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Review Article

Renal Sympathetic Denervation for the Treatment of Difficult-to-Control or Resistant Hypertension

Vasilios Papademetriou,[1] Michalis Doumas,[2] and Konstantinos Tsioufis[3]

[1] *Veterans Affairs and Georgetown University Medical Centers, 50 Irving Street, Washington, DC 20422, USA*
[2] *Aristotle University of Thessaloniki, Thessaloniki, Greece*
[3] *National and Kapodistrian University of Athens, Athens, Greece*

Correspondence should be addressed to Vasilios Papademetriou, v.papademetriou@yahoo.com

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Hypertension represents a major health problem with an appalling annual toll. Despite the plethora of antihypertensive drugs, hypertension remains resistant in a considerable number of patients, thus creating the need for alternative strategies, including interventional approaches. Recently, catheter-based renal sympathetic denervation has been shown to be fairly safe and effective in patients with resistant hypertension. Pathophysiology of kidney function, interaction and crosstalk between the kidney and the brain, justifies the use of renal sympathetic denervation in the treatment of hypertension. Data from older studies have shown that sympathectomy has effectively lowered blood pressure and prolonged life expectancy of hypertensive patients, but at considerable cost. Renal sympathetic denervation is devoid of the adverse effects of surgical sympathectomy, due to its localized nature, is minimally invasive, and provides short procedural and recovery times. This paper outlines the pathophysiological background for renal sympathetic denervation, describes the past and the present of this interventional approach, and considers several future potential applications.

1. Introduction

Resistant hypertension is defined as uncontrolled blood pressure despite the use of optimal doses of three antihypertensive agents, of which one is a diuretic [1–4]. Using this definition prevalence of resistant hypertension can be as high as 30% in some regions, but prevalence of true resistant hypertension is most likely around 5% in organized referral centers [2–4]. Although several factors contribute to "resistant hypertension" (poor patient adherence, physician inertia, inappropriate drug combinations or inadequate dosing, drug-interaction, and secondary causes), the fact is that a small percentage of hypertensive patients remain with unacceptably high blood pressure levels. It has been shown that a majority of patients with resistant hypertension and no identifiable secondary causes have activated sympathetic nervous system and increased sympathetic outflow (Figure 1). The high prevalence of hypertension in the general population renders this small percentage of patients significant, in terms of actual patient numbers. The above, combined with several limitations of drug therapy (cost, adverse effects, polypharmacy, etc.), create the need for other therapeutic options, such as devices and interventions.

Despite the availability of multiple medications, control rates are still very low worldwide. Although progress has been made in the USA and other countries, control rates remain around 50% in the US and much lower in the rest of the world. The present situation is reminiscent of the 40s and 50s when therapeutic options for hypertension were limited and radical sympathectomy became popular among hypertension experts. The beneficial effects of pharmacologic therapy shown first by the Veteran Administration study group [5, 6] and later confirmed by many other trials made pharmacologic therapy the preferred and only option for the treatment of hypertension.

Surgical sympathectomy was driven to total obscurity primarily due to serious adverse effects. It should be noted, however, that sympathectomy was the first attempt to

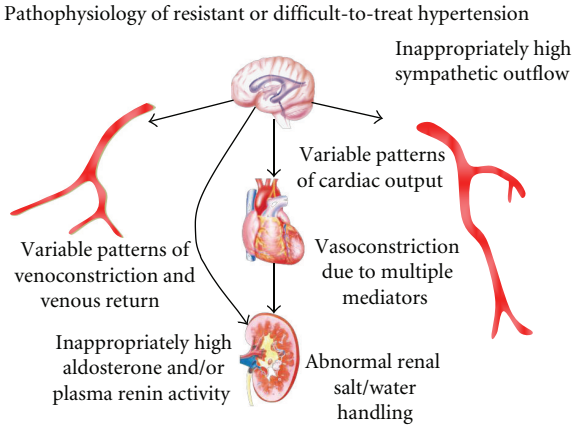


Figure 1: Demonstrates pathophysiology of resistant hypertension. Increased sympathetic outflow is a fundamental abnormality in most patients.

effectively confront malignant hypertension and its consequences through an interventional approach [7–12]. Indeed several studies have shown sympathectomy to be very effective in reducing blood pressure, and results were maintained in the long term (Figure 2). Recently another innovative approach has been used to decrease sympathetic outflow using an implantable device (Rheos) to electrically stimulate the carotid baroreceptors. Early results have shown adequate blood pressure and heart rate reduction (Figure 3), and feasibility studies have shown promising long-term results [13, 14]. However long-term randomized data are still pending.

