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# Catheter-based renal sympathetic denervation: A targeted approach to resistant hypertension

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## Introduction

Hypertension is a growing public health concern for which successful treatment often remains elusive. In the United States, an estimated one in three adults has hypertension and the global prevalence continues to climb, particularly in developing countries [1, 2]. Despite access to pharmacological therapies and resources to help patients achieve necessary lifestyle modifications, approximately half of patients fail to achieve recommended target blood pressure values [1]. This can perhaps be attributed to patient non-adherence as a result of physician inertia, polypharmacy, adverse drug events and patient resistance to a lifelong regimen for a largely asymptomatic disease. More than 50 years of drug development has worked to the benefit of many hypertensive patients. But such development has slowed and the time has come to consider non-drug therapies for this rampant disease. New therapeutic approaches that will overcome these obstacles are essential [3, 4].

A small, but significant, percentage of patients [5] with uncontrolled hypertension fail to meet therapeutic targets despite taking multiple drug therapies at the highest tolerated doses, a phenomenon called 'resistant hypertension'. This may suggest underlying pathophysiology resistant to current pharmacological approaches [4]. Innovative therapeutic approaches are particularly relevant for these patients, as their condition puts them at high risk of major cardiovascular events [6].

Renal afferent and sympathetic efferent nerves have been implicated in the pathophysiology of systemic hypertension [7–10]. As a result, a succession of therapeutic approaches have targeted the sympathetic nervous system to modulate hypertension, with varying success. Many of these early approaches involved radical sympathetic denervation, failing to target specific organs thought to be directly involved with the pathophysiology of the disease. While successful in reducing blood pressure, the broad nature of these approaches led to many perioperative and long-term complications, including bowel, bladder and erectile dysfunction, as well as the dreaded side-effect of postural hypotension [11–13].

But a more targeted approach of renal sympathetic denervation remains a potential therapeutic option and is emerging as a subject of active research. Recent studies have aimed to assess the safety and efficacy of a percutaneous, catheter-based approach designed to specifically ablate renal sympathetic nerves using a radiofrequency generator via the lumen of the main renal artery. In a safety and proof-of-principle study, and a separate randomized controlled trial, both published in the Lancet, in 2009 and 2010 respectively, this approach was shown to successfully reduce blood-pressure, without serious adverse events in patients with resistant hypertension [3, 4]. This article will review the recent literature regarding catheter-based renal ablation in the context of current knowledge of the pathophysiology of resistant hypertension, and will explore future directions for research regarding this new approach.

## Renal innervation and the pathophysiology of hypertension

For the first half of the 20th century, renal innervation was thought to extend only to the renal

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vasculature, and renal nerves were believed to have little functional consequence [14]. The subsequent demonstration that norepinephrine-containing renal sympathetic nerve terminals make contact with the renal tubular epithelial cell basement membrane [15] opened a new line of questioning regarding neural control of the kidney and its implications for clinical medicine.

Renal sympathetic nerves were discovered to stimulate neuroeffectors throughout the kidney, with graded effects at progressively higher frequencies of stimulation. At low frequencies, sympathetic nerve activation of juxtaglomerular cells increased renin secretion alone. With slightly higher frequencies, effects expanded to include reduced urinary sodium excretion via sympathetic nerve activation of the renal tubular epithelial cells, especially those of the proximal tubule and the thick ascending limb of Henle's Loop. Finally, at high frequency stimulation, renal vasoconstriction occurred with corresponding decreased renal blood flow and glomerular filtration rate via vascular smooth muscle cell contraction of the resistance vessels and preferential preglomerular vasoconstriction of the microvessels, expanding upon the already increased renin and reduced urinary sodium excretion. Thus, the impact of renal innervation occurs long before changes in renal hemodynamics can be seen (arterial pressure, glomerular filtration rate and renal blood flow) and, if renal sympathetic stimulation is sufficient to cause changes in renal hemodynamics, then it will also stimulate renin secretion and produce antinatriuresis (sodium retention) [14].

Such discoveries explained the observations of hypertension in patients with increased renin secretion and reduced urinary sodium excretion but normal renal blood flow and elevated glomerular filtration rate, using a new model: hypertension as a result of elevated renal sympathetic activity below the threshold that would affect renal hemodynamics [14]. Early studies which demonstrated that renal denervation could prevent, delay or markedly attenuate experimental hypertension in a variety of animal models further reinforced this explanation [8]. Thus, it was hypothesized that the etiology of hypertension was a central nervous system abnormality in the regulation of renal sympathetic nervous activity inducible by increased dietary sodium intake and environmental stress occurring in the proper genetic context [14].

