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EDITOR'S PAGE

Reflections on Renal Denervation

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Based upon earlier experience with surgical sympathectomy and considerable data in experimental animals, clinical studies began to evaluate whether transcatheter renal sympathetic denervation (RDN) by radiofrequency ablation could provide effective therapy for resistant hypertension. The initial reports were glowing, multiple (largely uncontrolled) publications ensued, the procedure received the European CE mark approval, and the European Society of Cardiology released a consensus statement that catheter-based renal denervation could be considered a therapeutic option in patients with drug-resistant hypertension. By 2013, it was estimated that approximately 10,000 patients had been treated with RDN throughout the world (1). Perhaps the ultimate barometer of the enthusiasm with which the scientific and industrial medical community viewed renal denervation was that Medtronic Inc. (Minneapolis, Minnesota) paid $800 million up front to purchase Ardian (Mountain View, California), the company that had developed the technology.

To that point, the evidence supporting the therapeutic efficacy of RDN for resistant hypertension was based largely upon the SYMPLICITY HTN-2 (Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension) trial (2), which was the only prospective controlled study conducted. Concerns were expressed even with respect to SYMPLICITY HTN-2 in regard to the lack of blinding and long-term follow-up, the potentially suboptimal administration of and adherence to medical therapy, and the failure to do ambulatory blood pressure monitoring. A meta-analysis published in 2013 found 294 papers dealing with renal denervation, virtually all of which yielded positive results; however, only 18 of these, consisting of 561 patients, satisfied their entry criteria. Nevertheless, the enthusiasm for the procedure was almost boundless, and there was speculation about the use of RDN for moderate hypertension and even in patients who did not want to take antihypertensive drugs. It remained only for the completion of SYMPLICITY HTN-3 (3), a protocol in which patients were blinded by performing a sham procedure, to obtain Food and Drug Administration approval and enable the procedure to diffuse into clinical practice.

As is now well known, to the utter amazement of nearly everyone, the SYMPLICITY HTN-3 trial failed to show a benefit of RDN over optimal medical therapy (4). Possible explanations include the introduction of the placebo effect, tightening of medical therapy, the application of ambulatory pressure monitoring, and even the lack of expertise of new investigators. The exact reasons for the unexpected results remain to be defined. Nevertheless, the most surprising aspect to me was the fact that the SYMPLICITY HTN-3 trial yielded negative results despite the impressive body of published data that provided evidence of the efficacy of the procedure. How could so many investigators doing so many independent protocols with so many different endpoints be wrong? How could so many editors and reviewers choose to accept so many papers that would ultimately appear to be misleading?

I want to acknowledge upfront that the *Journal* played a significant role in the dissemination of data that attested to the efficacy of RDN. We published a meta-analysis and an expert consensus statement, as well as 8 research papers on renal denervation, some with

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editorials (5–14). Although cautionary of limited early results, all articles reached a favorable conclusion on the procedure, and the original research papers provided evidence of therapeutic benefit. Many of the original research papers reported not only reductions of blood pressure, but also end organ benefits such as decreases in vascular stiffness, left ventricular hypertrophy, and recurrences of atrial fibrillation. All were subjected to rigorous peer-review, and were judged to be in a high-priority category for publication by the editors at our weekly meetings. In aggregate, they seemed to provide a firm scientific basis for the belief that RDN would be an effective therapy, and this was a sense that was certainly conveyed to our readers.

In reflecting on the discrepancy between the data that we published and the results of the SYMPLICITY HTN-3 trial, several thoughts to mind. As *JACC* editors, we tend to place a very high importance on novelty in deciding whether to accept or reject a submitted manuscript. Our criteria are sometimes abbreviated as "new, true, and relevant." I assume this is true of all journals; everyone wants to be the first to publish original information, and we find confirmatory data less appealing. Therefore, a new procedure, particularly one for which very promising early results exist, is likely to receive an extra boost when assigning priority for acceptance. In addition, a novel, rapidly emerging technology will stimulate a great deal of research and result in multiple publications and citations, all of which can affect the hateful, imperfect, but yet critically influential impact factor. Taken together, these considerations may help to explain how studies that have relatively small sample sizes, no or limited controls, and less than absolutely perfect methodology achieve such prominence in the medical literature.

The ultimate fate of renal denervation therapy for resistant hypertension remains unknown. Factors responsible for the negative results of the SYMPLICITY HTN-3 trial may be identified and rectified in future studies. Alternate techniques that are more effective at achieving sympathetic renal denervation may be developed. It is certainly not my intention to presume the death knell of the approach. However, it is well to consider that investigational results that are surprisingly good and lacking full understanding of the physiological mechanism of benefit should be viewed with caution. This is particularly true when the studies supporting benefit are of limited size, and not prospective, randomized, controlled, blinded trials. We should be wary of authors who are overly enthusiastic about their findings, and we must recognize the subconscious bias that may influence editors when selecting manuscripts for publication. The SYMPLICITY HTN-3 trial provided critically important information in regard to transcatheter renal denervation, but what it said about our process of developing and evaluating new technology was perhaps even more important.

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