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ORIGINAL ARTICLE

Catheter based radiofrequency ablation of renal nerves for the treatment of resistant hypertension

Ablazione transcatetere dei nervi renali per il trattamento dell'ipertensione resistente

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KEYWORDS
Resistant hypertension;
Renal nerves;
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Summary
Introduction: Resistant hypertension is a common and growing clinical problem characterized by the failure to attain target blood pressure levels despite adequate use of at least three antihypertensive agents.
Objectives: The aim of this article is to emphasize the role of novel approaches to treat resistant hypertension.
Materials and methods: After an excursus on the physiological role of renal nerves on kidney function, volume homeostasis and blood pressure control, this article describes the radiofrequency ablation technology to obtain kidneys denervation.
Results: Activation of the sympathetic nervous system plays a prominent role as a major regulator of circulatory and metabolic control. The kidneys have a particularly dense afferent sensory and efferent sympathetic innervation and are thereby strategically positioned to be origin as well as target of sympathetic activation. In this context, recent evidence suggests that a novel catheter-based approach to functionally denervate the human kidneys using radiofrequency ablation technology may provide a safe and effective treatment alternative for resistant hypertension and its adverse consequences.
Conclusions: Despite the availability of numerous safe and effective pharmacological therapies to treat elevated blood pressure, novel therapeutic approaches are warranted to improve the management and prognosis of patients with refractory hypertension. Several clinical trials are currently conducted and planned to further substantiate the blood pressure lowering efficacy of this novel renal denervation procedure.

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Introduction

Although a common and growing clinical problem, there is a lack of data on the exact prevalence of resistant hypertension, which is commonly defined as blood pressure (BP) above target levels despite the use of three agents in adequate doses from different classes including a diuretic. Evidence from the *National Health and Nutrition Examination Survey* and from large randomized clinical trials indicate that between 20-30% of hypertensive patients require three or more antihypertensive agents to achieve BP targets. Failure to reach target BP levels despite therapeutic intervention leaves patients at high risk for major cardiovascular events [1] and developing additional approaches to the current management of resistant hypertension consisting of lifestyle modification combined with poly-pharmacotherapy remains a priority.

The sympathetic nervous system and blood pressure control

Clearly, the pathogenesis of primary hypertension is multifactorial. However, the sympathetic nervous system plays an important role in circulatory and metabolic control and has undoubtedly been established as a major contributor to the development of hypertension with BP elevation being initiated and sustained by elevated sympathetic nerve activity. Increased sympathetic outflow to the heart resulting in increased cardiac output and neurally mediated vasoconstriction of peripheral blood vessel are obvious examples of neural pathophysiological pathways leading to elevated BP. The consequences of increased sympathetic outflow to the kidneys, perhaps most important in this context, are sodium and water retention, increased renin release and alterations of renal blood flow, effects that contribute substantially to BP elevations, both acutely and in the long term. Accordingly, targeting the sympathetic nervous system directly appears to be a logical therapeutic approach for the treatment of hypertension.

The specific role of renal sympathetic nerves for hypertension and cardiovascular outcomes

The renal nerves are major regulators of kidney function, volume homeostasis and BP control. Assessment of regional overflow of norepinephrine (NE) from the kidneys to plasma clearly demonstrated that renal NE spillover rates are markedly elevated in patients with essential hypertension [2] and are associated with hypertensive target organ damage such as left ventricular hypertrophy. Interestingly, activation of cardiorenal sympathetic nerve activity is even more pronounced in heart failure, a common clinical consequence of long term and sustained elevated BP. Indeed, renal sympathetic activation has been shown to predict of all-cause mortality and heart transplantation in patients with congestive heart failure. Similarly, elevated NE plasma levels have been identified as major contributors to adverse cardiovascular outcomes in end stage renal disease, another condition commonly characterized by substantially elevated sympathetic nerve activity [3].

