Renal denervation: symply trapped by complexity?

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**This editorial refers to ‘Predictors of blood pressure response in the SYMPPLICITY HTN-3 trial’, by D.E. Kandzari et al., on page 219.**

Where do we stand?

Seven years after the first patient was treated with the Symplicity Arch catheter by Murray Esler and colleagues in Melbourne, Australia,1 our knowledge about the renal sympathetic nervous system and its modulation by catheter-based renal denervation has significantly evolved. This minimally invasive approach was developed to destroy the renal afferent and efferent sympathetic nerves in the vessel wall of the renal arteries by means of radiofrequency energy.2 First-in-man studies and open-label registries documented that this technique lowers sympathetic nerve activity and blood pressure in certain patients with resistant hypertension.3–6 The treatment was delivered safely with minimal procedural complications and with no detrimental effect on renal function.7,8 Long-term vascular safety, however, remains to be confirmed as concerns have been raised that the procedure might induce renal artery stenosis in some patients.9 Moreover, in preliminary studies, regression of left ventricular mass and improvements in diastolic function,10 as well as anti-arrhythmic effects11 were observed following renal denervation. It was obvious that the results of previous published studies required validation in blinded, randomized, controlled clinical trials. While the first small randomized trial, Symplicity HTN-2 enrolling 106 patients to receive either renal nerve ablation or medical treatment alone without a sham procedure, confirmed the results obtained in registries, the blinded, sham-controlled Symplicity HTN-3 study randomizing 535 patients,9 again using Medtronic’s Symplicity device, did meet its primary safety endpoint, but disappointingly failed to reach its primary efficacy endpoint, defined as a statistically significant decrease in office blood pressure between the groups. The initial publication of this well-designed trial challenged the overall effectiveness and usefulness of catheter-based renal denervation, and all previously published studies appeared to be invalidated.

Symplicity HTN-3 was expected to provide the definitive statement on the value of renal denervation in antihypertensive treatment. Physicians, who have seen patients benefitting from the procedure, and scientists, who have proven that renal denervation effectively lowers blood pressures in different mammalian species (i.e. dogs, pigs, and rabbits), tried to understand why Symplicity HTN-3 did not meet its primary endpoint. Shortly after the presentation and publication of the results, several possibilities were discussed regarding why the results were disparate compared with prior clinical trials and registries, with the caveat that in-depth analyses on trial execution were still pending. Some argued that the absence of a positive finding in Symplicity HTN-3 was mainly related to adding a sham procedure and blinding of patients as well as follow-up assessors;12 others tried to provide more profound explanations.13

What can be learnt from Symplicity HTN-3?

In this issue of the journal, D. Kandzari et al.14 share interesting insights and hypotheses and critically examine the results of the Symplicity HTN-3 trial in the context of existing renal denervation data and clinical trial design.

(i) Although stable antihypertensive medication was required, 22% of all patients had medication changes 2–6 weeks prior to screening. Between baseline and 6-month endpoint assessment, medication changes were documented in another 39%.

(ii) Baseline office systolic blood pressure ≥ 180 mmHg, aldosterone antagonist use, and non-use of vasodilators were predictors of office systolic blood pressure change at 6-month follow-up in patients undergoing renal denervation.

(iii) The number of ablation attempts and energy delivery in all four quadrants (anterior, inferior, posterior, and anterior) were associated with greater reductions in office and ambulatory blood pressure change.

(iv) Non-African Americans receiving renal denervation had a significantly greater change in office blood pressure compared with those receiving sham treatment.
Subgroup analyses: who is the ideal candidate for renal denervation?

In contrast to previously published trials mainly conducted in Europe and Australia, about a quarter of the patients included in Symplicity HTN-3 were African-Americans. Of note, there was an interaction of ethnicity and office blood pressure, with a significant difference in office systolic blood pressure response between Caucasians and African-Americans. Interestingly, renal denervation was equally effective between Caucasians and African-Americans (−15.2 mmHg vs. −15.5 mmHg); however, sham treatment was particularly effective in African-Americans (−8.6 mmHg vs. −17.8 mmHg), which might be related to differences in drug adherence, especially to frequently prescribed vasodilators.

On average, patients received 5.2 ± 1.4 antihypertensive drugs at baseline, and in 39% of all patients medication changes were documented between baseline and 6-month endpoint assessment. This finding challenges the premise that patients were actually receiving maximally tolerated doses of antihypertensive at study entry, in spite of protocol mandate. Further, patient adherence has been shown to get progressively worse with higher pill burden. Changes in drug treatment, intentional or unintentional, may have added considerable noise to the blood pressure assessments in Symplicity HTN-3. Under these conditions, it appears difficult to demonstrate any incremental blood pressure-lowering effect of the procedure. Future study designs will have to address in particular the issue of stabilized medication regimens before and during the study period to avoid confounded blood pressure assessments.

Multivariate analyses identified prescription of an aldosterone antagonist at baseline as a positive predictor for changes in office systolic blood pressure after renal nerve ablation. Indeed, the role of aldosterone antagonists in patients undergoing renal denervation is of special interest. One might argue that renal denervation provides an additional blood pressure-lowering effect to pre-existing neurohormonal blockade in patients treated with aldosterone antagonists. On the other hand, the subgroup of patients receiving aldosterone antagonists were significantly younger (52.6 ± 9.5 years vs. 59.5 ± 10.2 years, P < 0.001) and had different co-morbidities (cardiomyopathy, 4.3% vs. 17.1%, P < 0.001; myocardial infarction, 6.7% vs. 15.9%, P = 0.015; type 2 diabetes mellitus, 50.4% vs. 35.4%, P = 0.017), which might have influenced the finding. Data from a European multicentre study on 346 patients with uncontrolled hypertension undergoing renal denervation, however, documented a significant reduction in mean 24-h blood pressure by 11.9/7.1 mmHg (P for both < 0.001) in the subgroup of patients (n = 78) who were treated with spironolactone, which was comparable with the blood pressure reduction in the entire cohort. In light of concerns about the long-term safety of spironolactone, and the fact that not all patients respond to such treatment, controversy exists as to whether use of aldosterone antagonists is a prerequisite eligibility criterion to undergo renal denervation.

