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New developments in the treatment of severe drug resistant hypertension

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Abstract

The purpose of this paper is to review the state-of-the-art of renal denervation system technology for treatment of drug resistant hypertension. We describe an investigational device that is currently tested in an on-going clinical trial. The denervation device uses the RF thermal ablation catheter attached to the RF generator. The RF catheter is inserted into the renal artery and positioned in the vicinity of the efferent and afferent parasympathetic innervations. Renal denervation is a minimally invasive, localized procedure and the procedural and recovery times are very short. The entire procedure lasts about 40 min. In early clinical trials, the systolic blood pressure in 87% of patients who underwent the denervation procedure resulted in an average blood pressure drop of greater than 10 mm Hg. The procedure has no systematic side effects, and appears to be beneficial in the management of hypertension in patients refractory to pharmacological therapy. (Cardiol J 2011; 18, 6: 707–711)

Key words: hypertension, renal denervation, RF ablation

Introduction

Hypertension is the leading attributable cause of death worldwide. It is a significant, costly and escalating global healthcare problem affecting approximately 1.2 billion people, and is associated with an increased risk of heart attack, stroke, heart failure, kidney disease and death [1]. Among adults aged 40––70, each increment of 20 mm Hg in systolic blood pressure (SBP; the top number) or 10 mm Hg in diastolic blood pressure (DBP; the bottom number) doubles the risk of cardiovascular disease [2]. Hypertension is estimated to directly cost the global healthcare system more than $500 billion annually.

Although pharmaceutical therapy plays a primary role in hypertension management, drugs alone are not effective for all patients [3]. As a result, despite lifestyle changes and the availability of modern antihypertensive agents, approximately 50% of patients with hypertension remain uncontrolled and approximately 15–20% of those are treatment resistant [4].

Renal denervation is a minimally invasive, catheter-based procedure that modulates the output of nerves that line the walls of the arteries leading to the kidneys [5]. The targeted nerves are part of the sympathetic nervous system, which has been found to play a central role in blood pressure regulation.

Renal sympathetic innervations

A dense network of postganglionic neurons that innervate the kidney form the efferent sympathetic innervations [5, 6]. 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 (Fig. 1). Renal sympathetic nerve activation enhances noradrenalin production for nerve endings and noradrenalin spillover, while interruption of renal sympathetic fibers

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results in a marked decrease of noradrenalin spillover (up to 95%). When renal sympathetic nerves are activated, β_1 adrenergic receptors enhance renin secretion and α_1 receptor activation results in increased sodium and fluid reabsorption, renal vasoconstriction, and decrease in renal blood flow.

Afferent renal sympathetic nerves originate mostly from the renal pelvic wall. The cell bodies of renal afferent nerves lie in the ipsilateral dorsal root ganglia. From there, ascending signals travel to the renal cardiovascular centers in the central nervous system. Afferent renal nerve activation promotes vasopressin and oxytocin release from the neuro-hypophysis. 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 make an important contribution to the regulation of systemic vascular resistance and blood pressure control.

Renal denervation system

Renal sympathetic denervation using a radiofrequency (RF) ablation catheter (Symplicity™, Ardian Inc, Palo Alto, CA, USA) presents several significant advantages over other treatment options for resistant hypertension [6]. It is a localized procedure, minimally invasive, and has no systematic side effects, and the procedural and recovery times are very short. The Symplicity™ Renal Denervation System comprises two main components:

— Symplicity™ catheter — low profile, endovascular energy delivery catheter;
— Symplicity™ generator — automated, portable RF generator.

The elements are designed to work together as an integrated system to ensure consistent performance.

Symplicity™ catheter

The Symplicity™ catheter (Fig. 2) is specifically designed for safe endovascular application in the renal artery. Key features include:

— 6 F compatible;
— ergonomic controls for rotation and articulation;
— self-orienting tip for confident, atraumatic vessel wall contact;
— released energy maximum 8 Watts;
— temperature 40–75°;
— generator automatically switches off if temperature is higher than 75°;
— energy application up to 5× for each renal artery, depending on length of renal artery;
— treatment time: 2 min per one energy application.

