Renal Denervation and Symplicity HTN-3
“Dubium Sapientiae Initium” (Doubt Is the Beginning of Wisdom)

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Recently, results of the Simplicity Hypertension-3 (HTN-3) study have been presented at the American College of Cardiology scientific sessions and simultaneously published in the New England Journal of Medicine.1 Ever since the sponsoring company announced on January 9, 2014, that the study failed to meet its primary efficacy end point, the scientific community has been anxiously awaiting the details of this pivotal study. Now that the results are in and details are known (to some extent), it is time to examine the facts carefully, put the data into perspective, and deliberate on the future of renal denervation (RDN) as a therapeutic option.

The Symplicity HTN-3 Study
The study was the first randomized, single-blinded, sham-controlled study in the RDN literature. The study included 535 patients with drug-resistant hypertension randomly assigned to optimal medical therapy plus RDN or to optimal medical therapy alone plus sham procedure. The procedure was performed by >100 interventionalists throughout the United States. The study met its primary safety end point: a composite of all-cause mortality, end-stage renal disease, embolic events resulting in end-organ damage, any vascular complication, hypertensive crisis, or renal artery stenosis. The study, however, failed to meet its primary efficacy end point. Results indicate that there was no significant difference in blood pressure (BP) reduction either in the office or as measured by ambulatory monitoring. At 6 months, office BP decreased by 14.1±24 mm Hg in the RDN group and by 11.7±26 mm Hg in the sham control group (P=0.255). The average 24-hour ambulatory systolic BP decreased by 6.75±15.11 mm Hg in the RDN group and by 4.79±17.25 mm Hg in the sham control group for a difference of 1.96 mm Hg (P=0.979) for superiority with a margin of 2 mm Hg, thus missing the major secondary end point of the study. Although the results are disappointing, they need to be viewed with caution and in the context of study design, patient population included, and the sham response and in the context of previously published studies.

First, the fact that Symplicity HTN-3 fulfilled the ethical precept of medicine primum non nocere—first do no harm is comforting, and it will allow research to continue.2 RDN has been shown to be safe in almost all previously published studies,2–9 and preservation of renal function has been established even in patients with baseline renal insufficiency.10,11 Vascular complications are rather rare, whereas renal artery stenosis is an infrequent event.2–4 Furthermore, after RDN, neural cardiovascular reflexes are preserved during exercise12 and upright posture.11

Potential Factors That May Have Contributed to a Negative Trial
In view of the results of Symplicity HTN-3a, number of questions need to be asked and carefully considered:

1. Is the concept of RDN correct? Do renal nerves really play an important role in the generation and maintenance of resistant HTN?
2. Are results from previous, uncontrolled studies wrong or misleading?
3. Are there any methodological issues that can explain the results of Symplicity HTN-3, and finally
4. Where does this study leave the field of RDN?

What Is the Rationale for RDN?
The scientific rationale for the development of the catheter-based RDN is based on the following: (1) the presence of activated sympathetic nervous system, (2) increased signals from afferent sympathetic nerves that result in sympathetic overactivity, (3) contribution of efferent sympathetic nerves on BP and sodium homeostasis, (4) the anatomic position of renal sympathetic nerves permitting transvascular interruption, (5) the efficacy of surgical sympathectomy in the past, and (6) experimental and clinical data with RDN to date.

A vast amount of evidence from experimental studies in animals and humans indicates beyond any doubt that sympathetic nervous system overactivity plays a crucial role in the development and persistence of hypertension.14,15 Kidneys hold an important role in sympathetic activity by acting as both generators and recipients of sympathetic signals.16 Afferent sympathetic fibers transmit signals from mechanoreceptors and chemoreceptors from the pelvis of the kidney to the brain. The processing of these signals results in sympathetic overactivity that affects the heart, peripheral vasculature, and renal function. Sympathetic impulses from the kidney promote sympathetic nervous system overactivity in response to renal injury in experimental studies.17 However, efferent sympathetic fibers from the brain course through the spine and innervate several parts of the body, including the kidneys. Renal efferent sympathetic nerves modulate renin release, sodium and water absorption, renal blood flow, and glomerular filtration rate.18 Experimental data by DiBona
and others confirmed and re-enforced these observations. Furthermore, Osborn et al demonstrated that low-frequency stimulation of the renal nerves in dogs can directly mediate renin secretion. Experiments in DOCA (deoxycorticosterone acetate)-treated miniature swine with established hypertension demonstrated that RDN results in immense natriuresis and BP reduction. Both the afferent and efferent fibers seem to contribute to the development and persistence of hypertension. Experiments in hyperinsulinemia-induced hypertension also demonstrated that RDN can prevent hypertension development, if done early, or can normalize BP after hypertension is established. Overall, experimental data formulate a strong scientific background and rationale for RDN.

