathetic nerve activity and improvement in blood pressure in the setting of severe resistant hypertension. In the following, we review the role of the renal sympathetic nervous system in blood pressure control and recent clinical experience with renal denervation. Furthermore, potential beneficial effects on diabetes control, obstructive sleep apnea, atrial and ventricular arrhythmias are discussed. *(Anadolu Kardiyol Derg 2014; 14: 186-91)*
Key words: hypertension, renal sympathetic denervation, diabetes, heart failure, sleep apnea

Introduction

The role of the renal sympathetic nervous system in blood pressure control as well as the effect of catheter-based renal sympathetic denervation on resistant hypertension and other conditions accompanied by sympathetic overactivity are reviewed.

Renal sympathetic nervous system

The kidneys receive (efferent) sympathetic nerve signals from the central nervous system. Equally important, they also relay information via afferent sympathetic nerve fibers to the central nervous system.

Efferent renal sympathetic nervous system

Signals from the cortex, ventrolateral nucleus of the hypothalamus, amygdala, baroreceptors and chemoreceptors are integrated predominantly in the rostral ventral medulla oblongata and solitary nucleus from where sympathetic signals are relayed to preganglionic nerves located in the intermediolateral substance of the spinal chord (the grey substance between the anterior and posterior horn). Preganglionic nerve fibers exit the spinal chord as part of the splanchnic nerve to supply the coeliac, superior and inferior mesenteric ganglion. Here, signals are, once again, relayed to postganglionic fibers that course within the renal artery adventitia to supply virtually every aspect of the kidney; the tubuloepithelial cells, juxtaglomerular apparatus and arterioles. On a molecular level, sympathetic nerve fiber endings adjacent to the tubuloepithelial cells release norepinephrine and neuropeptide Y. Norepinephrine binds to beta-and alpha-2 receptors, both present in the cell membranes of tubuloepithelial cells. Stimulation of beta-receptors inhibits, while stimulation of alpha 2-receptors activates the sodium/potassium ATPase with a net neutral effect. However, Neuropeptide Y also enhances the sodium/potassium ATPase, overall resulting in sodium/potassium ATPase activation causing sodium and water retention and, thereby, a blood pressure increase. Similarly, sympathetic nerve fibers innervate the granular cells of the juxtaglomerular apparatus. Norepinephrine causes activation of beta-1 receptors causing G-protein coupled adenyl cyclase activation and increased levels of cyclic AMP that leads to renin release. Renin, in turn, activates the renin-angiotensin-aldosterone system causing vasoconstriction, sodium and water retention and subsequently a blood pressure increase. Finally, sympathetic nerve fibers innervate arteriolar smooth muscle cells causing (via alpha-1a receptors) smooth muscle contraction and alteration of glomerular perfusion pressure. There appears to be a graded response with lower levels of sympathetic stimulation activating renin secretion and higher levels activating sodium and water resorption as well as renal arteriolar vasoconstriction.

Afferent renal sympathetic nervous system

The afferent limb of the renal sympathetic nervous system also plays an influential role in systemic blood pressure regula-

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tion. Afferent nerve fibers are located throughout the kidney, but are most prominent within the renal pelvis. Both mechanoreceptors and chemoreceptors provide feedback to stimulate the renal afferent nervous system. Mechanoreceptors monitor hydrostatic pressure within the renal pelvis and renal arterial and venous conduits. Chemoreceptors monitor the chemical composition within the renal interstitium and provide surveillance for development of ischemia. Signals are transmitted from the kidney via afferent sympathetic fibers (neurotransmitters: calcitonin gene related peptide and substance P) the nuclei of which are located in the dorsal root ganglia, to the ipsilateral posterior gray column (lamina I-III) where they are relayed to central nervous system autonomic centers (paraventricular nucleus of the hypothalamus and solitary tract nucleus in the brainstem) as well as to the contralateral kidney. Stimulation of the autonomic centers results in an increase in overall sympathetic tone causing vasoconstriction and fluid retention and consequently blood pressure increase whereas stimulation of the contralateral kidney results in changes in diuresis and natriuresis (renorenal reflex). The renorenal reflex has been shown to be eliminated by disruption of the afferent supply. The impact of renal afferent sympathetic nervous stimulation on blood pressure has been shown in animal studies that target activation or inhibition of this pathway. Induction of renal injury in rats by toxin injection or ischemia results in sympathetic nerve activation and blood pressure increase that can be attenuated or prevented by an interruption of the renal sympathetic nervous system. Dorsal rhizotomy (transection of the dorsal roots, the equivalent of complete interruption of afferent sympathetic fibers) results in decreased blood pressure sensitivity to dietary sodium intake (1) as well as diminished baroreflex control of the efferent renal system (2). In addition, a blood pressure reduction has been shown in renal insufficiency rat models (characterized by sympathetic overactivity) after dorsal rhizotomy (3).

