CONTEMPORARY REVIEW

The need for and the challenges of measuring renal sympathetic nerve activity

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Renal denervation (RDN) was primarily developed to treat hypertension and is potentially a new method for treating arrhythmias. Because of the lack of a standardized protocol to measure renal sympathetic nerve activity, RDN is administered in a blind manner. This inability to assess efficacy at the time of treatment delivery may be a large contributor to the ambiguity of RDN outcomes reported in the hypertension literature. The advancement of RDN as a treatment of hypertension or arrhythmias will be hampered by the lack of delivery assessment, a deficiency that the cardiovascular electrophysiology community, with its expertise in recording and mapping, may have a role in addressing and overcoming. The development of endovascular recording of renal nerve action potentials may provide a useful accessory tool for RDN. Innovation in this area will be crucial as we as a community reconsider the therapeutic value of RDN.

KEYWORDS Renal denervation; Cardiac arrhythmia; Hypertension; Neural recording; Sympathetic nerve activity

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Introduction

In 2009, renal sympathetic denervation, or simply renal denervation (RDN), came into focus with the publication of the Symplicity HTN-1 study, which seemed to strongly suggest that RDN can yield substantial long-term reduction in blood pressure in patients with resistant hypertension.[1] Then in 2010, the Symplicity HTN-2 study was published and seemed to support the results of the previous study that RDN was an effective treatment of essential hypertension.[2] However, both the HTN-1 and HTN-2 studies were criticized for limitations, such as lack of a valid control group.[3] This criticism was taken into consideration during implementation of the Symplicity HTN-3 study, which included patients who received sham treatment in a small control group half the size of the denervated group. However, the results were less than optimal. Although the denervated group showed a decrease in blood pressure among patients with resistant hypertension after 6 months, the reduction was not significant in comparison with the sham group.[4] Although the Symplicity HTN-3 study failed to confirm the existence of significant benefits from renal sympathetic denervation therapy, there is value to be attained by addressing the weakness in study design, especially as it pertains to delivery of therapy. As we pause and contemplate reentering the realm of potential therapeutic benefit with newer trial designs, an important requirement of information that confirms the completion of RDN during the procedure on the table should be an objective. It is indeed worthwhile to ponder our inability to record the viability of the very nerves we are trying to ablate.

The renal nerves are understood to be a key component in regulation of the sympathetic nervous system and thus have been targeted for denervation therapies.[5] In the past, nerve sympathectomy was performed in an attempt to diminish sympathetic activity by directly severing the connection.[6–9] Early forms of RDN were performed by reanastomosis of the renal artery and surgical ligation.[10] However, these strategies requiring invasive surgery eventually were discontinued and replaced by pharmacologic treatments in clinical practice. The recognition of pharmacologically resistant hypertension in patients has necessitated new therapies and interventions. Use of chemical agents such as 6-hydroxydopamine,[11–14] hypertonic saline, salicylic acid, guanethidine, and paclitaxel has been explored as a means to accomplish RDN in animal models such as the rat.[15] Alcohol-based denervation through a drug infusion catheter with multiple drug delivery heads has been developed to distribute the treatment more accurately.[16] Endovascular catheters provide relatively easy access from the femoral artery, allowing the administration of radiofrequency or ultrasound pulses to ablate the renal

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nerves from within the renal artery. This form of RDN is minimally invasive and forms the basis of the current therapeutic strategy.

A persistent weakness of RDN as a therapy thus far is the inability of the physician administering the treatment to assess any resulting impact on renal nerve activity. Without an accompanying technology for nerve monitoring, ablation of the renal nerves has simply been assumed to have been successful. Nevertheless, the therapy has widely been delivered without verification that the treatment was being applied at the appropriate location. This is especially relevant when considering the results of early studies, including the findings of Symplicity HTN-3, in which knowledge of whether equivalent or even sufficient treatment was delivered to all test subjects is not certain. A potential method to achieve indirect confirmation of renal sympathetic nerve activity (RSNA) has recently been presented. It involves the use of high-frequency stimulation at the ostium of the renal artery to elevate invasively recorded blood pressure >15 mm Hg, which would only be mitigated upon successful delivery of RDN.[17,18]