Selective renal sympathetic denervation (RSD) [15] is the latest and perhaps the most interesting approach used recently in an attempt to interrupt the influence of the sympathetic nervous system on the kidney and systemic hemodynamics.

The sympathetic innervation of the kidney is implicated in the pathogenesis of hypertension through effects on rennin secretion, increased plasma rennin activity that leads to sodium and water retention, and reduction of renal blood flow (RBF) [16, 17]. Complete bilateral renal denervation decreases the level of blood pressure in several experimental models, such as spontaneously hypertensive rats, DOCA hypertensive rats, two-kidney one-clip rats, obesity-induced hypertensive dogs, and aortic coarctation dogs [16].

In this paper we will briefly summarize the role of renal sympathetic innervation on blood pressure regulation and discuss the past and the present of RSD in the treatment of arterial hypertension.

2. Renal Sympathetic Innervations

2.1. Efferent Sympathetic Fibers. The sympathetic innervation of the kidney is achieved through a dense network of postganglionic neurons that innervate the kidney [18, 19]. The axons of preganglionic neurons exit the thoracic and lumbar sympathetic trunk and reach the pre- and paravertebralsympathetic ganglia. Renal preganglionic nerves run alongside the renal artery and enter the hilus of the kidney. Thereafter, they divide into smaller nerve bundles following the blood vessels and penetrate the cortical and juxtamedullary areas (Figure 5). Renal sympathetic nerve activation enhances noradrenalin production for nerve endings and noradrenalin spillover [20–22], while interruption of renal sympathetic fibers results in a marked decrease of noradrenalin spillover (up to 95% [16]). When renal sympathetic nerves are activated, b_1 adrenergic receptors enhance rennin secretion and a1 receptor activation results in increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow.

2.2. Afferent Renal Sympathetic Innervation. Afferent renal sympathetic nerves originate mostly from the renal pelvic wall [23–25]. Mechanoreceptors respond to stretch and chemoreceptors detect renal ischemia [16, 26]. The cell bodies of renal afferent nerves lie in the ipsilateral dorsal root ganglia (T6-L4). From there, ascending signals travel to the renal cardiovascular centers in the CNS. Afferent renal nerve activation promotes vasopressin and oxytocin release from the neuro-hypophysis[51]. Prior renal denervation of the stimulated kidney, however, attenuates these effects, suggesting that complete renal denervation effectively inhibits ascending afferent stimuli. Overall afferent sympathetic fibers may have important contribution in regulation of systemic vascular resistance and blood pressure control. Figures 5 and 6 depict schematically the sympathetic innervations of the kidney and the pathophysiologic role of efferent and afferent fibers.

3. Renal Sympathetic Denervation (RSD)

3.1. Historical Perspective. Partial sympathectomy was attempted more than 40 years ago in patients with malignant hypertension. Malignant hypertension was a devastating disease with a five-year mortality rate of almost 100% [27], thus interventional approaches have been tested for its treatment given the lack of effective drug therapy. Sympathectomy was mainly applied in patients with severe or malignant hypertension, as well as in patients with cardiovascular deterioration despite of relatively good blood pressure reduction by other means [7–12]. After the introduction of antihypertensive drugs, sympathectomy was reserved for patients who failed to respond to antihypertensive therapy or could not tolerate it.

Total sympathectomy was impractical and poorly tolerated by most patients. It had to include the abdominal organs in order to be effective, and it was thus termed splanchnicectomy. Sympathectomy was performed either in one or two stages, required a prolonged hospital stay (2–4 weeks) and a long recovery period (1-2 months) and more importantly a skilled surgeon to perform it. It was thus performed only in a few selected centres in the USA (Boston, Michigan, Cleveland, Rochester, Miami, and California) and in Europe. Pioneers with significant contribution in this field include Page, Craig, Peet, Isberg, Smithwick, Allen, and Adson.

