Renal Sympathetic Denervation: Hibernation or Resurrection?

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Abstract

The most current versions of renal sympathetic denervation have been invented as minimally invasive approaches for the management of drug-resistant hypertension. The anatomy, physiology and pathophysiology of renal sympathetic innervation provide a strong background supporting an important role of the renal nerves in the regulation of blood pressure (BP) and volume. In addition, historical data with surgical sympathectomy and experimental data with surgical renal denervation indicate a beneficial effect on BP levels. Early clinical studies with transcatheter radiofrequency ablation demonstrated impressive BP reduction, accompanied by beneficial effects in target organ damage and other disease conditions characterized by sympathetic overactivity. However, the failure of the SYMPPLICITY 3 trial to meet its primary efficacy end point raised a lot of concerns and put the field of renal denervation into hibernation. This review aims to translate basic research into clinical practice by presenting the anatomical and physiological basis for renal sym-

thetic denervation, critically discussing the past and present knowledge in this field, where we stand now, and also speculating about the future of the intervention and potential directions for research.

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The role of renal sympathetic innervation on blood pressure (BP) and volume homeostasis has been long recognized. Surgical sympathectomy was used almost a century ago for the treatment of malignant hypertension, but then abandoned due to intolerable side effects. Interest in renal denervation was revived with the introduction of transcatheter techniques, which were minimally invasive, easy to perform, low-risk and promised to deliver effective and reproducible ablation of sympathetic fibers along the renal artery adventitia, in order to attenuate sympathetic overactivity. Early studies provided impressive results in patients with resistant hypertension and those suffering from diseases associated with sympathetic overactivity. However, the enthusiasm was replaced by disappointment following the publication of the negative findings of SYMPPLICITY 3, the first large randomized study that was sham-controlled.

The discrepancy between the initial enthusiastic findings and the findings of SYMPPLICITY 3 calls for a meticulous and in-depth exploration of available data in this field. In fact, there is abundance of information about renal sympathetic nerves and renal denervation, with >7,000 studies found in PubMed and almost one third of these published during the last decade. It has to be acknowledged, however, that the scientific community was carried away by the initial enthusiasm (induced by the early studies), which was coupled by the inevitable rush of the pharmaceutical industry to expedite research. It seems clear now that some essential steps in experimental and clinical research were skipped and available information was not translated into wisdom.

This review aims to translate basic research into clinical practice by presenting the anatomical and physiological basis for renal sympathetic denervation, critically discussing the past and present knowledge in this field, where we stand now, and speculating about the future of the intervention and potential directions for research.

Renal Sympathetic Nerve Anatomy and Physiology: Clinical Implications

The important role of renal sympathetic innervation on volume homeostasis was first described by Claude Bernard [1] in 1859; he described that unilateral splachnic nerve stimulation was accompanied by antidiuresis of the ipsilateral kidneys whereas the unilateral section of the splachnic nerve was accompanied by enhanced ipsilateral diuresis. More than a century later, another landmark figure of human physiology, Guyton, highlighted the cardinal role of the kidneys in BP and volume regulation, describing the renal pressure-natriuresis curve and its alteration in hypertension [2, 3]. Extensive research about the anatomy, physiology and pathophysiology of renal sympathetic innervation has been carried out during the second half of the 20th century and has been recently further reinforced in the renal sympathetic denervation era.

Renal Nerve Anatomy and Clinical Implications

Renal sympathetic innervation consists of efferent and afferent sympathetic nerve fibers.

Afferent sympathetic nerves transfer stimuli from the kidneys to the central nervous system. The efferent sympathetic innervation originates from the brainstem area (rostral ventrolateral medulla, paraventricular hypothalamic nucleus and medullary rapae nuclei), travels

through the spinal cord, transfers at the pre-vertebral and para-vertebral sympathetic ganglia (celiac, aortorenal, posterior renal and superior mesenteric), runs alongside the renal artery, enters the hilus of the kidney and, finally, ends at the intrarenal vasculature (interlobar, arcuate and interlobular arteries, glomerular arterioles and juxta-glomerular apparatus), transmitting sympathetic stimuli mostly to the cortex of the kidney [4].

Afferent sympathetic nerves follow the opposite direction, sense renal ischemia and stretch through chemo- and mechanoreceptors located at the renal pelvic wall, and transmit the signals via the dorsal root ganglia to the renal cardiovascular centers in the central nervous system (rostral ventrolateral medulla, nucleus tractus solitarius, paraventricular hypothalamic nucleus and subformical organ) [5].