**Previous RDN Studies**

Both efferent and afferent sympathetic fibers course in the adventitia of the renal artery wall. Most of the sympathetic fibers are located 2 to 3 mm from the renal artery lumen, and they are amenable to catheter-based thermal ablation. Fibers, however, have been identified as far as 8 mm away from the lumen and are difficult to ablate using radiofrequency energy. Furthermore, anatomy varies from patient to patient, and standardized ablation may be incomplete using current methods. The early uncontrolled studies in humans demonstrated impressive results but also created several questions and uncertainties: For example, the first-in-human Symplicity HTN-1 study demonstrated a smaller office BP reduction in the first month that improved with time and thus created the impression of delayed response. This, however, was most likely because of different number of patients reported at different time points and adjustments made during the course of the study. Symplicity HTN-2 included a placebo arm, but placebo was not given; it was unblinded and unlike many other hypertension studies failed to show any placebo effect, making results difficult to interpret. Most studies that followed, implemented similar protocols to the early Symplicity trials, remained unblinded and included a single arm, and most of them presented reductions in office BP in the range of 20 to 30 mm Hg. BP reduction, however, seen on 24-hour ambulatory BP monitoring was consistently lower.

In fact, the considerable discrepancy between average office BP and average 24-hour BP reduction after RDN is one of the acknowledged drawbacks of RDN trials. Close examination of the data demonstrates that most disparities between office and ambulatory BP reductions are because of baseline differences between these 2 measures. In the Symplicity series, ambulatory BP monitoring was performed only in a small subset of patients (12/45 patients in Symplicity HTN-1 and 20/106 patients in Symplicity HTN-2), and ambulatory BP reduction was only 41% and 34% of office BP reduction in the 2 studies. This is much smaller than the reduction seen in hypertension drug trials. Similar disparities between office and ambulatory measurements have also been seen in the EnligHTN-1 (Enlighten-Hypertension-1) trial, which reported office BP reduction (−28/−10 mm Hg) that was significantly higher than ambulatory BP reduction (−10/−5 mm Hg), but both pressures were reduced early within the first month and remained stable throughout the follow-up period. Recently, a larger study specifically examined the BP response to RDN as measured by ambulatory BP monitoring. In patients with true treatment-resistant hypertension (n=303), there was a significant reduction in 24-hour systolic BP (−10/−10/−12 mm Hg; P<0.001) and diastolic BP (−5/−5/−7 mm Hg; P<0.001) at 3, 6 and 12 months, respectively, but once more ambulatory BP reduction was much smaller than the reported office BP reduction. There was no effect on ambulatory BP in patients with pseudoresistant hypertension (n=43). Another study from 10 European expert centers revealed a more modest decrease in office systolic/diastolic BP after RDN (−17.6/−7.1 mm Hg) and an even smaller (−5.9/−3.5 mm Hg) drop in 24-hour ambulatory BP. A more recent study compared the BP-lowering effect of RDN with clinically adjusted drug treatment in true treatment-resistant hypertension. Patients were randomized to RDN (n=9) performed with the Symplicity single-tip catheter or to clinically adjusted drug treatment (n=10). According to the authors, the study was stopped early for ethical reasons because RDN had uncertain BP-lowering effect. Both systolic BP and diastolic BP were significantly lower in the drug-adjusted group at 6 months, and absolute changes in systolic BP were larger in the drug-adjusted group. The authors state that adjusted drug treatment has superior BP-lowering effects compared with RDN in patients with true resistant hypertension. However, in the same study, RDN resulted in an ambulatory BP reduction of −10/−7 mm Hg, which is by no means clinically insignificant.

Thus, even this study is inconclusive, and results should be considered preliminary, requiring validation.

A major shortcoming of most studies preceding Symplicity HTN-3 has been the lack of valid controls, thus making it impossible to exclude BP reduction because of the Hawthorne effect. Obviously, there was a substantial Hawthorne effect in the sham control arm of HTN-3. This is a common finding in almost every hypertension study, and it is particularly true for patients with drug-resistant hypertension. This effect needs to be taken into account in future trials, and study design should be adjusted accordingly.

The clear message from these and other trials that included both office and ambulatory BP monitoring is the consistent BP reduction by both techniques. There is, however, substantial disparity in the magnitude of BP response between the 2 measures, and this can be attributed to a large extent to unintentional overestimation of office BP at baseline.