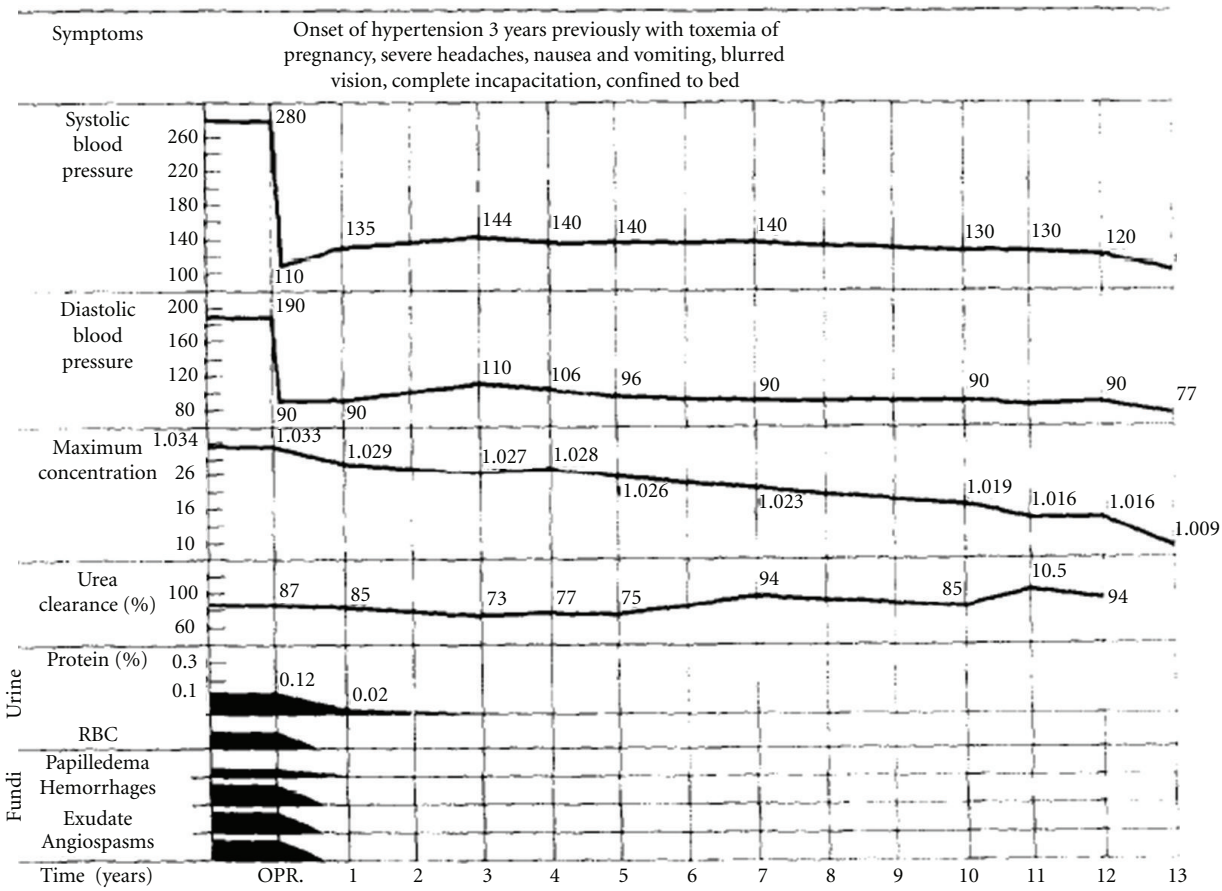


Figure 2: Long-term blood pressure control following surgical sympathectomy.

Ability to personalize and control the therapy

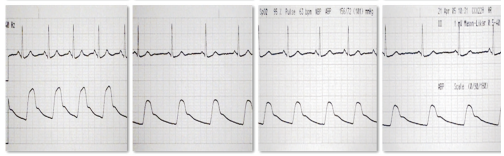
	Control	1 volt	2 volts	3 volts
				
Heart rate (bpm)	71	56	58	50
Blood pressure (mmHg)	210/96	168/73	156/72	144/66

Figure 3: Blood pressure and heart rate reduction using baroreceptor stimulation therapy (BST) from 1 to 3 volts. Note that acutely blood pressure was reduced from 210/96 to 144/66 and heart rate from 71 to 50 beats per minute.