From the clinical point of view, the most significant aspect of renal nerve anatomy regards the distance of sympathetic fibers from the lumen and the relative distribution of sympathetic fibers at the proximal and distal segments of the renal arteries [6]. Earlier autopsy studies reported that almost all sympathetic fibers are found between 0.5 and 2.5 mm from the lumen wall, and 90% are within 2 mm from the lumen [7], thus allowing for effective injury with transcatheter radiofrequency techniques. Two recent studies question these findings, however. The first study found that only 40% of the sympathetic fibers course within 2 mm from the lumen whereas 30% are found between 4 and 9 mm from the lumen [8], too far to be reached by low-energy radiofrequency ablation. The other study reported a segment-related distance from the lumen, with 75% of the sympathetic fibers situated within 3.4 mm from the lumen at the distal segment of renal arteries and within 9 mm from the renal artery wall at the proximal segment [9]. Further studies indicate that fibers in the renal artery branches are much more proximal to the lumen and perhaps more approachable by transcatheter techniques.

Recent experimental studies indicate that significant renal noradrenaline reduction (>80%) is achieved only when sympathetic nerve injury reaches a 10-mm distance from the lumen whereas a shorter distance injury (2–4 mm) is accompanied by a significantly lesser reduction of renal noradrenaline levels (40–60%) [10]. Moreover, it has been estimated that >75% of the sympathetic fibers need to be injured to achieve a 90% renal noradrenaline reduction [11].

Collectively, these findings suggest that currently used ablation systems are inefficient for achieving complete re-

nal sympathetic denervation at the proximal segment of the renal arteries. The therapeutic strategy should target either the meticulous circumferential ablation at the distal segments of the renal arteries, the use of higher power at the proximal segments (risking substantial endothelial and tissue injury) or alternative techniques with deeper penetration at low energy levels. Further experimental and clinical research is needed in this field to evaluate the best approach for an effective and safe injury of most renal sympathetic fibers. Circumferential ablation is absolutely necessary in order to achieve interruption of most fibers. Technique modifications that will permit nerve injury in the branches in addition to distal segments (where fibers converge close to the lumen) might prove very effective.

Renal Nerve Physiology and Clinical Implications

Efferent renal sympathetic nerves are implicated in the regulation of BP and blood volume. The activation of efferent renal sympathetic fibers enhances renin secretion and sodium reabsorption, induces renal vasoconstriction and reduces renal blood flow and glomerular filtration rate [12, 13].

Renin secretion is enhanced, even with weak stimulation of the efferent sympathetic fibers, either directly through activation of the β_1 -adrenergic receptors at the juxtaglomerular apparatus or indirectly via reduced pressure and sodium influx in the macula densa area. The downstream signal transduction in renin-producing cells involves cAMP, the G_{sa} -subunit of receptors, adenylyl cyclase and protein kinase A, and is regulated by intracellular and extracellular calcium concentrations.

Sodium and water reabsorption increases with moderate stimulation of the efferent renal sympathetic fibers. Increased sodium and water reabsorption is mediated by α_{1B} adrenoceptor stimulation and the downstream signal transduction involves protein kinase C, MAP kinase and phospholipases. Increased sodium and water reabsorption takes place at the late proximal tubule and at Henle's loop (thick ascending limb), and is associated mainly with Na^+/K^+ -ATPase activity and other sodium transporters (Na^+/H^+ exchangers 1 and 3, $Na^+/K^+/Cl^-$ – cotransporter and sodium bicarbonate cotransporter).

Renal hemodynamics are affected by strong stimulation of the efferent renal sympathetic nerves. Vasoconstriction of the renal arterial vasculature is mediated by α_{1A} adrenoceptor stimulation, and the downstream signal transduction involves phosphoinositide hydrolysis by phospholipase C. Renal vasoconstriction results in a mild reduction of renal blood flow and a subsequent milder reduction of glomerular filtration rate.

Overall, the functional effects of renal sympathetic activation are gradual and dose-dependent. Experimental evidence indicates that, as the sympathetic activity increases, plasma renin activity is increased by 40–180%, sodium excretion is reduced by 17–55%, renal blood flow decreases by 5–22% and glomerular filtration rate remains unaffected or decreases by 11% [5].

Renal sympathetic afferent nerve activation is associated with central stimulation of the sympathetic nervous system. Renal sympathetic afferent fibers are stimulated either by mechanoreceptors sensing increased pressure at the renal pelvic wall or chemoreceptors sensing renal injury. Experimental data are somehow conflicting, showing different effects of dorsal rhizotomy (section of the afferent sympathetic fibers) in various experimental models and different sodium intake levels. However, data in humans strongly point towards an excitatory role of renal afferents in systemic sympathetic activity, since bilateral nephrectomy is associated with attenuation of sympathetic overactivity in patients on hemodialysis or after transplantation [14, 15], and renal sympathetic denervation is associated with the reduction of systemic sympathetic activity [16].