**Methodological Issues That May Affect RDN Outcomes**
The purpose of the RDN procedure is to deliver transvascular thermal energy, through the renal artery wall, to interrupt the sympathetic fibers, both afferent and efferent that are coursing in the adventitia of the vessel. Radiofrequency energy has been the preferred source to date in most studies. The currently used systems can create discrete lesions of ≈2 to 3 mm in diameter and depth, depending on the target temperature. It has
been, therefore, determined that certain numbers of lesions are needed to achieve complete denervation. These lesions need to be distributed in a suitable pattern so as to achieve complete fiber interruption, but at different distance from the origin of the artery so as to avoid cross-sectional lesioning that may predispose to renal artery stenosis. This geometric placement of the lesions can be difficult to achieve with a single-tip catheter, seen on a 2-dimensional screen, attempting to create lesions in a 3-dimensional artery. The multielectrode systems can achieve the desired pattern of lesions with less manipulation and with less operator training. The operator’s specific experience with the ablation system, the learning curve of the procedure, and the selected catheter system can be crucial determinants of complete denervation. Catheter-based RDN is a blind procedure because no accurate intraprocedural markers of success have been identified as of yet. Variability in results might be, therefore, anticipated after RDN especially when using the single-tip catheter, which may result in incomplete denervation.

In Symplicity HTN-3, close to 90 centers participated and >100 interventionalists performed the procedure using a single-tip catheter. The inherent limitations of the catheter design, the small number of patients per center, and the unavoidable learning curve may have led to incomplete denervation in a considerable number of patients, which in turn may have contributed to smaller than expected BP reduction and inability of the study to achieve its primary efficacy end point.1 With no marker of RDN success, the interventionalists’ experience is irreplaceable.

What Symplicity HTN-3 Did Not Do?
Symplicity HTN-3 was not designed to provide any informative data on the most promising aspect of sympathetic neuromodulation, that is, its pleiotropic nature.3 Several reports have shown favorable impact of RDN on cardiac mass assessed by echocardiography and magnetic resonance, independently of BP reduction.33,34 In addition, RDN seems to improve glucose status,35,36 arrhythmias,37,38 and obstructive sleep apnea syndrome39 by reducing insulin resistance, end-diastolic left ventricular and atrial pressures, as well as by causing better natriuresis.40–42 Most interestingly, in certain models of experimental hypertension not accompanied by excess sympathetic activation, RDN causes BP drop not by reducing sympathetic outflow but mostly because of left shift of the pressure-natriuresis curve.43,44 These pathophysiological considerations on the fundamental compact of RDN on sodium balance should be assessed in future clinical trials. The use of different catheters and energy modalities (ie, radiofrequency, ultrasound, cryotherapy, or combination)39–41 ensuring more complete ablation of renal nerves would perhaps influence BP and metabolic and cardiovascular parameters up to a higher degree.

In this context, we strongly believe that there is an emerging need to discuss the appropriate design/methodology of randomized trials for the true role of RDN in the therapy of hypertension and cardiovascular diseases. The key point is that RDN is a method that has substantial pathophysiological background, with experimental and clinical studies supporting its effects.32,42 And in line with the famous quote of Rene Descarts, “Dubitum sapientiae initium” (Doubt is the beginning of wisdom), the lesson to be learned is that when a negative trial such as Symplicity HTN-3 is published, one should not only be skeptical to RDN but also to the trial itself. Symplicity HTN-3 has not proved or disproved that RDN works; it has, however, created an urgent need for further research.

Where Do We Go From Here?
The obvious question then is where does Symplicity HTN-3 leave the field of RDN? Certainly, it should not mean the end of it. Rather, Symplicity HTN-3 should be seen as the beginning of a new era in RDN: an era where studies are appropriately designed, appropriate controls are put in place, appropriate tools are used, and appropriate monitoring is implemented. The scientific community needs to pay attention to science and not to first impressions or enthusiastic dogmatists. Complete interruption of sympathetic fibers with RDN is essential for success. Attention, therefore, needs to be paid to that effect, and systems that can provide predictable and reproducible results should be used. The systems need to be easy to use, user-friendly, to require minimal manipulation, to be less operator dependent, and systems that can provide reliable fiber interruption.

We, therefore, need new studies that are randomized, blinded, placebo, and sham controlled. We need studies that address surrogate efficacy end points, such as BP control, but also outcome studies. We need studies that will address hard outcomes but studies with proper design powered enough to prove the concept. These studies should include large numbers of high-risk patients (event driven), and the patients should be randomized to optimal therapy alone or optimal therapy plus RDN.

Only then, we will know whether RDN works and whether it provides tangible benefits to our patients. Let’s use Symplicity HTN-3 as a new beginning, let’s do the right studies and move the field forward.

Disclosures
Drs Papademetriou and Tsioufis served as consultants and received modest honoraria from St Jude Medical, the makers of the EnliGHTN device. None of the authors is a stake or share holder to the company.

References


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