Radiofrequency ablation of sympathetic fibers

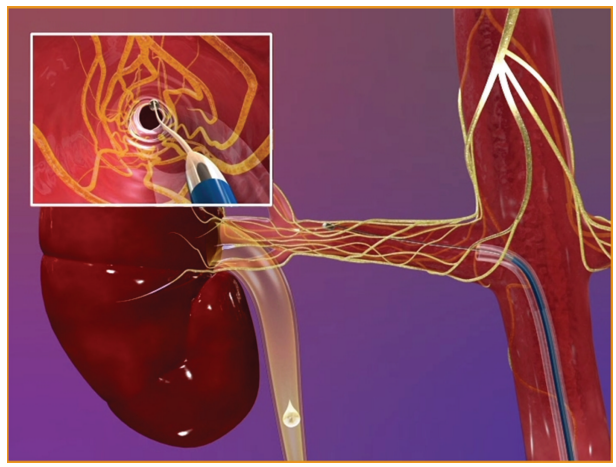


Figure 4: Sympathetic fibers, both efferent and afferent, are found in the adventitia of renal arteries. These fibers can be ablated using specialized catheters that deliver radiofrequency energy.

Sympathectomy proved to be effective in reducing blood pressure immediately postoperatively, and the results were maintained in the long term in most patients. Sympathectomy was associated with improved survival in the long run. Notably, in a large observational study of more than 2,000 patients (1,506 splanchnicectomy), survival rates were more than doubled in patients undergoing sympathectomy, and the benefits were evident in all stages of hypertension [28]. A satisfactory blood pressure response was observed in about half of the patients that underwent splanchnicectomy.