Renal Sympathetic Denervation: Past, Present and Future

There is no doubt that renal sympathetic denervation has a solid anatomical and physiological background, supporting its use for the attenuation of sympathetic overactivity and BP reduction. This review critically discusses prior evidence with sympathetic denervation, presents where we stand now and speculates about the future of renal sympathetic denervation while proposing directions for future research.

The Past

Manipulation of the sympathetic system to treat elevated BP was applied in the first half of the 20th century for the management of malignant hypertension, a debilitating disease with dramatic mortality rates at the time. Surgical sympathectomy, also called thoracolumbar splanchnicectomy, was an extensive operation that became popular between 1930 and 1950, and was widely used in specialized centers worldwide for patients with incurable malignant hypertension [17, 18]. It was effective, not only in reducing BP but also in reversing target organ damage, such as left ventricular (LV) hypertrophy, proteinuria and retinopathy. Even more importantly, it

was associated with impressive survival benefits. Indeed, the 5-year mortality rate was >50% for patients treated conservatively with drug therapy compared to <20% for patients undergoing surgical sympathectomy, in a large series of patients published in the 1950s [19]. However, in this high-risk population with malignant hypertension and advanced target organ damage, extensive sympathectomy was associated with meaningful BP reduction in only about 2/3 of patients undergoing the procedure. Important to note is that sympathectomy, and more so renal denervation, is not for everyone. The use of surgical sympathectomy was abandoned during the second half of the 20th century, for 2 main reasons. First, the operation was associated with significant perioperative mortality (3–5%) and the adverse effects were intolerable, with pronounced postural hypotension limiting daily activities, impotence, bowel abnormalities and hyper- and hypohidrosis being the most frequent problems. Second, the advent of pharmacological therapy provided several antihypertensive drugs that were effective for BP reduction in the majority of patients and possessed a favorable safety profile compared to surgical sympathectomy, with fewer and better-tolerated adverse events.

Nevertheless, the interest about the inhibition of the sympathetic nervous system was not abandoned for several reasons: (1) the sympathetic nervous system was implicated in the pathogenesis of arterial hypertension from the earlier stages up to the end points (target organ damage, heart failure and sudden death), (1) sympathetic nervous system overactivation was observed not only in hypertension but also in a variety of clinical conditions, including chronic kidney disease, heart failure, obstructive sleep apnea, cardiac arrhythmias, polycystic ovary syndrome and cirrhosis, and (3) available drugs interfering with the sympathetic nervous system (centrally acting agents, β -blockers and α -blockers) did not provide complete or at least major attenuation of sympathetic overactivity, such as that provided by drugs inhibiting the renin-angiotensin system (ACE inhibitors and angiotensin receptor blockers).

The Present

The reciprocal relationship between the brain and the kidneys regarding sympathetic nervous system activity was matched with recent technological advancements permitting the transcatheter injury of renal sympathetic fibers, in an attempt to manage drug resistant hypertension better.

Renal sympathetic denervation is a minimally invasive interventional procedure that involves the percutaneous

injury or interruption of renal sympathetic fibers using some form of energy (radiofrequency ablation, ultrasound and cryoenergy) or neurotoxic agents (vincristine, ganglionic blockers and ethanol). Up to now, 6 devices have been approved in Europe for renal sympathetic denervation in patients with resistant hypertension, while many others are currently under development. Of note, the approval of devices in Europe does not require efficacy or even safety data.

Renal sympathetic denervation was first applied in patients with resistant hypertension in an effort to address an unmet need. Indeed, resistant hypertension is frequently encountered and affects a substantial portion of hypertensive patients (13% in some studies and 4–5% from more conservative estimations), and is associated with increased rates of target organ damage and cardiovascular morbidity and mortality [20, 21]. BP control is not achieved in patients with resistant hypertension despite the use of ≥ 3 antihypertensive drugs, including a diuretic, in maximal tolerated doses. It is not unusual to administer 6, 7 or even 8 drugs to patients with hypertension refractory to drug therapy.

Renal sympathetic denervation was first studied in 50 patients with resistant hypertension using transcatheter radiofrequency ablation. This proof-of-concept study (SYMPPLICITY 1) included 45 patients that underwent renal sympathetic denervation, while 5 with inappropriate renal artery anatomy for renal denervation served as controls. BP was gradually and impressively reduced during the follow-up period of the study, reaching a 27/17-mm Hg drop 1 year after the procedure, while no safety issues were revealed [22]. Although these results were uncontrolled and unblinded, and should be viewed with caution, the study created a lot of enthusiasm and called for randomized trials [23].