Human evidence linking the sympathetic nervous system and blood pressure

The impact of the renal sympathetic nervous system on blood pressure has also been demonstrated in humans prior to current catheter-based renal denervation procedures. Patients with chronic kidney disease have provided evidence of the interaction between the sympathetic nervous system and hypertension. The increased sympathetic tone in patients with chronic kidney disease requiring dialysis normalizes following bilateral nephrectomy (4). The increased sympathetic activity persists if native kidneys are not removed and even persists following kidney transplant if the native kidneys remain (5). Similar trends have been shown with reduction in hypertension following nephrectomy in patients with kidney disease including those with unilateral disease and single nephrectomy [e.g. for pyelonephritis or congenital hypoplasia (6-8)] and in patients with bilateral disease and bilateral nephrectomy (9, 10). Though in the aforementioned observations, improvements in blood pressure control could be explained by interruption of sympathetic signals to and from the diseased kidneys, it is also conceivable that explantation of the diseased kidneys mediates the blood pressure improvement by a reduction in renin-angiotensin-aldosterone system activity that is typically increased in patients with chronic kidney disease whose kidneys remain in place. However, the renal sympathetic nervous system seemingly has a greater impact. For example, patients with chronic kidney disease generally experience a greater blood pressure reduction with central sympatholytic therapy (e.g., clonidine) than with blockade of the renin-angiotensin system (11). The mechanism for increased renal sympathetic activity is unclear, but may be related to renal ischemia as sympathetic nervous system activity decreases following angioplasty in patients with renal artery stenosis (12). Blood pressure has also been shown to improve following unilateral nephrectomy in patients with renal artery stenosis (13).

Percutaneous renal sympathetic denervation

The established role of the sympathetic nervous system in blood pressure management and the substantial influence of the kidney on hypertension as well as the location and exquisite sensitivity of the renal sympathetic nerve fibers to heat have led to the development and use of catheter-based renal sympathetic denervation by radiofrequency ablation in the human population. The safety of percutaneous renal nerve denervation via renal arterial catheterization and subsequent application of radiofrequency energy was shown in studies involving pigs. The immediate effects of radiofrequency ablation on arterial integrity were demonstrated by optical coherence tomography (OCT) in pigs and include arterial transmural tissue coagulation and loss of endothelium replaced by fibrotic tissue and almost complete re-endothelialization, respectively, within 10 days of ablation (14). The OCT studies also showed successful destruction of the renal sympathetic nerves (15). Autopsy evaluation at six months following ablation showed sustained denervation as well as arterial fibrosis involving 10 to 25 percent of the media and adventitia, but no evidence of renal artery stenosis or device-related microscopic renal injury (16). Importantly, a significant reduction in renal catecholamine content by approximately 50% typically occurs lending support to the hypothesis that catheter-based application of radiofrequency energy in fact does what it is intended for, a reduction in renal sympathetic nerve activity.

Catheter-based renal sympathetic denervation in humans was assessed in an initial feasibility, safety and efficacy trial known as the Symplicity-1 trial using the Symplicity catheter system (Medtronic Inc., Minneapolis, MN, USA) (16). The procedure begins by establishing femoral artery access with a 6F sheath followed by abdominal aortography identifying the take-off of all (including accessory) renal arteries. Anticoagulation and analgesia therapies are administered with continued maintenance of adequate pain control as the procedure is frequently associated with intense abdominal and/or lower back pain. The renal artery is then selectively engaged with a 6F guide catheter (typically a short internal mammary or renal double curve catheter) and selective renal angiography performed. The radiofre-

quency catheter is a soft-tipped catheter with a radiofrequency electrode at the distal end. The tip of this catheter can be flexed and turned via a hand control. It is gently advanced into the mid to distal segment of the renal artery and, by flexing or neutralizing the catheter tip, wall contact is established and, by turning the catheter, different quadrants of the renal artery can be reached. Radiofrequency energy (8 W) is applied for 2 minutes each. After ablation in one location, the catheter is pulled back in a step-wise fashion with radiofrequency application in a spiral-circumferential manner. Typically 4-8 ablations are performed per artery optimally spacing the ablation points at least 5 mm apart. The radiofrequency energy delivery is regulated by temperature and impedance feedback from the catheter tip to limit injury to surrounding tissue.