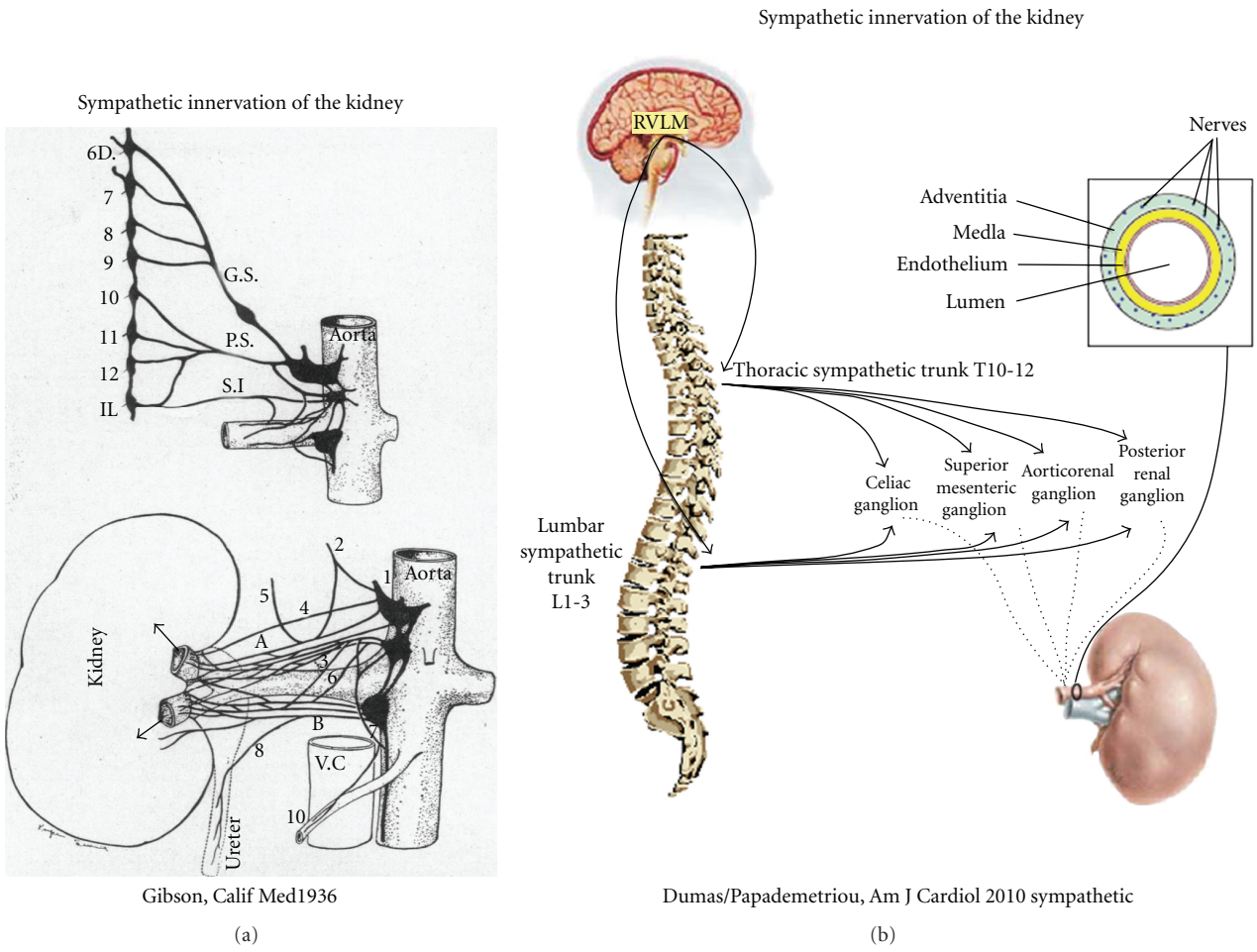


Figure 5: Schematic representation of sympathetic innervations of the kidney.

The two major limitations of splanchnicectomy were the required surgical expertise and the frequent adverse events occurring with this procedure. Adverse events were common, annoying, some of them serious, and included orthostatic hypotension, orthostatic tachycardia, palpitations, breathlessness, anhidrosis, cold hands, intestinal disturbances, loss of ejaculation, sexual dysfunction, thoracic duct injuries, and atelectasis. The advent of effective antihypertensive therapy made surgical sympathectomy unattractive and undesirable for most patients.

4. Current Use of Renal Sympathetic Denervation (RSD)

Renal sympathetic denervation presents a major improvement with several significant advantages over the radical sympathectomy that was performed five decades ago. It is a localized procedure, minimally invasive, and has no systematic side effects, and the procedural and recovery times are very short (see Figure 4). The technique was pioneered by Sobotka, Krum, and others who performed the first study of catheter-based RSD [14]. The study included 50 patients with resistant hypertension, with 45 of them fulfilling eligibility anatomical criteria. Renal sympathetic ablation was achieved using a radiofrequency ablation catheter inserted through the femoral artery and selectively engaging the renal artery bilaterally (Symplicity, Ardian Inc., Palo Alto, Calif, USA). This proof-of-principle trial was carried out in patients with resistant hypertension (i.e., systolic blood pressure ≥ 160 mmHg on three or more antihypertensive medications, including a diuretic). The primary objective of the study was safety and efficacy. The primary endpoint was change in office blood pressure at 1, 3, 6, 9, and 12 months after the procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after the procedure in some patients. The efficacy of RSD was confirmed in a subgroup of 10 patients by the use of noradrenaline spillover technique. Renal sympathetic ablation resulted in impressive blood pressure reductions that were maintained during the 12-month follow-up period (Figure 7). Five patients that were ineligible for the study due to anatomical reasons were used as controls; blood pressure in these patients gradually increased during the follow-up period.