The kidneys have a dense afferent sensory and efferent sympathetic innervations. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control such as the heart and peripheral blood vessels, by modulating posterior hypothalamic activity. Interestingly, abrogation of renal sensory afferent nerves has been demonstrated to reduce both BP and organ specific damage caused by chronic sympathetic overactivity in various experimental models. Postganglionic sympathetic efferent nerve fibres innervate all essential renal structures including the renal vasculature, the tubules and the juxtaglomerular apparatus. Consequently, renal sympathetic activation results in volume retention and sodium reabsorption, renal blood flow reduction, and renin-angiotensin-aldosterone system activation. Targeting renal efferent sympathetic stimulation therefore appears as an obvious therapeutic strategy. Indeed, recent efforts to functionally denervate the human kidney by directly and specifically targeting both efferent sympathetic and afferent sensory nerves has sparked substantial interest as a novel treatment strategy particularly for resistant hypertension.

Beneficial consequences of therapeutic renal denervation

Renal denervation has been widely applied in experimental models of various conditions characterized by heightened sympathetic drive and consistently demonstrated the importance of renal sympathetic efferent and sensory afferent nerves and their contribution to the pathophysiology of hypertension, heart failure and chronic kidney disease.

In a large number of diverse animal models of experimental hypertension including genetic, salt sensitive, and obesity hypertension, bilateral renal denervation prevented the development or attenuated the magnitude of hypertension [4].

Although more difficult to assess in humans, there is very convincing evidence of increased sympathetic activity in various forms of hypertension including essential hypertension, obesity related hypertension, renal hypertension, hypertension associated with obstructive sleep apnea, and preeclampsia.

Novel catheter based approaches to renal denervation

Against this background, a recent safety and proof-of concept study for the first time applied a novel catheter based technique to selectively denervate the kidneys in patients with treatment resistant hypertension [5]. In this approach renal sympathetic nerve ablation is achieved percutaneously via the lumen of the renal artery using a catheter connected to a radiofrequency (RF) generator. After introducing the treatment catheter (Symplicity® by Ardian, Inc., Palo Alto, California, USA) into each renal artery discrete RF ablations lasting up to 2 minutes each are applied in order to achieve up to six ablations separated both longitudinally and rotationally

within each renal artery (*fig. 1*). Catheter tip temperature and impedance are constantly monitored during ablation and RF energy delivery is regulated according to a predetermined algorithm.

A total of 45 patients with a mean age of 58 ± 9 years and an average BP of 177/101 ± 20/15 mmHg despite concurrent use of a mean of 4.7 ± 1.5 antihypertensive agents were treated. The median duration of the procedure to achieve bilateral denervation was 38 minutes. Vascular safety analysis consisting of renal angiography at 14-30 days after the procedure and MR angiographies at 6 months post-procedure revealed no instances of renal artery aneurysm or stenosis or other long-term adverse events. A renal artery dissection occurred in one patient which required stenting without further adverse consequences. Although participating patients were repeatedly exposed to contrast media during serial angiographies renal function remained unchanged, indicative of a favourable vascular and renal safety profile. The ablation procedure was accompanied by diffuse visceral non-radiating abdominal pain which did not persist beyond the RF energy application and could be managed by intravenous narcotics and sedatives.

