Review Article

Renal Artery Denervation in Hypertension Management

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ABSTRACT

Renal denervation (RDN) as a treatment option for hypertension has experienced a see-saw of increase and decrease during its development. After successful outcomes reported in case registries, the first randomized sham-controlled trial, SYMPLICITY-HTN-3, did not show significantly lower office or 24-h ambulatory systolic BP. However, faults in the design and conductance were identified and blamed for the negative results. New sham-controlled randomised trials with improved methodology have been initiated and studies have reported significant BP reductions of about 10 mmHg in office and 6 mmHg in 24-hour ambulatory systolic BP. These data provided the biological proof that RDN lowers BP in patients with hypertension. These trials have renewed clinical and scientific interest in defining the appropriate role of RDN in hypertension treatment. In addition, issues that need to be addressed in future include development of investigations to determine the extent of RDN at the time of the procedure and the potential of renal nerve fibres to regain their potency at later stage following the ablation procedure.

Keywords: Blood pressure, Hypertension, Renal denervation.

INTRODUCTION

It is estimated that over 1 billion people worldwide have hypertension (HTN) and that over 9 million annual deaths can be attributed to complications of HTN such as myocardial infarction, stroke, and renal failure. The prevalence of HTN has been rising, adding to the need for expanding the availability of interventions to reduce blood pressure (BP). Importantly, even modest reductions in BP are associated with large reductions in the rates of cardiovascular events. Resistant hypertension remains a serious clinical unmet need as this patient population is exposed to a three-to-five-fold higher risk of cardiovascular events including ischemic heart disease, congestive heart failure, stroke, chronic renal failure, and peripheral vascular disease.

The role of invasive management strategies, alongside medications, is a growing area of interest as a possible solution for this patient profile. Current invasive strategies that have been tried and include:[1]

1. Catheter-based renal artery denervation (RDN)
2. Baroreceptor activation therapy
3. Arteriovenous shunts

RENAL ARTERY DENERVATION

The history of RDN dates back to the year 1953, when the method of splanchnicectomy (surgical removal of renal nerves) was reported as a treatment option in patients with severe primary hypertension.[2] In the 1990s, interventional techniques with radiofrequency were developed and proof-of-concept studies found significant reductions in BP after RDN.[3-5]

Pathophysiology

RDN affects both afferent sensory and efferent sympathetic nerves: it inhibits the efferent pathway that effects tubular reabsorption of water and sodium and increases vascular resistance and renin release.[6] This reduction of the efferent sympathetic nerve activity to the kidney, indicated by a decrease of renal noradrenaline release in experimental studies, represents one part of the blood pressure (BP) lowering mechanisms of RDN. On the other hand, afferent sensor signalling to the central sympathetic nervous system is reduced after RDN, causing a decrease in sympathetic nerve activity of the central nervous system and thereby also to various organs such as peripheral

resistance vessels, the heart, and the kidneys.[7,8]

Clinical Trials for Renal Artery Denervation

SYMPLICITY-1[9] was the first in-human feasibility and safety study for RDN, published in The Lancet in 2009. Primary endpoints included safety and blood pressure reduction. There were 153 patients; all deemed treatment resistant, taking more than three antihypertensive with an average office blood pressure of 175/98. The Symplicity™ Renal Denervation catheter (Medtronic) was used with a single electrode tip requiring between four and eight ablations of 2 minutes in a circumferential fashion along the renal artery. This showed sustained 4-12 and 36 month reductions in office blood pressure measurements with few procedural complications,[10] thus confirming safety. **SYMPLICITY-2**[11] was a multicentre, randomised, controlled, clinical trial, following the promising success of the first trial, published in The Lancet in 2010. Investigators used the same catheter as the previous trial and followed similar methodology with addition of a control arm. There were 106 patients with resistant hypertension, on an average of five antihypertensive, randomised in a 1:1 fashion to RDN or medication, with crossover allowed at 6 months. Results showed a significant and sustained reduction in office blood pressure measurements at 6 months with a mean reduction of 33/11 mmHg in those treated with RDN and few procedural complications.[12]

On the other hand, **SYMPLICITY-3**[13] was a prospective multicentre, randomised, double blinded trial, with 535 patients evaluated, assigned in a 2:1 fashion to undergo RDN with the Symplicity Medtronic catheter or renal angiography alone, a sham procedure. Primary efficacy endpoints looked at office blood pressure measurements at 6 months, and secondary endpoints included ambulatory recordings. Primary safety endpoints looked at major adverse events. This trial showed no statistically significant difference in baseline blood pressures, both office and ambulatory, in both groups at 6 months, which was contradictory to the previous trials. There was no significant safety difference thus confirming procedure safety.

Drawbacks of SIMPLICITY-3 trial:

A thorough workup of the study results revealed several aspects which certainly contributed to the negative outcome of the study. The results of the SYMPLICITY HTN-3 study have to be interpreted in the context of a rather heterogeneous study group, e.g., one fourth of patients in the treatment arm and nearly one third of patients in the control group were of African-American ethnicity. There were medication changes documented in 39% of patients during the study period. Because of limited operator experience with the ablation catheter, only 6% of patients in the RDN group had a complete circumferential ablation pattern in the main renal arteries that was recommended in the protocol. The SYMPLICITY HTN-3 trial also included patients with isolated systolic HTN and these patients appeared to have a reduced BP response to RDN. These aspects contributed to the negative results of the study in terms of efficacy but provided evidence of the safety of the RDN procedure.