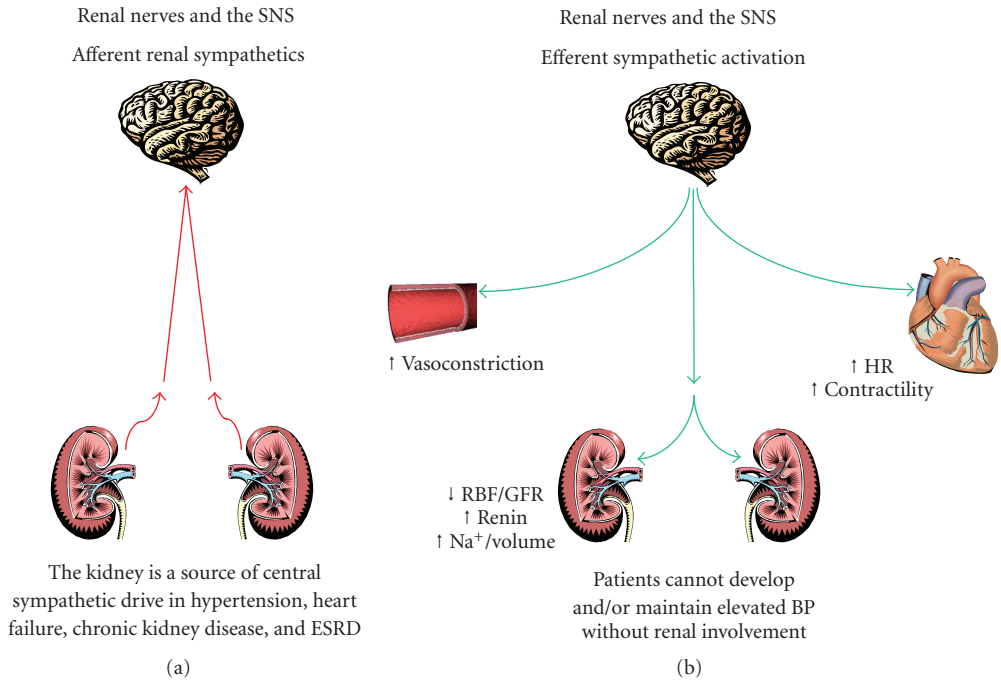


Figure 6: Afferent and efferent sympathetic innervations of the kidney.

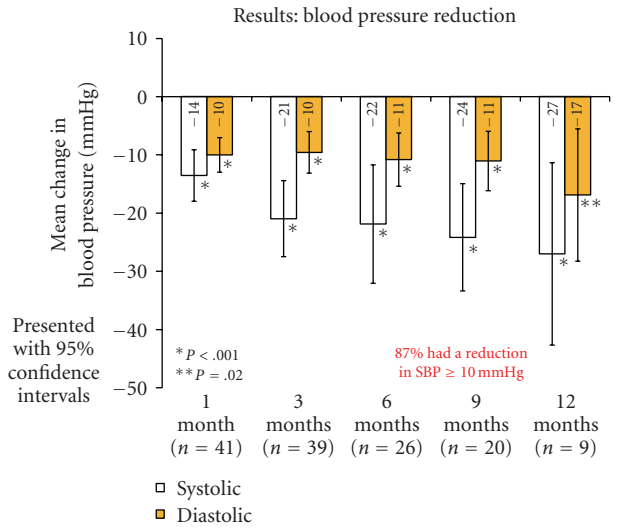


Figure 7: Blood pressure response following bilateral renal sympathetic denervation using a radiofrequency ablation catheter.

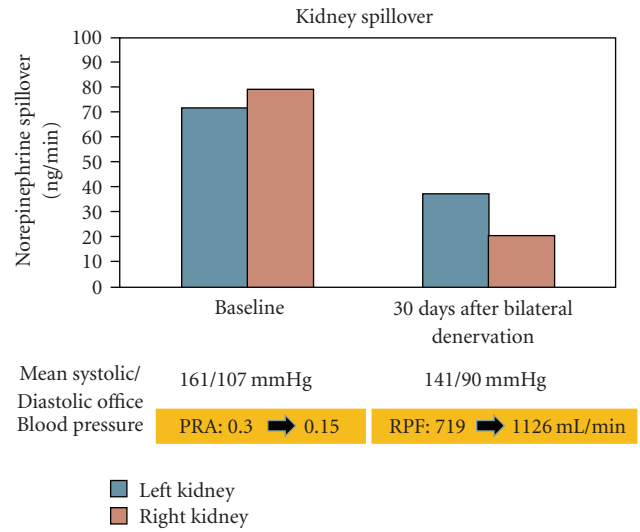


Figure 8: Noradrenalin spillover of both the right and the left kidneys at baseline and 30 days after sympathetic renal denervation.