RDN has also remained a nonspecific treatment in that it may simultaneously affect both afferent and efferent nerves without the ability to identify by how much each direction of signal travel has been affected. In addition, negative effects of thermal denervation (the most common treatment delivery system) on the renal arterial wall tissue that surrounds the nerves being targeted have been identified. Although ideally the minimal amount of endothelium and the nerve cells would be the only tissues within the vessel wall to sustain damage because of their greater sensitivity to heat, a cycle of RDN has been shown to significantly affect arterial wall elasticity and failure strength, mainly by disrupting collagen in the extracellular matrix.[19]

One confounding issue that has not yet been widely acknowledged in research studies or in clinical cases of RDN is the presence of renovascular anomalies in subjects receiving the treatment. Although classically each kidney has a single renal artery and supernumerary kidneys are rare, supernumerary renal arteries are not uncommon.[20,21] Detailed investigation revealed that patients with supernumerary renal arteries in whom not all of the vessels were denervated saw a less distinct effect from RDN.[22] However, upon denervation of all of the renal arteries, the results were comparable to those obtained from patients with a single renal artery.[22] This is yet another aspect to be considered when looking at the results of RDN studies.

Considerations for mapping renal sympathetic nerves

The kidneys communicate with the central nervous system directly through the afferent nerve fibers. Increased afferent renal nerve activity, which modulates posterior hypothalamic activity, is directly responsible for the increased sympathetic activity to the kidney and other organs responsible for cardiovascular and blood vessel regulation.[10,23,24] In different animal models, it has been demonstrated that ablation of renal afferent nerves is beneficial to organs specifically damaged by the effects of sympathetic overactivity, including high blood pressure.[10,24–26] Renal efferent nerves were also found to influence arterial pressure rise by enhancing renin release, tubular sodium reabsorption, and sodium retention.[27,28] Selective ablation of either afferent or efferent sympathetic nerve activity has provided valuable insights into potential therapeutic targets. Thus, the sympathoadrenal system was implicated as the axis through which the removal of afferent or efferent renal nerves controlled arterial pressure.

Because there is no existing technique to ascertain accurate targeting of the sympathetic nerves, RDN therapy is simply applied at various locations along the renal artery in the hopes of ablating nearby or embedded nerve bundles. Although the relative size of the sympathetic nerves along the renal artery remains similar throughout, their distribution is uneven.[29] Nerve distribution also seems to vary between species.[29] As well, efferent fibers seem to significantly outnumber afferent fibers throughout all tested animals, although they were found to exist in an intermixed fashion.[30,31] It is important to accumulate additional understanding of the distribution of renal nerves along the renal artery to allow targeting of sites with the highest density of nerve bundles. However, to reach a consensus on the effects of RDN, a standardized method of measurement and quantification of RSNA must first be established. Because the nerves are intermingling in nature, endovascular targeting of either afferent or efferent nerves selectively for ablation and for measuring nerve activity is tricky using the available technology. However, endovascular ablation and measurement of afferent and efferent activity would be great additions. It is possible that afferent and efferent nerves do not become inactivated evenly to the same extent. Given the different physiologic roles of the afferent and efferent nerves, the physiologic outcome of RDN may be different depending on how much of each of the afferent and efferent nerves remains active and functional after RDN. Thus, assessing "afferent vs. efferent effects" may be important in predicting the outcome of RDN and may well be the focus of the next wave of innovation. The aim of this article is to highlight the limitations of existing methods so as to direct future innovations to overcome the current pitfalls.

Renal nerve anatomy and physiology

There is an established link between overactivity of the sympathetic nervous system and the onset of pathophysiological conditions such as hypertension, cardiac arrhythmia,[32] and adverse prognoses in patients with cardiac failure.[33] Afferent renal sympathetic activity is important in the renal control system and in regulation of renorenal reflexes, along with reflex control of many other bodily functions.[5,34] Renal efferent nerves have also been found to influence arterial pressure elevations by enhancing renin release, tubular sodium reabsorption, and sodium retention.[27,28]