Indeed, the first randomized study (SYMPPLICITY 2) was published a year later and verified the results of the proof-of-concept study. In total, 106 patients with resistant hypertension were randomly assigned either to renal sympathetic denervation ($n = 52$) or continuation of administered antihypertensive medication ($n = 54$). Once again, the BP reduction was very impressive at 6 months after renal sympathetic denervation (32/12 mm Hg) and the safety profile of the procedure was reassuring [24]. SYMPPLICITY 2 strengthened the enthusiasm about this new interventional approach for the management of resistant hypertension and associated target organ damage as well as for other disease conditions characterized by sympathetic overactivity [25]. It was noted, however, that the study was not blinded and not appropriately con-

trolled, since no BP reduction was observed in the control group, which is highly unusual and subject to bias. The impressive findings of the 2 SYMPLICITY studies and the approval of the device in central and north Europe paved the way for many studies that confirmed the efficacy and safety of renal sympathetic denervation in everyday clinical practice [26]. Soon after, the first in-human study with another catheter (ENLIGHTEN 1) provided further credibility to the renal denervation concept [27], which was strengthened by later reported findings with all tested devices [26].

In parallel, the enthusiasm about renal sympathetic denervation spread beyond hypertension specialists and interventional cardiologists and took a frenetic form, due to accumulating evidence pointing towards 'pleiotropic' benefits with this new therapeutic technique. Indeed, substantial benefits were reported regarding the structural and functional abnormalities of the heart that are associated with hypertension, glucose homeostasis, atrial fibrillation, sympathetically mediated ventricular arrhythmias, and also in other disease conditions characterized by sympathetic overactivity, such as chronic kidney disease, heart failure, obstructive sleep apnea and polycystic ovary syndrome [17, 18, 26]. Of great clinical significance, renal sympathetic denervation was found to not only be effective in reducing BP, but also associated with significant additional effects, such as the reappearance of the menses in polycystic ovary syndrome, the reduction of the number and severity of apneic episodes in sleep apnea syndrome, superior reduction of LV mass compared to conventional drug therapy, and so on. Renal sympathetic denervation was thus perceived as a 'panacea' by a large part of the scientific community, capturing the imagination about the potential applications of this minimally invasive approach.

In fact, the structural benefits in the heart accompanying renal denervation might better describe what we call 'pleiotropic' effects. It is well known that LV mass regression is strongly dependent on BP reduction. However, the preliminary data from small clinical studies are that denervation-induced LV mass regression cannot be attributed to BP reduction alone. In a study of 66 patients with resistant hypertension, LV mass decreased comparably in nonresponders (BP reduction <10 mm Hg), responders (mean BP reduction of 18.6 mm Hg after intervention) and super-responders (mean BP reduction of 50.4 mm Hg after intervention), suggesting a beneficial effect independent of BP reduction [28]. Another study of 72 patients (55 in the intervention group and 17 in the control group) revealed similar BP-independent reduc-

tions of LV mass, as assessed by cardiac magnetic resonance [29]. These findings cannot be considered totally unanticipated; LV mass reduction with antihypertensive therapy varies across different drug categories, with RAS inhibitors being more effective and β -blockers being less effective for similar BP reduction [30], also confirmed in the LIFE trial [31]. The BP-independent mass reduction and the observed benefits even in poor responders might suggest that sympathetic attenuation might mediate – at least in part – the structural benefits, since sympathetic overactivity has been associated with LV hypertrophy [32]. However, further studies and more convincing data are needed to verify the so-called 'pleiotropic' effects of renal denervation and clarify the contributing mechanisms.

In the midst of the enthusiasm about renal sympathetic denervation, however, a number of cardinal rules of clinical research have been ignored by many physicians. First, the majority of studies had an open-label design with no controls, let alone sham controls, thus leading to an overestimation of BP reduction [33]. The reduction of BP using ambulatory BP monitoring also seemed to be significantly less (about one third) than that observed with office measurements [34]. Finally, a marked heterogeneity in BP response coupled with the lack of accurate response predictors, the lack of accurate intraprocedural tests to assess the magnitude of sympathetic injury and the need for large studies to evaluate the long-term effects of renal sympathetic denervation on hard cardiovascular end points were additional fields still to be addressed and clarified by intensive research.

The results of the SYMPLICITY HTN-3 trial tempered the enthusiasm of the scientific community towards renal sympathetic denervation. This was a large, randomized, sham-controlled study performed in 535 patients with resistant hypertension in the USA. The study met its primary safety end point but failed to meet its primary efficacy outcome [35]. Office BP was significantly reduced at 6 months post-procedure (14.1 mm Hg), but a similar decrease was observed with sham operation as well (11.7 mm Hg), and the difference between the intervention and the control group was not statistically significant. The same was evident for ambulatory BP reductions (6.75 vs. 4.79 mm Hg, respectively), and so the study also failed to meet its major secondary efficacy end point.