This proof-of-concept study opens new avenues in the treatment of resistant hypertension. The study provided the first evidence that catheter-based ablation of renal sympathetic fibers is safe and effective. Only two adverse effects occurred (one renal artery dissection and one femoral artery pseudoaneurysm). These were complications related to the percutaneous technique and not to radiofrequency ablation. Postprocedural anatomic adverse events were evaluated by renal angiography at one month in 18 patients and renal magnetic resonance angiography (MRA) at six months in 14 patients. The study is important because it demonstrates for the first time in humans that RSD can reduce blood pressure in a safe way and results are sustained in the long term. In fact follow-up data in an expanded group of patients ($N = 153$) indicate that blood pressure lowering is maintained for >2 years after the procedure with favorable target organ consequences.

Although these results were impressive, the study created several concerns and many questions were left to be explored: There was no proper control group, since the study was

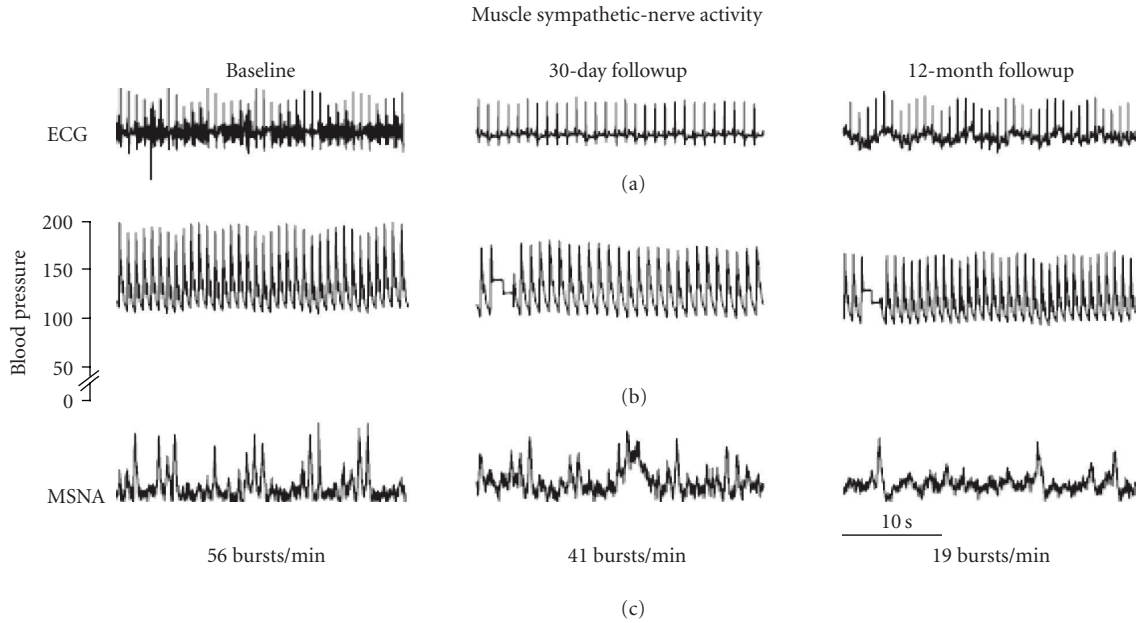


Figure 9: Results of microneurography before and after renal nerve ablation. Panel (a) shows the results of bilateral renal denervation, as assessed by the radiotracer dilution method, at baseline and 30 days after the procedure. After ablation, decreases in renal norepinephrine spillover were observed in both kidneys (48% in the left kidney and 75% in the right kidney), indicating substantial modulation of renal sympathetic efferent nerve activity after the procedure. Simultaneously, a marked reduction in whole-body sympathetic nerve activity was apparent, with a decrease in whole-body norepinephrine spillover of 42% (b). Panel (c) shows a reduction in muscle sympathetic-nerve activity (MSNA), as assessed in the peroneal nerve on microneurography, after bilateral renal nerve ablation, which highlights the possibility that inhibition of afferent renal-nerve activity may contribute to the reduction in central sympathetic drive.

not randomized or placebo (sham-operation) controlled. A proper workup of resistant hypertensives was not performed prior to randomization, in order to exclude patients with white coat hypertension, poor adherence, secondary forms or hypertension, or other correctable types of resistant hypertension. Furthermore, predictors of blood pressure response have not been identified, generating unavoidable concerns when it comes to an interventional approach.