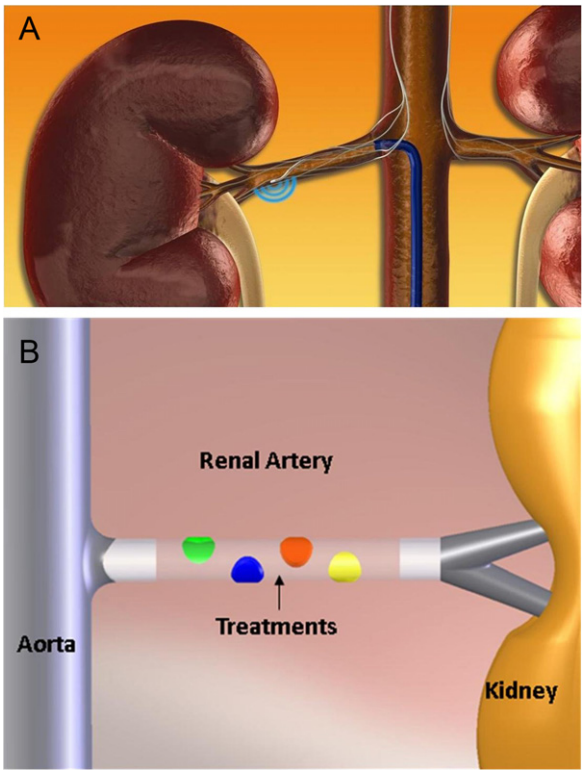

Figure 1 A, B) Schematic illustration of the percutaneous catheter-based approach to functionally denervate the human kidney. Similar to a routine angiogram access to the renal artery is obtained via a sheath in the femoral artery. The treatment catheter is then introduced into the renal artery and discrete RF ablation treatments lasting 2 minutes each are applied along the renal artery as illustrated. Up to 6 ablations are performed in each artery which are separated both longitudinally and rotationally to achieve circumferential coverage of the renal artery. Catheter tip temperature and impedance are constantly monitored during ablation and RF energy delivery is regulated according to a predetermined algorithm.

Radiotracer dilution methodologies were applied to assess overflow of NE form the kidneys into the circulation before and after the procedure to assess the effectiveness in reducing renal sympathetic nerve activity. These analyses revealed a substantial reduction in mean NE spillover of 47% (95% confidence interval, CI: 28-65%) at 1 month post-bilateral denervation.

Most importantly, the ablation procedure was associated with a significant and progressive reduction in both systolic and diastolic BP up to 12 months follow-up with mean (± 95% CI) decreases in office BP of −14/−10 ± 4/3, −21/−10 ± 7/4, −22/−11 ± 10/5, −24/−11 ± 9/5 and −27/−17 ± 16/11 mmHg at 1, 3, 6, 9 and 12 months, respectively.

Since sympathetic nerves have the potential to regrow, long term durability of renal denervation remains an important question. It is however reassuring that a very recent analysis summarizing the experience from longer term follow-up of the initial cohort (N = 45) and similar patients subsequently treated with catheter-based renal denervation in non-randomized and uncontrolled fashion (total N = 153) further support the efficacy of renal nerve ablation with post-procedure office BP being reduced by 32/14 mmHg at 24 months follow-up [6] (*fig. 2*). Based on these data durability of the effect appears to be evident up to at least 2 years.

Additional observations from mechanistic studies may shed some light into potential mechanisms involved in the BP reduction achieved by this approach. As discussed above, experimental data clearly indicates a role for afferent sensory nerves. Although afferent signaling cannot be measured directly in humans, the recent demonstration of a substantial and progressive reduction in central sympathetic outflow from baseline through to 12 months follow-up is perhaps indicative of alterations in afferent fibre signaling that may play an important role in the BP effects associated with this procedure. Furthermore, it is also noteworthy that that renal denervation decreased renin secretion by around 50% and that cardiac baroreflex sensitivity was also improved after renal denervation (from 7.8 to 11.7 ms/mmHg). In addition, cardiovascular imaging using MRI revealed a substantial reduction of left ventricular (LV) mass from

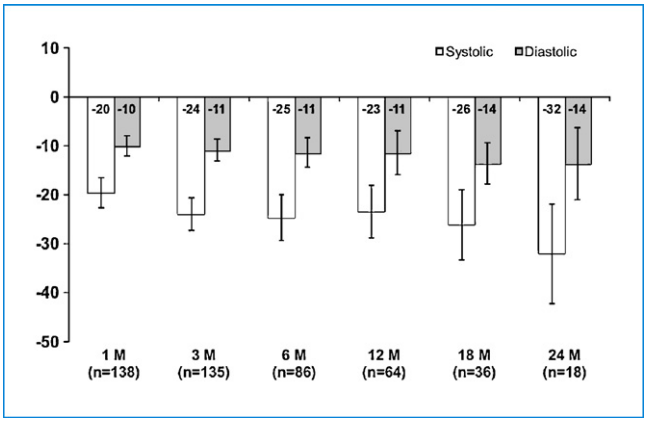

Figure 2 Mean systolic and diastolic blood pressure changes from baseline after renal denervation with up to 2 years of follow-up.