It addressed the correct patient population and adhered to the clinical and research guidelines. The question is: why did it fail to demonstrate the expected benefit [36]? Although much iteration of reasons has been ex-

pressed, most (serious) investigators agree that the main reason was partial or inadequate denervation. A subsequent analysis by Kandzari et al. [37] suggested that only a minority of patients (19/364) had an appropriate number and circumferential placement of lesions (>12 lesions are needed, present in all 4 quadrants).

Reasons Proposed for the Failure of SYMPLICITY HTN-3 to Achieve Its Primary Objective

There is no doubt that SYMPLICITY 3 was larger than the first 2 studies (SYMPLICITY 1 and 2) and better designed, due to the use of sham operation in control subjects. However, as with every study, SYMPLICITY 3 had its own disadvantages and limitations, and while performed better than earlier studies, it nonetheless manifested several operational flaws that rendered its interpretations ambiguous. We list these below.

Learning Curve

More than 100 interventional cardiologists participated in the study and the vast majority of them performed <3 procedures, raising concerns about the 'learning curve' effect. Indeed, a learning curve is observed with any new intervention, especially when no accurate markers of success exist, as is the case with renal sympathetic denervation.

Incomplete Denervation

A recent post hoc analysis of the SYMPLICITY 3 findings identified predictors of BP response following renal sympathetic denervation [37]. When procedural data were carefully evaluated, it was found that the BP response increased with the increasing number of ablations delivered and the successful delivery of circumferential (4-quadrant) ablations. Indeed, when <10 ablations were delivered, the BP (difference between the intervention and the sham procedure) was not reduced but actually increased by 12.1 mm Hg for office BP, i.e. favoring the sham procedure. In contrast, when >13 ablations were delivered, the BP reduction was 14.1 mm Hg for office BP, thus favoring the intervention group. Similar findings were observed with ambulatory BP monitoring. Another procedural parameter affecting BP response to renal denervation was the successful delivery of 4-quadrant ablations. Systolic BP (SBP) was greatly decreased when successful circumferential ablations were performed in both renal arteries (-24.3 mm Hg) compared with 1 renal artery (-16.1 mm Hg) or none (-14.2 mm Hg). Similar findings were observed with ambulatory and home BP monitoring.

Lack of Predictors

Additional baseline predictors of BP response to renal denervation were also identified, including the race group of the study participants and the type of antihypertensive drug administered. Renal sympathetic denervation was effective in non-African-American participants. SBP reduction in these patients was greater with renal denervation than with sham operation (15.2 vs. 8.2 mm Hg, respectively). The trial provided little interpretable information about African-Americans, an important target population. Finally, the BP response was affected by the type of antihypertensive drug, showing a positive relationship in patients taking mineralocorticoid receptor antagonists and a negative relationship in those taking direct vasodilators.

It needs to be highlighted, however, that the above-mentioned predictors of BP response to renal denervation come from a post hoc analysis of the study. Therefore, the findings should be considered as exploratory and hypothesis-generating and should be confirmed by prospective studies, appropriately designed to address these issues.

Medication Stability

Medication stability is critical at study entry and during the study. In the non-positive SYMPLICITY HTN-3, 38% of patients had changes in their medications whereas in the positive DENER study, a standardized treatment protocol was followed [38]. For this reason, European experts on renal denervation suggest that, in future renal denervation trials, it is crucial to standardize concomitant antihypertensive therapy (preferentially all treated with a combination of RAS inhibitors, calcium antagonists and diuretics) with a stable run-in period of at least 4–8 weeks, and to monitor drug adherence as a potential confounder of BP response (by pill-counting, electronic pill dispenser use and toxicological drug analysis).

The Future

The future of renal sympathetic denervation is currently up for grabs. SYMPLICITY HTN-3 was followed by numbness and hibernation in the field. Yet more research is needed to find viable solutions for the management of resistant hypertension and other disease conditions.

Before we adopt widespread use of this catheter-based procedure for the treatment of hypertension, a number of questions need to be addressed:

- 1 How much denervation do we need to have a meaningful effect on BP?

- 2 Is there a threshold for renal denervation or a dose response?
- 3 Do we need 100% of the fibers ablated or is partial injury enough?
- 4 Knowing that a great proportion of fibers are found as far as 12 mm from the lumen, how do we get there?
- 5 How can we monitor success in the lab?
- 6 How do we measure success in the animal lab?
- 7 Do we need a 90–100% reduction in tissue noradrenaline?
- 8 Does radiofrequency ablation have a chance to meet the above requirements?
- 9 How can other approaches, e.g. ethanol and HIFUS, play a role?