Another major concern with the radiofrequency-induced renal sympathetic nerve ablation was the potential for development of suitable substrate for renal artery stenosis due to intimal injury. Tissue damage and fibrosis have been observed with radiofrequency ablation in other areas of the body (i.e., left atrium for atrial fibrillation, tumor ablation, etc.). it is important to note, however, that the energy delivered in other conditions is much higher compared to the one required for RSD, thus rendering RSD potentially harmless. Credence to this argument comes from the findings of Krum et al. [14, 15]. They reported that no signs of renal artery stenosis were observed during the six-month follow-up period, using magnetic resonance angiography, and no evidence of renal artery stenosis was found in the expanded group of patients with >2 year follow-up.

Further insights into mechanisms of hypertension control through RSD were published in a recent case report of a 59-year old patient with long-standing uncontrolled hypertension on a multidrug regimen [29]. In this case, baseline renal nor-epinephrine spillover from both the left and right kidneys, was approximately three times the normal level, indicating increased renal sympathetic neuronal efferent activity. Bilateral renal sympathetic nerve ablation resulted in marked reduction of blood pressure and decrease of norepinephrine spillover by 48% from the left kidney and 75% from the right kidney (Figure 8). This reduction in renal norepinephrine spillover was associated with a 57% increase in renal plasma flow. Whole-body norepinephrine spillover was reduced by 42%, providing evidence of afferent renal nerve interruption resulting in decreased central sympathetic outflow. Furthermore, muscle sympathetic nerve activity, assessed by microneurography, decreased toward normal levels at 30 days and 12 months after renal denervation (Figure 9).

Recently a second catheter-based RSD study—the Simplicity HTN-2 [30] study—was published confirming the initial results in a controlled sample. In this multicentre, prospective, randomised trial, patients with a baseline systolic blood pressure of 160 mmHg or more (≥150 mmHg for patients with type 2 diabetes) were randomly assigned to renal denervation with previous treatment or to maintaining previous treatment alone (control group). The primary endpoint was change in seated systolic blood pressure at 6 months. Out of 190 patients screened for eligibility, 106 were randomized to renal denervation ($n = 52$) or control ($n = 54$) groups. Office-based blood pressure measurements in the renal denervation group decreased by 32/12 mmHg (baseline of 178/96 mmHg, $P < .0001$), whereas they did not differ from baseline in the control group (change of 1/0 mmHg (21/10), baseline of 178/97 mmHg, $P = .77$

systolic and $P = .83$ diastolic). Between-group differences in blood pressure at 6 months were 33/11 mmHg ($P < .0001$). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls ($P < .0001$). No serious procedure-related or device-related complications were noted, and occurrence of adverse events did not differ between groups. Results of this study are reassuring and take the concept one step further. Nonetheless concerns about long-term safety and efficacy still remain.

5. The Future of RSD

Certainly results of these two studies employing catheter-based SRD open new avenues for the treatment of patients with resistant or difficult-to-control hypertension. Future research needs to investigate whether RSD can be applied in milder forms of hypertension, for noncompliant patients, patients intolerant to medication, and in several other conditions, such as hypertension with left ventricular hypertrophy (LVH), congestive heart failure, and chronic kidney disease.

6. Conclusions

Resistant hypertension represents a significant challenge in everyday clinical practice. Catheter-based RSD represents an innovative new technique to effectively reduce blood pressure in these patients. The pathophysiology of hypertension supports the use of RSD in the treatment of many patients with essential hypertension.

A vast amount of evidence suggests beneficial effects of sympathectomy on life expectancy in patients with severe or malignant hypertension and in the prevention of cardiovascular complications in patients with milder forms of hypertension.

RSD will significantly enrich the therapeutic armamentarium for hypertension treatment and control. Indeed if RSD proves to have long-lasting beneficial effects, patients would have a choice between interventional therapy or cure of hypertension and lifelong drug therapy with associated expense and potential side effects. It may be far fetched, but, RSD may become in the future a viable alternative to lifelong drug therapy.

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