Catheter-based renal denervation: is it an ‘easy’ procedure?

In addition to other reasons, performance of an insufficient procedure has been postulated as a potential reason for non-response to treatment. In Symplicity HTN-3 all procedures were performed using the first-generation technology, a single electrode mono-polar catheter system (Symplicity Flex, Medtronic, MN, USA) that was used to provide radiofrequency energy to the vessel wall. There was no
means of assessing proper wall contact or effective destruction of renal sympathetic nerves intraprocedurally. In contrast to earlier Symplicity studies, non-physician industry representatives were present at all cases, which is particularly noteworthy, as the majority of interventionists were unfamiliar with the procedure and had only performed 1–2 procedures beforehand. Except for the recommendation that 4–6 ablations should be delivered to each renal artery beginning at the distal end of the artery and rotating in a helical pattern, no other instructions were provided by the protocol. This clearly affected the quality of the procedural performance in Symplicity HTN-3. Indeed, the average number of radiofrequency ablation attempts was 11.2 ± 2.8, out of which only 9.2 ± 2.0 (84%) were complete ablations of 120 s duration, which is considerably lower compared with previous studies. Overall, the number of ablation attempts ranged from 1 to 26, with the vast majority of the patients receiving ≥8 ablation attempts. The larger numbers of ablations were mainly related to the appearance of generator codes and premature interruptions of energy delivery forcing the operator to repeat ablations at the same site. Interestingly, in Symplicity HTN-3, the number of ablation attempts positively correlated with greater changes in office blood pressure (P = 0.01).

Recently, the variation in distribution and density of the renal sympathetic nervous system in humans, the ultimate target of renal denervation, has been assessed in detail. It has been nicely shown that the highest average number of nerves was observed in the proximal and middle segments of the renal artery and the lowest in the distal segments. The mean distance from the lumen to the nerves was the longest in the proximal and the lowest in the distal segments, with the circumferential distribution being most pronounced in the ventral and the least pronounced in the dorsal regions (Figure 1). These data suggest that asymmetric and most probably distal renal artery targeting is required to achieve effective denervation of renal afferent and efferent nerves and that the variability in the target nerve anatomy determines whether or not nerve blockade is achieved, particularly with the use of single electrodes. Indeed, full four-quadrant ablation on both renal arteries has been accepted as the clinical standard. However, retrospective analyses from Symplicity HTN-3 derived from site co-ordinator recordings, proctor assessments in the catheterization laboratory, and data from the angiography core laboratory revealed that only 6% of all patients received two four-quadrant ablations (both sides), 20% received one four-quadrant ablation (either right or left), and 74% received no four-quadrant ablation. Circumferential treatment, as recommended in the trial protocol, was associated with numerically more pronounced reductions in blood pressure, although this was not statistically significant (P = 0.1). In the small group of patients receiving two four-quadrant ablations on both sides (n = 19), office systolic and ambulatory blood pressure changes (–24.3 mmHg and –10.3 mmHg) were similar to those of previous published studies.

What is needed now?
The pause that Symplicity HTN-3 created in the field of device-based antihypertensive therapies helped to refine technologies and
techniques, and reflect on the need of future science. The degree of renal denervation has been documented by norepinephrine spillover in a small subgroup of 10 patients in Symplicity HTN-1. Although 30 days after the procedure the reduction in nerve traffic was on average only 47%, i.e. less than what has been described in animal studies, it appeared to be sufficient as the antihypertensive response was adequate. Recently, Murray Esler published the effectiveness of catheter-based renal denervation as assessed by renal norepinephrine spillover before and 30 days after the procedure in a slightly larger population of 17 patients (Figure 2). Again, the response to renal denervation was 40% on average, but was highly variable, ranging from 0 to 80%. Such a variability of treatment effects of renal denervation has also been documented in pre-clinical studies in pigs, when four radiofrequency ablations have been applied in the main renal artery (Figure 3). These results argue in favour of an incomplete and insufficient ablation of renal sympathetic nerves as a major cause of inadequate blood pressure responses to catheter-based interventions and inevitably lead to some questions. (i) Can catheter design and/or specific treatment strategies help to reduce the variability and increase conformity of the response renal nerve ablation? (ii) Does renal denervation exert a class effect or will different devices with distinct electrode designs and/or energy delivery show similar efficacy and safety?

It might have indeed been oversimplistic to assume that one single interventional therapy could uniformly treat a heterogeneous disease, such as hypertension. The post-hoc analyses derived from the overall negative Symplicity HTN-3 trial helped to generate interesting hypotheses related to confounding variables and to provide important insights for the design of future renal denervation studies, which will be launched soon. Specifically, recruiting centres should have experienced hypertension specialists and interventionalists available, and stabilization of medication and blood pressure before randomization appears particularly important. Furthermore, treatment strategies should be refined and ablations should probably be performed more distally where the deployed energy is able to reach the renal nerves in the adventitia. Finally, multielectrode devices are probably more reliable in achieving effective renal nerve blockade than single electrode catheters.

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