It is now known that autonomic control of the kidney is predominantly sympathetic, and mediated by a dense network of post-ganglionic sympathetic neurons in the kidney [16, 17]. Hypertension is characterized by excessive stimulation of this sympathetic neural network, evidenced by high rates of renal norepinephrine spillover into the circulation, and increased systemic sympathetic nerve firing, possibly modulated by afferent renal sensory nerves [10, 18]. This excessive sympathetic outflow to the kidney increases both renin release and tubular sodium reabsorption, and often reduces renal blood flow [8, 9].

In addition, afferent signals from the kidney directly contribute to neurogenic hypertension by modulating central sympathetic outflow [19–21]. Afferent renal sympathetic nerves originate mostly from the renal pelvic wall and respond to either mechanoreceptors that detect stretch, or chemoreceptors that detect renal ischemia [8, 21–24]. These fibers, which have cell bodies in the ipsilateral dorsal root ganglia (T6–L4), ascend to the central nervous system, mainly to the hypothalamus, where they evoke functional changes and a central sympathetic response [25–27].

Prior to the advent of effective antihypertensive drugs, non-selective surgical sympathectomy, often called 'splanchnicectomy', as it needed to include the abdominal viscera [5], was used to denervate the kidney for the treatment of severe hypertension, representing a direct interventional application of this new model of hypertension [12, 28]. While the technique effectively improved survival in a population with a devastating mortality rate of almost 100% in five years [5, 29], it was associated with many debilitating side-effects such as postural hypotension, orthostatic tachycardia, palpitations, intestinal disturbances and erectile dysfunction, attributed to non-specific sympathetic denervation of the viscera and lower extremity vasculature [5, 14].

It is also worth noting that, in addition to improving blood pressure in about half of patients, it also rendered blood pressure more sensitive to antihypertensive drugs [29]. The use of newly developed endovascular catheter technology for selective renal denervation is an innovative twist on this old idea, taking advantage of its potential benefits, while avoiding its historic downfalls.

## Renal sympathetic denervation

In this newly developed approach, a catheter connected to a radiofrequency generator (Symplicity by Ardian Inc., Palo Alto, CA, USA) is introduced percutaneously to the lumen of the main renal artery via femoral access and used to disrupt renal nerves located in the adventitia of these arteries,

without affecting other abdominal, pelvic, or lower extremity innervations [3, 4]. This technique aims to ablate efferent sympathetic and sensory afferent fibers of the renal nerves, both of which are thought to contribute to the blood pressure-lowering effect of catheter-based renal denervation [30]. Preclinical studies performed by Ardian Inc. in juvenile swine reported the effectiveness of this technique at achieving renal denervation without causing severe vascular or renal injury up to six months following the procedure [3].

This technique has some significant advantages over the radical sympathectomy performed prior to the advent of anti-hypertensive drugs. These advantages potentially make it a viable therapeutic option for patients with resistant hypertension and for patients with other diseases thought to be associated with hyperactive renal sympathetic and afferent activity, such as chronic kidney disease and congestive heart failure. These advantages include short procedural and recovery times, the use of a minimally invasive approach and the localization of the procedure to the kidney, thereby avoiding the systemic side-effects that have plagued patients in the past [5].

## Early clinical results

An initial cohort study, performed by Krum et al. [3], demonstrated the efficacy of this novel catheter-based device at producing both renal denervation and corresponding, clinically and statistically significant reductions in blood pressure over a 12 month period (reductions of 14/10, 21/10, 22/11, 24/11, and 27/17 mm Hg at one, three, six, nine, and 12 months, respectively), without serious adverse effects, in a group of 45 patients who met specific clinical criteria for resistant hypertension (blood pressures of ≥ 160 mm Hg, or ≥ 150 mm Hg for patients with type 2 diabetes, despite compliance with three or more antihypertensive drugs). Periprocedural adverse events were limited to a pseudo-aneurysm at the femoral access site and one renal artery dissection upon placement of the catheter prior to the delivery of radiofrequency energy in that artery, at which point the procedure was aborted; both of these instances were related to the percutaneous technique, rather than the radiofrequency ablation, and were treated without subsequent, long-term complications over the 12 months following the procedure.