184 to 169 g (78.8 to 73.1 g/m^2) at 12 months follow-up compared to baseline [7].

In terms of procedural safety, a total of 4 acute complications occurred including 3 groin pseudoaneurysms and 1 renal artery dissection, all of which could be managed without further sequelae. One patient required stenting of a renal artery ostial stenosis that was present at baseline but grew by 6 months. Of note, no RF energy had been delivered in this location. Estimated glomerular filtration rate (eGFR) was reduced by −1.4 mL/min (95% CI: −4.6 to 1.7) at 3 months and by −2.8 mL/min (95% CI: −6.4 to 0.8) at 12 months, a reduction that was less pronounced that one would expect from the natural history reported in similar patients [8,9].

Very recently, results form the first randomized controlled clinical trial including a total of 106 patients were published [10]. Inclusion criteria were similar to those of the initial safety and proof-of concept trial with patients required to have a baseline systolic office BP $\geq$ 160 mmHg ($\geq$ 150 mmHg for patients with type 2 diabetes) despite compliance with $\geq$ 3 antihypertensive medications. Patients were then randomized to either undergo renal ablation treatment (N = 52) or to continue with conventional drug treatment as part of the control group (N = 54). It was attempted to keep concomitant antihypertensive agents unchanged in both arms through 6-months when the primary endpoint of seated office systolic BP was measured.

Both groups had similar baseline characteristics and antihypertensive regimen with the exception of eGFR which was lower in the active treatment group (77 mL/min vs 86 mL/min, p = 0.013). Periprocedural events requiring treatment were rare and consisted of one femoral artery pseudoaneurysm, one postprocedural drop in BP resulting in a reduction in antihypertensive drugs, one urinary tract infection, one extended hospital admission for assessment of paraesthesias, and one case of back pain that was treated with analgesics and resolved after one month. Seven (13%) of 52 patients who underwent renal denervation had transient intraprocedural bradycardia requiring atropine.

In keeping with the results from the first trial, a significant difference in the primary endpoint of seated office BP of 33/11 mmHg ($p < 0.001$ for both systolic and diastolic BP) was noted between the renal denervation group and the control group. Home BP recordings confirmed the observed office BP changes with a reduction in home BP by 20/12 ± 17/11 mmHg in the renal denervation group and a rise of 2/0 ± 13/7 mmHg in the control group ($p < 0.001$) (*fig. 3*). BP control defined as systolic BP < 140 mmHg was achieved in 39% of patients in the denervation group and in 3% of patients in the control group. In terms of safety, renal function measured by both serum creatinine based eGFR, and cystatin C levels were unchanged from baseline in both groups at 6 months. Six-month renal vascular imaging identified one patient with possible progression of an underlying atherosclerotic lesion, which required no therapy.

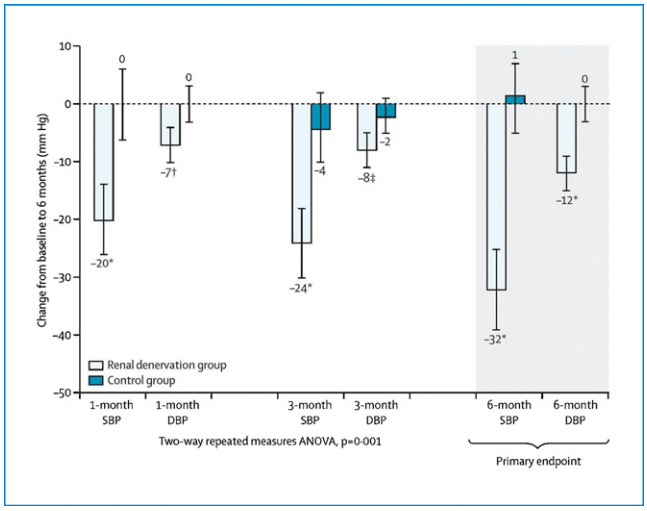

Figure 3 Change in systolic and diastolic office blood pressure in the renal denervation group and the control group, respectively.