In Symplicity-1, 45 patients with severe resistant hypertension were enrolled to undergo radiofrequency renal sympathetic denervation (16). The procedure resulted in a significant 27 mm Hg systolic and 17 mm Hg diastolic blood pressure reduction at one year. Improvement in blood pressure control allowed for antihypertensive medication reduction in nine patients. Notably, there were four patients that required an increase in their antihypertensive medication regimen; however, the blood pressure reduction remained even after censoring these patients from analysis. No significant blood pressure reduction occurred in 13 percent of people following renal denervation. These were considered non-responders (defined as systolic blood pressure reduction of <10 mm Hg). Renal norepinephrine spillover and total body norepinephrine spillover were significantly decreased in the 10 patients who underwent measurement, once again lending support to the hypothesis that renal denervation does what it is intended for, a reduction in renal and overall sympathetic tone. Likewise, muscle sympathetic activity, a surrogate for overall sympathetic tone decreased after denervation and a reduction in cardiac mass was observed in cardiac magnetic resonance imaging (17). The reduction in muscle sympathetic nerve activity has been further confirmed by Hering et al. (18) Procedural complications occurred in two patients with one renal artery dissection secondary to catheter manipulation successfully treated with stenting and one femoral artery pseudoaneurysm. Patients from Symplicity-1 as well as others who underwent renal sympathetic denervation were entered into a registry that showed sustained blood pressure improvement of 33 mm Hg systolic and 14 mm Hg diastolic at 24 months post-procedure for the 18 people with follow-up data (19).

The Symplicity-1 trial was followed by the Symplicity HTN-2 trial to further assess renal sympathetic denervation in a randomized fashion. Symplicity HTN-2 included 106 patients with severe resistant hypertension who were randomized to renal sympathetic denervation and conventional medical therapy or conventional medical therapy alone. The primary endpoint was 6-month systolic blood pressure (20). Renal sympathetic denervation was found to be more effective at blood pressure reduction than medical therapy alone with a decrease in office blood pressure by 32 mm Hg systolic and 12 mm Hg diastolic in the sympathectomy group and no significant change in the medical therapy control group. A decrease in systolic pressure of 10 mm Hg or more occurred in 84% of patients who underwent renal sympathetic denervation compared to 35% in the medical therapy control group. Similarly, in patients who underwent 24-hour ambulatory blood pressure measurements there was a significant, albeit smaller blood pressure reduction of 11/7 mm Hg. No significant change in ambulatory blood pressure occurred in the control group. With the exception of a pseudoaneurysm formation managed with ultrasound-guided compression, there were no relevant adverse events. No changes in renal function or urine albumin to creatinine ratios were identified in either group. Continued monitoring showed sustained blood pressure reduction at 12 months with a mean decrease of 28 mm Hg in systolic office pressure in the renal denervation group. Patients from the control group were allowed to crossover to renal denervation therapy after six months provided the blood pressure remained uncontrolled with a systolic blood pressure greater than 160 mm Hg. The crossover group experienced similar blood pressure reductions with a significant 24 mm Hg decrease in systolic blood pressure at 6-month follow-up.

Renal sympathetic denervation has also been explored in patients with resistant hypertension of milder severity with systolic blood pressure between 140 and 160 mm Hg (21). The pilot study included 20 people with mild resistant hypertension who underwent renal sympathetic denervation and were prospectively evaluated. Blood pressure decreased by a mean of approximately 13 mm Hg systolic and 5 mm Hg diastolic at six months. Mean 24-hour ambulatory blood pressure monitoring showed a similar, but less pronounced 11/4 mm Hg blood pressure reduction at six months. No procedural complications occurred in this study group.