Aiming primarily to assess safety and proof-of-principle, Krum's study [3] had a relatively small sample size, lacked a proper control group (unrandomized and not placebo-controlled), did not restrict medication adjustment or maintain strict recruitment criteria, and failed to exclude secondary forms of resistant hypertension. These faults limit the extent to which these results can be applied to the clinical management of hypertension and associated disorders. In spite of these limitations, the study supports the potential of this approach to effectively and persistently reduce blood pressure without long-term complications in populations with resistant hypertension and the resultant need for further study of this novel procedure.

It is also of note that, in the 12 month follow-up period, the blood-pressure lowering results did not attenuate, indicating that the ablated nerve fibers did not recover or regrow, and that compensatory, blood pressure-restoring mechanisms did not develop throughout the duration of the follow-up period. These results speak to the potential of the procedure to have a persistent antihypertensive effect [3]. The regrowth of renal sympathetic efferent nerves in kidney and heart transplant models have raised concerns regarding the maintenance of blood pressure-lowering effects over the long term. However, the functional significance of this regrowth is not yet known and will require exploration in future studies. In contrast, the afferent sensory fibers of the renal nerves are not known to have this regenerative potential [31] and are likely to play an important role in the blood pressure-reducing effect of renal denervation, as evidenced by the significant decrease in central sympathetic drive associated with this technique (measured indirectly as a reduction in whole-body norepinephrine spillover) [30].

Building upon this work, the Symplicity HTN-2 investigators (Esler et al. [4]) performed a randomized controlled trial (Symplicity HTN-2 Trial) to study the effectiveness and safety of catheter-based renal denervation with the Symplicity Catheter System (Ardian, Mountain View, CA, USA) to reduce blood pressure in a similar, but larger, population of patients with resistant hypertension, defined using the same criteria as the previous study by Krum et al. [3]. This study of 106 patients, each randomly allocated either to undergo renal denervation with previous treatment, or to maintain previous treatment alone (control), found a 33/11 mm Hg reduction in office-based blood pressure in the renal denervation group compared to the control group at six month follow-up ($p < 0.0001$ for systolic and diastolic blood pressure). These changes were paralleled by similar reductions in: (1) home-based blood pressure measurements; (2) average blood pressure measurements derived from 24-h ambu-

latory blood pressure recordings; and (3) the need for anti-hypertensive drugs. Of the patients analyzed, ten (four who underwent renal denervation and six from the control group) had drug increases prior to the follow-up. In a sub-analysis that censored data from these patients following their drug increases, there was an absolute difference in blood pressure reduction between the two groups of 31/11 mm Hg ($p < 0.0001$ for systolic and diastolic blood pressure). The results of this important study further support those from Krum's proof-of-principle study regarding the effectiveness of catheter-based renal denervation at reducing blood pressure in patients with resistant hypertension.

This randomized controlled trial also addressed both acute and chronic procedural safety. Of the 52 patients who underwent renal ablation, 12 (23%) experienced a peri-procedural event of some kind, including seven incidences of transient intraprocedural bradycardia requiring atropine (none of which had any sequelae in the six months to follow-up), one femoral artery psuedoaneurysm, one post-procedural drop in blood pressure, one urinary tract infection, one extended hospital admission for assessment of parasthesias, and one case of back pain. With respect to chronic procedural safety, there was no statistically significant difference in the change in renal function at six months between the two groups (assessed by serum creatinine, estimated glomerular filtration rate, cystatin-C concentration and albumin-to-creatinine ratio), nor were there any instances of new stenosis (> 60% occlusion confirmed by angiogram) at the sites of radiofrequency delivery. Even so, there is some concern regarding tissue damage and resulting structural changes to the renal artery, as severe adverse events have been observed in other instances in which radiofrequency ablation has been utilized, such as atrial fibrillation [32, 33]. The comparatively low frequency of energy used in this technique makes such changes less likely. However, the long-term impact on renal artery structure of this procedure remains unclear [5].

The Symplicty HTN-2 investigators reported five additional "serious adverse events" requiring hospital admission in patients who underwent renal denervation (compared to three controls with such events); these included both hypotensive and hypertensive episodes, as well as a transient ischemic attack, angina requiring a coronary stent, and one episode of nausea and edema perhaps relating to underlying hypertension [4].