While the available evidence indicates that catheter-based renal denervation has a favourable safety profile and results in substantial and sustained BP reduction in patients with drug resistant hypertension, the benefit of renal denervation may not be restricted to BP lowering alone. Hypertension is frequently associated with metabolic alterations such as overweight and obesity, impaired fasting glucose, impaired glucose tolerance, and insulin resistance. Sympathetic activation has clearly been identified as an important contributor to this detrimental clinical scenario [11]. Sympathoinhibition would therefore be expected to improve glycemic control [12]. Indeed, in a subset of patients from both renal denervation (N = 37) and control groups (N = 13) detailed assessment of glucose metabolism was performed by assessing fasting glucose, insulin, C-peptide, HbA1c, calculated insulin sensitivity (HOMA-IR) and glucose levels during oral glucose tolerance test (OGTT) at baseline and at 1 and 3 months follow-up post renal denervation. In addition to the BP fall observed in the treatment group (−32/−12 mmHg) after 3 months, fasting glucose (from 118 ± 3.4 mg/dL to 108 ± 3.8 mg/dL (p = 0.039)), insulin levels (from 20.8 ± 3.0 μIU/mL to 9.3 ± 2.5 μIU/mL; p = 0.006)), C-peptide levels (from 5.3 ± 0.6 ng/mL to 3.0 ± 0.9 ng/mL; p = 0.002) and the HOMA-IR (from 6.0 ± 0.9 to 2.4 ± 0.8; p = 0.001) also improved significantly after 3 months. Additionally, mean 2-hour glucose levels during OGTT were reduced significantly by 27 mg/dL (p = 0.012) while there were no significant changes in neither BP nor any of the metabolic markers described above in the control group [13].

Further support for such a beneficial role comes from investigations of yet another group of patients commonly characterized by overweight or obesity, sympathetic nervous system activation, insulin resistance and BP elevation, namely women with polycystic ovary syndrome. Using the gold standard methodology of euglycaemic hyperinsulinaemic clamp, it was demonstrated that insulin sensitivity improved by 17.5% in the absence of any weight changes at 3 months after renal denervation [14]. Of note, glomerular hyperfiltration and urinary albumin excretion were also reduced indicating that the benefits of renal denervation may also extend to renal structure and function, as suggested previously [3,15,16].

Summary and future perspectives

In summary, findings from these initial safety and proof-of-concept and one randomized controlled study indicate that

renal nerve ablation achieved via a novel catheter based approach using RF energy is safe and has the potential to improve BP control and alleviate the sequelae of elevated BP in patients with resistant hypertension. These beneficial effects appear to be mediated via interference with both efferent sympathetic and afferent sensory nerves and are likely to extend to improvements in metabolic control.

Whether this novel approach may also be useful in less severe forms of hypertension or in other conditions characterized by heightened renal sympathetic nerve activity, such as chronic and end-stage renal disease, needs to be determined in future studies. On the basis of the known pathophysiology, patients with either chronic or end-stage renal disease and those with heart failure also appear to be very suitable candidates for such an approach, given the evidence from both experimental and human studies to indicate that efferent sympathetic and afferent sensory signalling are crucially involved in the sympathetic activation almost invariably present in these patients. Another cohort of patients who may benefit form such an approach are those intolerant to pharmacological treatment. Several clinical trials are currently conducted and planned to further substantiate the BP lowering efficacy of this novel renal denervation procedure and to identify patient cohorts that are likely to benefit from such an approach.

Conflict of interest

Dr Schlaich and Dr Esler are principal investigators in ClinicalTrials.gov: NCT00483808 and ClinicalTrials.gov: NCT00551304 sponsored by Ardian Inc. Dr Schlaich and Dr Esler are supported by NHMRC of Australia Senior Research Fellowships. Dr Hering is supported by the Foundation for Polish Science-KOLUMB.

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