Study limitations

Although the findings of Symplicity-1 and Symplicity HTN-2 are promising, the studies are not without limitations. Symplicity-1 trial was an unblinded prospective cohort study that did not have a control group for comparison. Hence, a selection bias, a placebo effect and observer bias cannot be ruled out. Though Symplicity HTN-2 was a randomized trial, the investigators and patients were not blinded to the treatment. Therefore, once again, an observer bias and placebo effect cannot be excluded. In addition, a Hawthorne effect remains a possibility. In both trials patients with accessory renal arteries were excluded. However, in our experience (small subgroup), denervation with the Symplicity catheter can be performed safely in renal arteries >3.0-3.5 mm with somewhat less pronounced but significant and no less important blood pressure reduction (in press). Due to the labor intensive and invasive nature of norepinephrine spill-over and muscle sympathetic nerve activity measurements, these parameters were not measured in Symplicity-2 patients. Therefore, it cannot be determined whether baseline sympathetic nerve activity predicts response. Currently, the only two described independent predictors of response are the baseline blood pressure, with a more pronounced response in patients

with higher baseline blood pressures, (19-22) and baseline baroreceptor sensitivity with a more pronounced blood pressure lowering effect the lower the baseline baroreceptor activity (23). Lastly, patients with more than mild renal insufficiency were excluded in these two trials. Hence, though no significant change in glomerular filtration rate occurred and 12-month data in a smaller cohort of patients with renal insufficiency who underwent renal denervation did not show a reduction in glomerular filtration rate (24) the long-term effects on renal function have not yet been examined.

Any invasive therapy is accompanied with risk of vascular injury. Given reported cases of pulmonary vein stenosis after radiofrequency pulmonary vein isolation, renal artery stenosis after renal denervation is a concern. Notably, the radiofrequency ablation energy applied for renal sympathetic denervation is substantially lower than used in pulmonary vein isolation with 8 W used in renal sympathetic denervation and higher power (up to 30 W) applied during pulmonary vein isolation. In this context, imaging surveillance at six months with magnetic resonance angiography, computed tomography angiography or ultrasound evaluation in 81 patients showed no treatment site irregularities or stenoses that were not present prior to the procedure (19). Review of a renal sympathetic denervation registry identified one patient with pre-existent mild renal artery stenosis in a location remote from radiofrequency application that progressed to a hemodynamically significant stenosis at six months requiring renal artery stenting (19). Though the overall incidence of this complication appears to be low, it is noteworthy that there are two reports of renal artery stenoses that developed at ablation sites (25, 26) and that, due to the frequent inconsistent follow-up and absence of long-term data, a final conclusion regarding this risk cannot yet be made.

The variable response of renal sympathetic denervation with no or little change in blood pressure in approximately 15 percent of people remains unexplained. Interestingly, the response rate increased over time with only 10 percent of patients identified as nonresponders at three years indicating a delayed response in a small subset of patients (27). The lack of response may result from incomplete denervation or unrecognized secondary hypertension; however, there may be a group of hypertensive people that have normal sympathetic tone and their renal sympathetic activity does not play a major role in maintenance of their elevated blood pressure. Ensuring complete renal denervation by monitoring the heart rate, blood pressure and catecholamine spillover in response to electrical stimulation of renal adventitia has shown promise in dog models. It may provide a method of assessing immediate procedural success (28). The activity of renal efferent sympathetic fibers in hypertensive patients is variable as demonstrated by normal renal norepinephrine spillover in some patients despite increased skeletal muscle sympathetic activity complicating assessment of sympathetic activity (29). Elucidation of patient and disease characteristics that indicate a favorable response to renal sympathetic denervation will provide better guidance in patient selection for future procedures.

Although not a known limitation at this time, the question of re-innervation and return of resistant hypertension remains. Functional sympathetic nerve re-innervation has been identified in cardiac muscle following heart transplantation (30) so functional re-innervation of efferent fibers following ablation is a plausible consideration. Re-innervation in transplanted kidneys has been shown histologically; (31) however, transplanted kidneys are thought to remain functionally denervated (32). Available data for patients who underwent renal sympathetic denervation in Symplicity-1 show sustained blood pressure reduction at 24 months (19), therefore currently there is no evidence to suggest re-innervation within this time period.

Future directions

In addition to resistant hypertension, renal sympathetic denervation may also benefit other disease processes characterized by sympathetic overactivity.