The catheter has a flexible RF tip that can be precisely manipulated, similar to RF ablation catheters used in percutaneous electrophysiology procedures.

Symplicity™ generator

The RF generator (Fig. 2) is fully automated, allowing the clinician to focus on the procedure rather than the equipment. Key features include:

— automatically controls each RF energy delivery;
— hands-free pedal activation;
— compact and lightweight;
— built-in control mechanisms maximize safety;
— temperature and impedance monitoring protect against excessive energy delivery.

Procedure

The 6 F Symplicity™ catheter is introduced through the skin into the femoral artery, located in the upper thigh, and is then threaded up into the renal artery leading to each kidney [7, 8]. It is connected to the Symplicity™ generator, which produces low-power RF energy (Fig. 3).

The renal nerves lie in adventitia, encircling the renal arteries. Once in place within the renal artery, the tip of the Symplicity™ catheter is placed against the arterial wall in several places where it delivers RF energy to the surrounding sympathetic nerves according to a proprietary, computer-controlled algorithm. The median procedure time is 38 minutes. Typical procedure comprises 4 treatments in right renal artery and 4 treatments in left renal artery. Intravenous narcotics and sedatives are used to manage pain during delivery of RF energy. The treatment does not involve a permanent implant and is performed under conscious sedation [9].

Early clinical results

Controlled trials of catheter-based renal denervation in patients with resistant hypertension showed that this procedure resulted in significant reductions in blood pressure without any major complications [10].

The initial trial (Symplicity I) was conducted at 24 centers in Europe, Australia, and New Zealand [10]. In the study, 106 patients with resistant hyper-

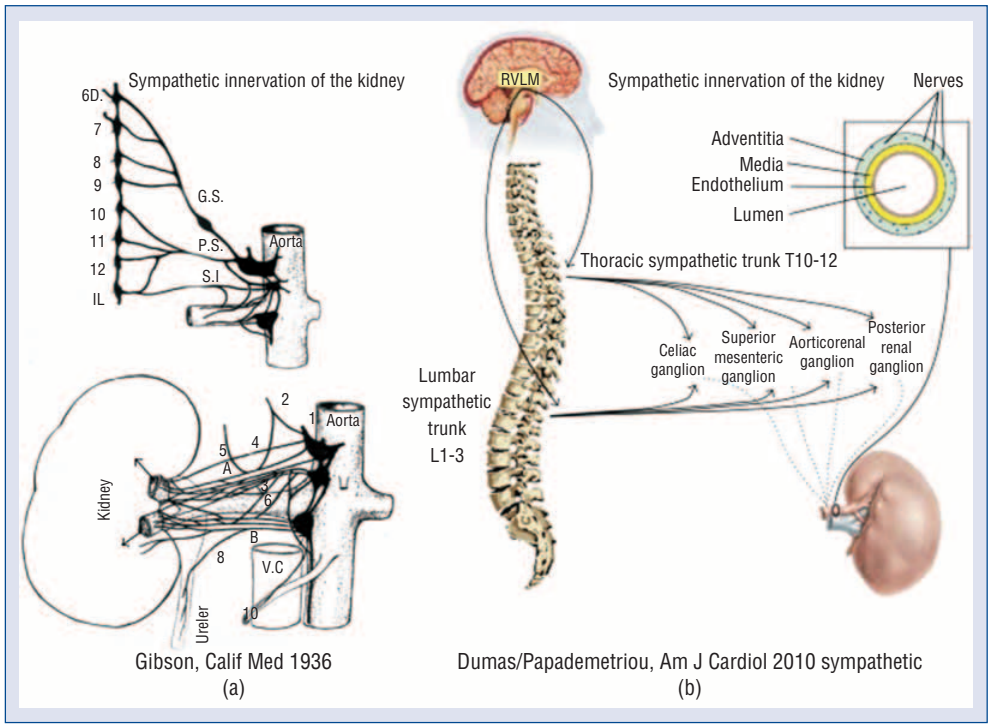

Figure 1. Simplified representation of sympathetic innervations of the kidney.

