Editorial

Renal denervation for the treatment of hypertension: If at first you don’t succeed, try and try again

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There is great public health interest in identifying new therapeutic approaches to treat hypertension. Great strides have been made in the medical treatment of hypertension over the past 50 years, but despite these advances, the number of patients with uncontrolled or treatment-resistant hypertension remains a burgeoning problem associated with a significant burden of resulting cardiovascular morbidity and mortality.

The advent of catheter-based approaches to effect renal denervation, down-modulating the sympathetic nervous system in a minimally invasive fashion, sparked tremendous enthusiasm for physicians worldwide. The promise of catheter-based renal denervation was one that represented a therapeutic holy grail—a way of treating a prevalent and morbid disease with a fix that was durable, permanent, and not subject to medication non-adherence or patient side effects. In early studies, the data on renal denervation were almost too good to be true, demonstrating marked and sustained reductions in blood pressure with the use of a broad range of devices and technologies. Yet these studies only served to further increase expectations for the broader dissemination of renal denervation therapies.

It was not until the completion of the SYMPLICITY HTN-3 trial, a randomized controlled trial of renal denervation with a radiofrequency ablation catheter, that the field of renal denervation underwent its first true reality testing. In this trial of 535 patients with treatment-resistant hypertension randomized to renal denervation with the Symplicity Flex monopolar electrode catheter compared with a sham procedure, blood pressure was reduced in both study arms, but with no significant further improvement observed with denervation compared to control. Since the presentation and publication of these results, a whole host of explanations for the failure of the trial have been posited, including: variability in patient selection and poor adherence to a stable medical regimen, variability in measurements of blood pressure (the primary endpoint of the trial), and variability in operator experience and catheter technique.

While the institution of even more rigorous study procedures may be able to improve on the results of SYMPLICITY HTN-3 by further optimizing patient selection, endpoint ascertainment, and medication adherence, a fundamental issue that remains problematic is whether there were potential technical problems with the renal denervation procedures as performed within the trial. In light of these concerns, several novel technologies aimed at reducing the variability of renal denervation procedures (including a further iteration of the Symplicity catheter) are set to soon begin investigation in trials around the world. These trials represent a real and scientific attempt to resuscitate interest in a field that exhibited great promise for the treatment of a genuinely important public health problem.

In this light, the study by Yalagudri and colleagues in this issue of Indian Heart Journal represents an initial attempt to address potential limitations of the original Symplicity catheter through the use of manual saline irrigation at the time of radiofrequency ablation. By providing active surface cooling of the electrode tip, the authors describe a method of potentially increasing the degree of thermal injury provided by an...
ablation catheter. One hypothesis for the limited efficacy of renal denervation seen in the SYMPLICITY HTN-3 trial relates to an inadequacy of effective ablation. The use of saline irrigation to the tip of the radiofrequency catheter in order to effect a larger and deeper ablation lesion may be one method of overcoming an inadequate denervation procedure. In addition, it is an innovative solution to overcome the lack of availability of the proprietary Symplicity generator box. However, this approach is not without potential risks. For one, the absence of temperature monitoring (with algorithmically determined modulation of variable power output) may result in creation of too deep or large an ablation lesion. Although the authors did not describe any major adverse safety effects with their approach, a larger sample of patients is needed before this method can be deemed truly safe. Nonetheless, it is laudable that the authors opted to study their novel technique and publish their results in a peer-reviewed journal, rather than simply just applying these techniques in practice with the backing of anecdotal evidence alone.

What next is needed in the field of renal denervation? It is our sincere hope that the use of preclinical studies is expanded prior to the implementation of new techniques and technologies of denervation therapies. For example, a system such as those proposed in the study by Yalagudri et al could first be studied in animals in order to optimize ablation parameters while carefully monitoring safety (e.g. depth of lesions created). Preclinical studies serve a critical role in aiding our understanding of how best to perform renal denervation, and how to maximize efficacy and minimize safety concerns. Even in the months following the results of SYMPLICITY HTN-3, several preclinical studies examining the location of renal sympathetic nerves as well as the most effective ablation strategies to treat these nerves have been presented and published, and have already begun to inform future trials of renal denervation therapies. Further advances in fine-tuning optimal patient selection and in intraprocedural monitoring of denervation efficacy are also sorely needed.

The fact that several preclinical and patient-based studies are going ahead despite the blow that was dealt to the field when SYMPLICITY HTN-3 was completed demonstrates how much potential benefit and hope there is for a safe and durable treatment option for patients with hypertension. Nonetheless, while continued perseverance is required in order to move the field forward, there are only so many large setbacks that can be endured before the field eventually runs out of steam. As Yalagudri et al demonstrate, sometimes small, incremental steps are required in order to regain lost momentum.

Conflicts of interest

All authors have none to declare.

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REFERENCES