From the clinical point of view, 4 aspects are of paramount importance in order to advance our knowledge and define the future of renal sympathetic denervation: the accurate identification of responders, technological advancements in the procedure, long-term morbidity and mortality data and studies on other diseases such as heart failure, chronic kidney disease and arrhythmias [39].

Identification of Responders

The BP response to renal denervation shows a pronounced heterogeneity. Data from randomized and open clinical studies with renal denervation strongly indicate that the BP is excessively reduced in some patients, others experience a modest but still clinically significant BP reduction and in others, the BP is either minimally decreased or even increased.

The heterogeneity of BP response to renal sympathetic denervation is not surprising and should be considered in the general context of antihypertensive therapy. First, historical data with sympathetic splanchnicectomy show that only 45% of surgically treated patients experience a substantial BP reduction [19].

Second, arterial hypertension is a multifactorial disease with several mechanisms involved in its pathogenesis. The relative contribution of any mechanism to the development of hypertension is highly variable between patients; a system might be mainly implicated in 1 patient and marginally implicated in another patient. Therefore, it seems naïve to expect that any therapeutic strategy can be effective for all hypertensive patients. Seventy years of antihypertensive therapy have taught us a hard lesson: the inhibition of any mechanism implicated in BP elevation is effective only in a portion of patients (30–50%), either

because this mechanism is not involved in BP elevation or because its inhibition is associated with the activation of another mechanism that counterbalances BP reduction.

Third, resistant hypertension or elevated BP refractory to drug therapy is a highly heterogeneous condition. Factors contributing to treatment resistance are either physician- or patient-related [40]. Physician-related factors include: clinical inertia, inappropriate combinations of antihypertensive drugs (i.e. dual RAS inhibition), inadequate doses of antihypertensive drugs (especially diuretics), a failure to add mineralocorticoid receptor antagonists, technical mistakes in office BP measurements (especially in the elderly), a failure to recognize white-coat hypertension by using ambulatory or home BP monitoring, and a failure to diagnose secondary forms of arterial hypertension (especially primary aldosteronism, which is common and unlikely to respond to renal denervation). Patient-related factors include: poor adoption of lifestyle modification measures (especially salt restriction, weight reduction and regular exercise), poor adherence to antihypertensive drug therapy and administration of drugs known to raise BP (especially NSAIDs that are available over the counter).

The astute physician needs to take into account all the abovementioned factors before proceeding to renal denervation. For example, it was not surprising that renal denervation was not more effective than medical therapy, when antihypertensive drugs were given under supervision or the patients were followed in highly specialized centers [41, 42], given the poor adherence to antihypertensive therapy and the large number of physician-related factors contributing to treatment resistance, respectively. However, supervised administration is not feasible in everyday clinical practice, nor is there an adequate number of highly specialized centers for following the millions of hypertensive patients with resistant hypertension. Further credence to the latter comes from epidemiological data suggesting that almost 13% of hypertensive patients have treatment resistance in everyday life [43, 44].

Based on the above, it is of paramount importance to identify the predictors of BP response to renal denervation, in other words, to identify the ‘right patient’ for this interventional approach. Up to now, only largely elevated SBP (>180 mm Hg) has been associated with greater reductions of BP, a fact that is evident with drug therapy as well. It has to be noted, however, that although the response rates are better in these patients, not all patients with largely elevated BP respond to renal denervation. The predictors of BP response identified in SYMPPLICITY

3 (race, use of mineralocorticoid receptor antagonists and non-use of direct vasodilators) need to be confirmed by further studies.

From the pathophysiological point of view, it seems rational to assume that renal denervation would be effective in patients with frank sympathetic overactivity. However, up to now, this concept has not been confirmed by clinical studies [26]. This might be due to either imperfect assessment of sympathetic activity or to the effects of concomitant antihypertensive therapy on sympathetic activity perplexing the findings of sympathetic tests. The accurate assessment of sympathetic activity is neither easy nor feasible in everyday clinical practice. Muscle sympathetic nerve activity and noradrenaline spillover are the gold standards, but are highly demanding methods that accurately applied only in some highly specialized centers worldwide. More crude methods of sympathetic activity that could be more easily applied in everyday clinical practice (heart rate, plasma catecholamines and MIBG scintigraphy) have not been able to predict BP response to renal denervation.

Therefore other predictive methods are urgently needed that will be easy to perform in everyday clinical practice, are widely applied and reproducible and, most of all, will provide an accurate prediction of BP response to renal sympathetic denervation, identifying the 'right patient' for this interventional approach.