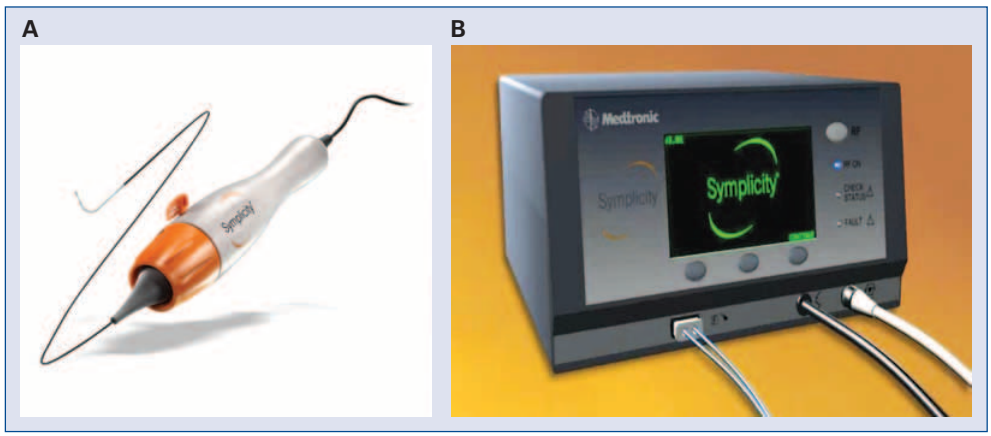

Figure 2. Symplicity radiofrequency (RF) catheter for RF ablation of efferent and afferent parasympathetic innervations (**A**). Symplicity RF generator (**B**).

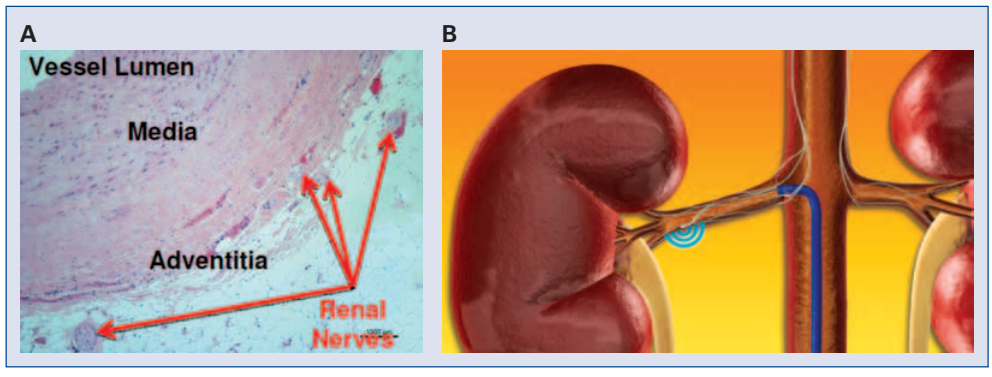

Figure 3. Sympathetic fibers, both efferent and afferent, are located in the adventitia of renal arteries (**A**). These fibers can be ablated using specialized catheters that deliver radiofrequency energy (**B**).

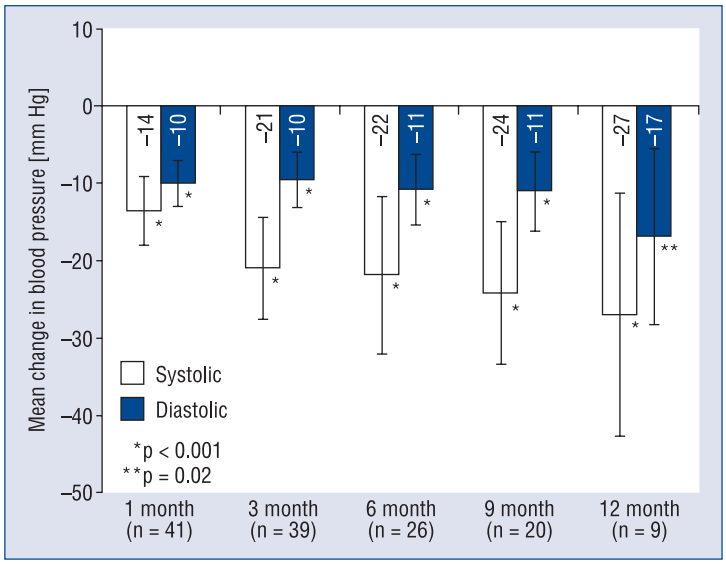

Figure 4. Summary of results from the Symplicity-HTN-2 Trial; results: blood pressure reduction; 87% had a reduction in systolic blood pressure (SBP) ≥ 10 mm Hg; presented with 95% confidence intervals.

