Commentary

Interventional Cardiology

Raising Lazarus: reassessing renal denervation after SIMPLICITY HTN 3

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Keywords: hypertension • renal denervation • SIMPLICITY

On March 29, 2014 during the late breaking clinical trial session of the American College of Cardiology (ACC) Scientific Meeting in Washington, DC (USA), the final results of the SIMPLICITY HTN 3 trial were presented. The presentation and the ensuing publication of this well-designed, large-scale, randomized, sham-controlled clinical trial assessing efficacy of renal denervation (RDN) tempered the effusive enthusiasm generated by observational data and two smaller promising trials for a technology that was already in widespread use outside of the USA [1]. In addition, the results of this landmark trial polarized the cardiology community into those who believe that the findings exposed RDN as a flawed technology, and those who opine that this trial may only be a roadblock with the development of this technology – an opinion we share. Since there have been a myriad of editorials and commentaries describing the design problems in SIMPLICITY HTN 3, we do not intend to rehash those issues. Instead, we offer several insights with respect to how RDN technology could be revitalized for future translational and clinical studies.

Hypertension: possible genetic influences

SIMPLICITY HTN 3 was the first large-scale RDN trial that was multi-ethnic in its patient demographics, including a large cohort of African–Americans (the preceding SIMPLICITY HTN 1 and 2 trials included predominantly Caucasians) [2]. African–Americans are commonly known to harbor genetic variants that confer resistance to β-blocker therapy, such as polymorphisms in *DRB1*, *ADRB2* and *ADRAC2C* and other components of the β-adrenergic signaling pathway [3]. As such, it is conceivable that the effect of RDN, through the inhibition of autonomic hypertension maybe diminished in African–Americans.

Currently, the largest source of hypertension genetics stems from large-scale genome-wide association studies (GWAS). Current GWAS studies offer convincing insight linking many of the comorbidities of hypertension to single linkage units within specific alleles, although these linkage maps lack the fidelity necessary to hone in on the identities of the individual molecules responsible [4]. Research into a handful of proteins encoded by hypertension genes has revealed, as expected, that the genetic basis of hypertension is multi-factorial: for example, overexpression of TLR4, a molecule involved in angiotensin-mediated signaling has been shown to induce hypertension in a small animal model, without affecting baseline adrenergic tone [5]. Furthermore, modification of the Na-sensitive domains of the GWAS-nominated candidate gene *PLEKHA7*, have shown that this molecule regulates salt-sensitive hypertension but not other forms of hypertension, *in vivo* [6]. Such studies are beginning to shed light on the molecular basis of hypertension and its complex etiology. Still, the fundamental mechanistic questions surrounding hypertension remain unclear. For example, is the genetic profile and drug response of patients with autonomic hypertension different from those with angiotensin-mediated hypertension, or hypertension due to altered

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vasoreactivity? Alternatively, could these multi-factorial molecular etiologies of hypertension be interlinked such that alteration of one pathway obligately affects the function of another? As a result of these findings, one can infer that there is a significant degree of genetic variation within the human population, and that by virtue of its complexity, response to hypertension therapies maybe varied among different people. As such, we currently have no *a priori* mechanism to identify patients in whom RDN is likely to succeed.

Establish an assay for biological confirmation

Another criticism leveled against SIMPLICITY HTN 3 was the absence of a biological confirmation of successful RDN. However, observational data and two clinical trials were overwhelmingly positive; hence, biological confirmation was not thought to be necessary. With the negative results of SIMPLICITY HTN 3, validation of denervation has now become an active area of investigation, as our understanding of which renal artery nerves are responsible for renal-mediated hypertension is limited. There are distinct groups of sympathetic, parasympathetic, and somatic sensory (nociceptive) neurons in the renal artery adventitial and periadventitial space, and which of these are ablated during RDN is unclear. Moreover, we have only recently begun to understand the anatomical distribution of the renal nerves within the renal artery. Second, the percentage of sympathetic nerves that require ablation in order to achieve sustainable reduction in blood pressure is unknown. Sympathetic fibers are predominantly localized to the distal and dorsal locations of the renal artery trunk. Hence, the consequences of renal denervation may differ depending on the physical location of the nerves being ablated [7]. Third, we currently have no reliable procedural method to confirm that successful RDN occurred.

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Surrogate markers of RDN are also vital to allow for preliminary investigations of novel technologies in a cost-effective manner. Direct renal vein measurement of norepinephrine has been utilized to assess for renal injury in animal models with mixed results [8]. Norepinephrine and other adrenergic neurotransmitters are nonspecific and show high levels of temporal variation making it difficult to attribute any change to renal denervation alone. Moreover, the destruction of nociceptive neurons during the renal denervation process induces pain, which translates into greater changes in the sympathetic output and secreted adrenergic neurotransmitters. We propose that a more elegant approach to assess biological confirmation may be to utilize markers specific to injured neurons or regenerating neurons, which will be more sustainable and predictable. For instance, CGRP, tyrosine hydroxylase or substance P are robustly produced by nociceptive and sympathetic neurons after sustaining injury and may be detectable in the serum of patients after renal denervation in the periprocedural period [9–11]. These peptide mediators are thought to be effectors of neurogenic inflammation and are robustly released from terminal vesicles in sympathetic and nociceptive neurons following distal injury. While there is a plethora of data supporting the presence of these molecules in sites of nerve injury, no study has to date investigated whether these mediators can be detected in serum following renal denervation. If this theory holds, the chemical detection of these molecules could be an elegant strategy for biological confirmation.

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The other problem with respect to assessing the efficacy of RDN is our lack of understanding regarding the sustainability of denervation. As demonstrated in the positive clinical studies conducted thus far, the antihypertensive effect of RDN appears to last for at least for 2 years postdenervation. However, it will be necessary to assess whether these effects persist in the long-term. The use of short-term markers of nerve injury will not be useful in this context and so the use of long-term biomarkers should therefore be explored. One such biomarker that could be used is the neurotrophic growth factor, neurotrophic growth factor (NGF). NGF is a member of a family of neuronal-specific growth factors termed neurotrophins. These molecules are pivotal for embryologic neural development and provide trophic signals and guidance cues for sprouting axons within the target field during development [12]. Interestingly, sympathetic and nociceptive neurons, which comprise much of the innervation to the renal vasculature, share a common embryologic origin requiring signaling via NGF and its receptor TrkA. It is well established that these neurons revert to their embryologic genetic programs after sustaining injury, and that their somatic targets such as the renal artery tissue produce NGF to promote sustained regrowth of these damaged axons [13]. The measurement of serum

NGF after renal denervation, therefore, provides an opportunity to assess for biological confirmation of renal denervation in a highly specific manner.

With a rational biologic basis and nearly half a century of science behind it, we feel that the weight of the evidence favors RDN as a successful therapy. Whether it will deliver on its promise as being the solution to refractory hypertension or the panacea for a range of other autonomic cardiovascular problems remains to be seen. The results of SIMPLICITY HTN 3 trial are sobering, but should not dissuade us from further investigations of RDN, particularly translational efforts that seek to elucidate fundamental mechanisms of RDN. This trial gives us an opportunity to seek answers to questions that were not previously answered, explore new device technologies and emerge with more elegant solutions ripe for new clinical trials. To those colleagues who have stated that SIMPLICITY HTN 3 ended the field of RDN, we simply state that it's time to raise Lazarus from the dead.

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RL Wilensky was an investigator in the SIMPICITY HTN3 trial and is listed as a co-author on the paper. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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