Procedural Advancements

The importance of an extensive injury of the sympathetic nerve fibers to achieve adequate renal sympathetic denervation was highlighted in the first part of this review, which described the clinical implications of renal nerve anatomy. In summary, a circumferential injury of at least 75% of the sympathetic fibers is needed in order to attain adequate and clinically significant renal sympathetic denervation. However, experimental and clinical data indicate that renal denervation results in modest and highly variable reductions in sympathetic activity, when noradrenaline spillover is used for the assessment [45–47]. Therefore, it can be rationally assumed that renal denervation is not being completely achieved. Further credence to this comes from the post hoc analysis of the SYMPPLICITY 3 trial, in which the BP response to renal denervation increased along with the number of ablations delivered and the successful delivery of circumferential ablations, in other words, with more complete injury of sympathetic fibers.

Nevertheless, currently used systems to achieve renal denervation seem to have a limited capacity to attain adequate injury of renal sympathetic nerves. Although technology has advanced beyond the initially used single-tip catheter, current systems using low-energy radiofrequency ablation achieve sufficient nerve injury up to 2–3 mm from the lumen. Given the recent data from autopsy studies suggesting that renal sympathetic nerves are situated further away at the proximal segment of the renal arteries, it seems that (using current technology) the interventionalist should aim for a meticulous circumferential injury at the distal segments of the renal arteries, where renal nerves are situated closer to the lumen, within the capacity of radiofrequency ablation to induce renal injury. However, 2 things need to be noticed. First, data from autopsy studies is not solid and further studies are needed to determine, without any doubt, the exact anatomy of the renal nerves in large numbers of cadavers with diverse characteristics (hypertensives, normotensives, old, young and those with concomitant diseases such as chronic kidney disease). Second, large clinical studies are needed to confirm whether a distal approach is sufficient to attain successful renal denervation and should be preferred; such studies are currently underway.

Another direction of research should be to achieve technological advancements that will allow for deeper penetration of energy and subsequent complete injury of renal sympathetic fibers, even at the proximal segments of the renal arteries, but without producing any substantial injury of the endothelium, renal artery wall and perivascular tissue. Up to now, renal denervation has proved to be a fairly safe approach, with only a few cases of renal artery stenosis reported so far among the thousands of patients to undergo the procedure. The fundamental rule of medicine 'Primum non nocere' (first do no harm) should be the cornerstone of future technological advances.

Another significant direction for future research is to identify the markers of successful sympathetic nerve injury to be used during the procedure. Renal sympathetic denervation can be currently considered as a 'blind' procedure. No test is currently available to assess the magnitude of the nerve injury and the subsequent extent of renal denervation during the procedure. Regional renal noradrenaline spillover could be assumed as an ideal candidate, but cannot be used during the procedure. Several other tests have been proposed as intraprocedural markers of successful sympathetic denervation, such as electric stimulation of the renal arterial nerves, renal blood flow and renal resistive index [26, 48], without obtaining wide

application and unanimous acceptance, however. The identification of a feasible and accurate test that could assess sympathetic activity during the procedure is of paramount importance for the future of renal sympathetic denervation.

Long-Term Data

Renal sympathetic denervation was only recently introduced in clinical practice and therefore long-term data are not yet available. Relevant data regarding the long-term safety of the procedure, the persistence of BP reduction over time and the effects of renal denervation on cardiovascular outcomes are needed.

The long-term safety of the procedure needs to include the careful assessment of renal anatomy and function as well as the ability of denervated patients to confront volume depletion (diarrhea, extensive use of diuretics and shock). Renal artery stenosis rarely occurs in the short term following renal denervation. Although long-term data are needed, it does not seem very likely that renal artery stenosis will appear several years after the procedure. The effects of renal denervation on renal function are anticipated to be beneficial due to the strong ability of BP reduction to attenuate the deterioration of renal function over time. Although some concerns have been expressed previously [49, 50], these might be due to the acute BP reduction and the extensive use of spironolactone and high-dose diuretic therapy.

The persistence of BP reduction is another important issue, since experimental data suggest the reinnervation of renal sympathetic fibers. However, whether reinnervation actually takes place in humans and, if so, whether it is functional and not only anatomical, remains questionable. Up to now, there is evidence pointing towards a re-elevation of BP after renal denervation, due to sympathetic fiber reinnervation. Moreover, it has to be kept in mind that BP increases with age due to arterial stiffening, and this age-related elevation in BP should be separated from the potential effect of sympathetic reinnervation.

Resistant hypertension is associated with significant target organ damage and increased rates of cardiovascular morbidity and mortality [20, 21, 26]. It is thus anticipated that BP reduction will provide significant benefits in this patient population [51]. Moreover, the 'pleiotropic' effects of renal denervation (LV mass reduction, improved diastolic function, reduction of albuminuria and improved glucose homeostasis) are expected to provide additional benefits. However, these assumptions

need to be confirmed by large randomized studies. Such studies have been designed and were about to begin when the negative findings of SYMPPLICITY 3 put them on hold.