tension (SBP of ≥ 160 mm Hg, or ≥ 150 mm Hg for those with type 2 diabetes, despite taking three or more antihypertensive drugs) were randomized on a one-to-one basis to undergo renal denervation with previous treatment (n = 52) or to maintain previous treatment alone (control group; n = 51). The trial designers wanted to "isolate the effect of the denervation", which is why the decision was made to keep the patients' medications uncontrolled.

The Symplicity I trial [10] showed promising results: 89% of patients saw their blood pressure drop dramatically. At 12 months, the average decline in SBP was 27 points and the decrease in DBP was 13 points. There was no evidence that the procedure harmed vessels or kidney function. The one--year follow-up showed that the effect on blood pressure was long lasting.

The Symplicity-HTN-2 [9] results show that six months after the ablation, average office-based blood pressure in the renal-denervation group was reduced by 32/12 mm Hg (average baseline 178/ /96 mm Hg), whereas it did not differ from baseline in the control group (change of 1/0 mm Hg from baseline of 178/97 mm Hg). The between-group differences in blood pressure at six months were 33/11 mm Hg ($p < 0.0001$).

Of the patients in the ablation arm, 87% had a 10 mm Hg or greater drop in SBP compared with 35% of controls ($p < 0.0001$). The remaining 16% of those in the ablation arm were considered to be 'non responders', because they had only a 0 to 9 mm Hg drop in blood pressure. The procedure appears to be long-lasting. It was thought initially that sympathetic nerve re-growth might mitigate the treatment effect, but in the patients treated in the pilot studies, no loss of antihypertensive effect has been seen over a follow-up of two years (Fig. 4).

In October 2011, Medtronic Inc. which recently acquired Ardian, announced the start of Symplicity-HTN-3, the company's U.S. clinical trial of the Symplicity® Renal Denervation System™. Symplicity-HTN-3 is a randomized controlled trial designed to evaluate the safety and effectiveness of renal denervation with the Symplicity Renal Denervation System in patients with treatment-resistant hypertension.

The study will enroll approximately 530 treatment-resistant hypertension patients across 60 U.S. medical centers. All patients and hypertension follow-up assessors will be blinded to the randomization assignments to remove any potential for bias. The primary end-points of the study are the change in blood pressure from baseline to six months and incidence of major adverse events up to six months following randomization.

More information about Symplicity-HTN-3 and renal denervation is available online at www.SymplifyBPtrial.com

Regulatory status

The Symplicity™ catheter is approved for clinical use in the EU and Australia. It is not approved by the U.S. Food and Drug Administration (FDA).

Its use in the United States is limited by U.S. law to clinical studies approved by the FDA.

Conclusions

Percutaneous, catheter based, therapeutic renal sympathetic denervation is simple and safe. Significant and sustained reductions in blood pressure were achieved in patients with multi-drug resistant hypertension. There was no significant decline in (and indeed a suggestion of preservation of) renal function with renal denervation [9].

Therapeutic renal sympathetic denervation involves a brief, simple percutaneous procedure. The procedure seems to be beneficial in the management of hypertension in patients refractory to pharmacological therapy. More prospective randomized controlled trials are required to definitively determine the role of this therapy in essential hypertension, and in allied disorders (renal hypertension, heart failure, and resistant hepatic ascites).

Future directions

More research needs to be done to extend the renal denervation concept to other forms of hypertension and to look at the efficacy in subgroups of patients with hypertension and possibly in other indications, because stimulated sympathetic nerves are important in other diseases, such as heart failure [11, 12].

Acknowledgements

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