Since then, based on the experience gained from the SYMPLICITY HTN-3 study, several new trials have been initiated to re-evaluate the method with improved study methodology and with more homogeneous study

Table 1: Characteristics of the SPYRAL HTN-ON MED, HTN-OFF MED and RADIANCE-HTN SOLO renal denervation therapy trials

Characteristics	SPYRAL HTN-ON MED	SPYRAL HTN-OFF MED	RADIANCE-HTN SOLO
Number of patients	80	80	146
Design	sham-controlled		
Antihypertensive medication	1-3	–	–
Method	radiofrequency	radiofrequency	radiofrequency
Catheter	SymplicitySpyral™	SymplicitySpyral™	Paradise®
Primary endpoint	Change in 24-hr ABPM after 6 months	Change in 24-hr ABPM after 3 months	Change in systolic daytime 24-hr ABPM after 2 months

Table 2: Study outcomes in systolic 24-hour ABPM and systolic office BP

Parameter	SPYRAL HTN-ON MED	SPYRAL HTN-OFF MED	RADIANCE-HTN SOLO
Mean difference in systolic 24-hr ABPM after 6/3/2 months*	–7.4 mmHg (–12.5 to –2.3) p = 0.0051	–5.0 (–9.9 to –0.2) p = 0.0414	–6.3 mmHg (–9.4 to –3.1) p = 0.0001 (day time)
Mean difference in systolic office BP after 6/3/2 months*	–6.8 mmHg (–12.5 to –1.1) p = 0.0205	–7.7 mmHg (–14.0 to –1.5) p = 0.0155	6.5 mmHg (–11.3 to –1.8) p = 0.007

populations. In this context, the results of three randomised, sham-controlled studies (SPYRAL HTN-ON MED, HTN-OFF MED and RADIANCE-HTN SOLO RDN, table 1) have been published in 2018. The results were encouraging, since they consistently delivered a clear biological signal that RDN decreases BP in patients with primary hypertension.

The SPYRAL HTN-ON MED study, including subjects on one, two, or three antihypertensive drugs who received either RDN by means of radiofrequency ablation or sham procedure in a 1:1 ratio, showed a significant difference of -7.4 mmHg in 24-hour ambulatory and -6.8 mmHg in office systolic BP in favour of RDN six months after treatment.[14] In addition, there were two studies evaluating the pure effect of RDN independent of antihypertensive drug treatment - the SPYRAL HTN-OFF MED and the RADIANCE-HTN SOLO study. In the former, subjects were randomised 1:1 to either RDN or sham procedure and similar to the HTN-ON MED study RDN were performed applying radiofrequency energy. After three months of follow-up, the investigators observed a difference of -5 mmHg in 24-hour ambulatory BP and a difference of -7.7 mmHg in systolic office BP, also in favour of RDN.[15] In the above-mentioned RADIANCE-HTN SOLO study, subjects were also randomised in a 1:1 ratio to either RDN or sham procedure, but the RDN procedure was performed by means of a catheter system based on ultrasound energy. After two months, there was a difference of -6.3 mmHg in daytime ambulatory BP and of -6.5 mmHg in office systolic BP in favour of RDN (Table 2). Recently, the six-month results of this study were published. In addition to a now confirmed sustained BP-lowering effect, subjects in the RDN group were prescribed significantly fewer antihypertensive drugs than subjects in the sham group.

Future perspectives of RDN

The renaissance of RDN as a valid treatment strategy for treating primary hypertension, complementary and in addition to lifestyle modification and drug therapy, offers many exciting perspectives. While RDN was initially only considered as a last resort for patients with treatment resistant severe hypertension, data from the above-mentioned studies indicate that the intervention may also gain importance when treating patients with uncomplicated hypertension with renal sympathetic nerves playing a crucial role not only in the pathogenesis of hypertension but also in other cardiovascular processes such as heart failure, cardiac arrhythmias, and chronic renal failure, RDN could become even more than solely a treatment option for hypertension. In particular, since increased sympathetic nerve activity contributes to the progression of chronic kidney diseases, RDN might become a new treatment option in this group of patients, as RDN decreases two progressive factors of chronic kidney disease at the same time, namely hypertension and increased sympathetic tone to the diseased kidneys.

However, some questions still remain to be answered. One point that has to be investigated further is which method of RDN radiofrequency energy, ultrasound energy or alcohol injection is the safest and most effective one. Furthermore, it would be of importance to identify predictors of patient BP lowering response. Finally, there remains the question of whether functional reinnervation might occur after RDN treatment, as has already been found after heart transplantation.

CONCLUSION

RDN has experienced several rises and falls during its development. The results of the latest RDN studies are

promising and finally provide evidence that RDN is effective in lowering BP in hypertensive patients. Ultimately, RDN may become another pillar of treating patients with hypertension, aside from drug therapy and lifestyle modification. Nevertheless, there are still aspects that have to be examined in detail in currently ongoing sham randomised studies prior to recommending the application of RDN in daily clinical practice. An interventional procedure with sustained blood pressure reduction resulting in improved clinical outcomes would be a very welcome addition to the cardiology field in the management of resistant hypertension.

BARORECEPTOR ACTIVATION THERAPY

Baroreceptor activation therapy (BAT) is another exciting investigational area for an interventional role in treatment of hypertension. This was also initially evaluated in the 1950s and1960s, prior to the development of the wide array of antihypertensive medications currently available. At that time electrical stimulators were used to activate the afferent pathway of the baroreceptor reflex to treat angina initially, then hypertension.[16] However they were limited by procedural complications, surpassed by medications and became a defunct procedure.

ARTERIOVENOUS SHUNTS

Patients with advanced chronic obstructive pulmonary disease underwent studies of arteriovenous (AV) shunt creation with the theory to improve oxygenation, cardiac output, and functional capacity. Large and unexpected blood pressure reductions were noted suggesting that this may be a treatment option for resistant hypertension.[17] Creating a shunt reduces total systemic vascular resistance by moving blood into the high-capacity venous system, thus reducing blood pressure.

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