Naturally, a risk of complications would be expected to accompany any invasive procedure, particularly in patient populations with significant underlying morbidity, such as resistant hypertension. This study plays an important role in elucidating at least a portion of the risk associated with catheter-based renal ablation. However, the six month follow-up time and relatively small sample size of this study limit its ability to be generalized with respect to safety and expected adverse events. Thus, it remains to be determined what the risks of catheter-denervation are likely to entail and whether or not such risks are acceptable in the context of the expected benefit of the procedure for the individual patient. The durability of the effect will also be an extremely important endpoint.

Other limitations of the recent literature include baseline differences between the control and renal denervation groups, as well as bias related to potential conflicts of interest. At baseline in the initial randomized control trial [4], the renal denervation group had a greater percentage of males (65%, compared to 50% of controls), higher rates of type 2 diabetes (40%, compared to 28% of controls) and coronary artery disease (19%, compared to 7% of controls), and more patients on five or more medications at baseline (67%, compared to 50% of controls), perhaps indicating more severe cases of hypertension. This over-representation of co-morbidities and severe cases among those who underwent renal denervation may have skewed the results in the direction of greater blood pressure reduction than might have been seen in the general population of patients with resistant hypertension following catheter-based renal denervation. In the same way, these differences may also have predisposed the renal denervation group to higher rates of complications than might have been seen in the control group.

## Discussion

Preliminary clinical results suggest that catheter-based renal denervation utilizing the Symplicity catheter could be a feasible, effective and safe therapeutic option for patients with resistant hypertension. Still, there are many questions that must be answered regarding the technique's effectiveness and safety before the acceptance of this approach in the clinical setting.

In-depth follow-up is essential to measure the long-term impact of this technique. For instance, the presence of nerve fiber regrowth and recovery, particularly of efferent nerve fibers, as well as the development of compensatory blood pressure-increasing mechanisms, must be assessed over

a longer time than the 12 months reported in Krum's proof-of-principle trial. In addition, long--term follow-up is required to measure cardiovascular impact. The Symplicity HTN-2 Trial utilized a composite cardiovascular endpoint, but assessed it only at six month follow-up. In this short time, five of the 100 subjects that were not lost to follow--up (three who underwent renal denervation and two controls) were admitted to hospital, all for hypertensive emergency. This endpoint would perhaps be more significant over a longer period of time, and could be extremely important in elucidating the risks and benefits of the technique with respect to cardiovascular disease. A longer follow-up period in a larger population of patients is also required to assess safety before the application of this technique in clinical practice. Such modifications would allow for a more accurate assessment of the true risks associated with the procedure.

In the Symplicity HTN-2 Trial, 84% of patients achieved a ≥ 10 mm Hg decrease in systolic blood pressure (compared with 35% of controls) and 39% achieved a systolic blood pressure of less than 140 mm Hg at six months (compared with 6% of controls) [4]. Thus, there is a clear range of responsiveness to this technique. Additionally, a small percentage of patients experienced adverse events. It is critical that those factors that put patients at higher likelihood of benefit from this procedure, and at higher risk of experiencing an adverse event, be identified so that ideal candidates for the procedure can be targeted and high risk candidates avoided.

The extent of ablation-induced afferent denervation and the impact that this will have on blood pressure and its sequelae still remains to be elucidated. Periprocedural pain [4] and increased central sympathetic outflow [30] suggest that there is, at least, afferent nerve injury, and that the afferent nerves are probably involved in the procedure and its effects. Still, more work needs to be done to tease apart the underlying mechanism of this effect and the role of afferent renal nerves in the pathophysiology of hypertension.

Such ground-breaking studies of this new approach for use in patients with resistant hypertension pave the way for future research in other patient populations. For instance, this technique might be used to treat milder, but still resistant, forms of hypertension or hypertension in patients with severe kidney disease or renal artery stenosis. All such patients were excluded from the recent studies. Catheter-based renal denervation might also have applications for the treatment of other diseases thought to be associated with excessive sympathetic outflow, such as chronic kidney failure, cardiac failure and cirrhosis with ascites [5].

In summary, catheter-based renal sympathetic denervation shows great promise as a safe and effective therapeutic technique for patients with hypertension and, potentially, for other diseases thought to be associated with renal sympathetic and afferent overstimulation. To further elucidate the potential clinical applications of this novel technique in the setting of resistant hypertension, a larger randomized controlled trial with more prolonged and in-depth follow-up is planned, with results expected in the years to come.

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