Patients with diabetes mellitus were shown to have improved insulin sensitivity and glucose metabolism following renal sympathetic denervation (33-35). These benefits may be the result of improved skeletal muscle blood flow. Decreases in sympathetic nervous system activity and corresponding decreases in adrenergic alpha-1 receptor stimulation may improve skeletal muscle blood flow, capillary density and muscle fiber types and, thus, improve glucose transport into skeletal muscle cells (36). Reductions in gluconeogenesis, glucagon secretion and renin-angiotensin system activity may also help improve glucose metabolism and insulin resistance. Another potential benefit of renal sympathetic denervation in the diabetic population may result from prevention of diabetic nephropathy. Renal denervation has been shown to prevent glomerular hyperfiltration in rats, (37) a process that contributes to development of diabetic nephropathy in patients with type 1 diabetes (38, 39). Additional studies are needed to better elucidate the potential benefits of renal sympathetic denervation on limiting the deleterious effects of diabetes.

Atrial and ventricular arrhythmias have also been shown to improve (40, 41) and a reduction in left ventricular mass and improved diastolic parameters were reported after renal sympathetic denervation (42). Likewise, an improvement in apnea/hypopnea indices has been reported in hypertensive patients with obstructive sleep apnea who underwent renal sympathetic denervation (35).

Finally, patients with heart failure may benefit from renal sympathetic denervation. Sympathetic overactivity is commonly observed in heart failure patients (43) and associated with increased mortality (44). The benefits of inhibiting beta adrenoreceptors and the renin-angiotensin system on heart failure mortality are well known (45, 46). The reduction in sympathetic activity with renal sympathetic denervation might be expected to have similar benefits. Not surprisingly, decreased left ventricular filling pressures and improved left ventricular systolic function has been demonstrated following renal denervation in rats (47). Future studies will provide a better understanding of

renal sympathetic denervation and the subsequent changes in heart failure pathophysiology.

The encouraging data outlined in this review has stimulated the design of a number of new devices and concepts for renal denervation, the discussion of which is beyond the scope of this review. Briefly, ultrasound application to the renal sympathetic nerves invasively and non-invasively and chemical neurolysis (injection of neurotoxic substances into the renal artery adventitia) are being explored by a number of companies. To illustrate the enthusiasm to explore the effects of renal denervation, more than 95 studies have been listed in www.clinicaltrials.gov and the number of publications on the subject of renal denervation has increased several fold since the first catheter-based case in 2009.

There are a number of ongoing studies the outcomes of which will determine future directions of renal denervation. Two deserve mention. Symplicity-3 is a large randomized controlled trial comparing renal denervation in addition to antihypertensive medications to antihypertensive medications alone with both, a blinded patient (sham procedure) and follow-up investigator. Enrolment is complete and first results are expected in the first quarter of 2014. This will be the first trial that attempts to eliminate observer bias as well as a placebo and Hawthorne effect. EnligHTN-IV is a large randomized sham-controlled trial using a multi-electrode radiofrequency ablation catheter (St. Jude Medical, St. Paul, MN, USA). In this trial, cardiovascular events will be a primary endpoint. The results are expected in 2017.

Finally, radiofrequency application has recently been explored for the treatment of primary pulmonary hypertension resistant to conventional medications with a dramatic reduction in mean pulmonary artery pressure from 55 mm Hg to 36 mm Hg and pulmonary vascular resistance from 1800 to 760 dynes in a small cohort of patients. This is one of the most pronounced improvements in pulmonary artery pressure reported to date (48).

Conclusion

Renal sympathetic denervation provides an additional therapeutic option for patients with mild and severe resistant hypertension. Blood pressure reduction is sustained as demonstrated in ongoing surveillance studies with continued blood pressure control at three years following the procedure. As with all procedures, there is an inherent risk of procedural complications, but these are primarily limited to a very low incidence of arterial injury at the time of procedure. The benefits of renal sympathetic denervation likely extend beyond blood pressure control and may occur in other conditions characterized by a high sympathetic tone such as sleep apnea, diabetes, dysrhythmias and heart failure. Ongoing and future studies will provide further data evaluating the impact of renal denervation on hypertension and other conditions of sympathetic overactivity. It should be kept in mind, however, that hypertension remains silent until a catastrophic event occurs. Hence, in a perfect world, demonstration of a reduction in cardiovascular endpoints would eventually be desirable.

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