Studies on Other Disease Conditions

Sympathetic overactivity contributes to several forms of target organ damage. Thus, the beneficial effects of renal denervation on LV mass, diastolic function, urinary albumin excretion and endothelial function were not unanticipated. However, whether these benefits are translated into cardiovascular benefits remains to be proven. For example, a study, similar to the LIFE trial, on patients with hypertension and LV hypertrophy, to assess if renal denervation provides additional benefits to standard medical therapy would be of great clinical interest.

Sympathetic overactivity is frequently encountered in a variety of clinical conditions, including chronic kidney disease, heart failure, obstructive sleep apnea, polycystic ovary syndrome and cirrhosis. In addition, sympathetic overactivity is implicated in the pathogenesis of some forms of arrhythmias (atrial and ventricular) and sudden death. Pilot studies on most of these conditions have shown promising results [26]. It is therefore time to move forward with randomized trials to evaluate the effect of renal denervation in these conditions. Chronic kidney disease, heart failure and arrhythmias appear to be the first candidates.

Chronic kidney disease seems a good candidate for renal denervation because diseased kidneys are the source of sympathetic overactivity and the surgical resection of native kidneys in patients either on hemodialysis or posttransplantation can be associated with the attenuation of sympathetic overactivity and BP reduction [14, 15]. Small clinical studies point towards a beneficial effect of renal denervation and pave the way for randomized trials [50].

Heart failure is another good candidate because sympathetic overactivity is implicated in its pathogenesis; pharmacological neurohormonal modulation has proved to be the cornerstone of therapy in heart failure patients [52]. Heart failure with preserved ejection fraction is of particular interest, since no therapeutic strategy has proved to provide survival benefits up to now. Pilot studies on heart failure patients are encouraging and randomized trials are eagerly awaited.

Sympathetic overactivity is involved in some forms of atrial and ventricular arrhythmia [52, 53]. Preliminary

studies in atrial fibrillation and sympathetically mediated ventricular arrhythmias seem promising and remain to be verified by large randomized studies.

Ongoing Studies

There are currently 2 ongoing clinical trials. Medtronic has initiated the SPYRAL HTN Global Clinical Program with SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED [54]. The SPYRAL HTN-OFF MED trial is evaluating renal sympathetic denervation in the absence of antihypertensive medications compared to a sham-controlled population. This off-medication trial will help isolate the effect of renal denervation on BP reduction, and it was requested by both the FDA and many clinicians. The SPYRAL HTN-ON MED trial is evaluating renal denervation compared to a sham-controlled population with patients on a standardized treatment regimen of 3 antihypertensive medications, including a thiazide-type diuretic, a dihydropyridine calcium-channel-blocker and an ACE inhibitor/angiotensin receptor blocker for at least 6 weeks prior to randomization and expected to maintain the regimen for at least 6 months. By specifying specific medications at the maximum tolerated dose, medication variability will be reduced; the study is more likely to provide a clinically meaningful answer allowing for a more controlled assessment of the impact of renal denervation in the presence of background medications. Each arm will aim to study up to 100 patients with an office SBP ≥ 150 mm Hg and <180 mm Hg and an average ambulatory blood pressure monitoring SBP >140 and <170 , who will be randomized at a 1:1 ratio to receive re-

nal denervation or the sham procedure. A similar design has been adopted by the REINFORCE study sponsored by the Boston Scientific Corporation.

Hopefully, these and other future appropriately designed trials will eventually resolve all the uncertainties regarding the BP effects of renal sympathetic denervation and contribute to defining its place in clinical practice.

Conclusion

Renal sympathetic denervation is an innovative, minimally invasive approach for the management of resistant hypertension. The anatomy, physiology and pathophysiology of renal sympathetic innervation provide a strong background supporting an important role of renal nerves in BP and volume homeostasis. In addition, historical data on surgical sympathectomy and experimental data on renal sympathetic denervation both indicate a beneficial effect of renal sympathetic denervation on BP levels. Clinical studies with transcatheter radiofrequency ablation have demonstrated impressive BP reduction, accompanied by beneficial effects in target organ damage and other disease conditions characterized by sympathetic overactivity. However, the failure of the SYMPPLICITY 3 trial to meet its primary efficacy end point raised a lot of concerns and put the field of renal denervation into hibernation. The future of renal sympathetic denervation depends on the identification of response predictors, technological advances that secure a complete or at least near-complete injury of renal sympathetic fibers and proof of long-term cardiovascular benefits in patients with resistant hypertension and/or other diseases.

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