

Interventional therapy for resistant hypertension: new hopes and old concerns!

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Hypertension contributes to 62% of all strokes and 49% of all cases of heart disease and is the most prevalent controllable disease in developed countries, affecting 20–50% of adult population [1]. Nevertheless, it has been estimated that only 5–30% of patients with hypertension achieve adequate blood pressure control [2], with challenges to obtain target values mainly ascribed to insufficient diagnosis, ineffective treatment, or low patient adherence to lifelong medical therapy. However, even when these difficulties are overcome and patients are on three or more antihypertensive drugs, about 20–30% will still continue to present with high pressure values, a condition known as “resistant hypertension.” Given these unsatisfactory results [3], the rationale for establishing alternative treatment options, rather than just appropriate ones, appears legitimate. Renal sympathetic denervation by means of percutaneous, catheter-based ablation technique is a novel emerging therapeutic strategy, currently under clinical evaluation.

Rationale for targeting renal sympathetic nervous system

Hemodynamic load, neurohumoral modulators, and renal sympathetic activity control the regulatory actions of the kidneys. Chronic activation of the latter is considered a maladaptive response and has been attributed an important role in the initiation, development, and maintenance of hypertension [4]. Two main mechanisms have been proposed as triggering events for chronically elevated sympathetic nervous activity (SNA): 1) primarily elevated afferent SNA [8] and 2) intrarenal pathology, such as ischemia, hypoxia, or other injury, that results in an increase

in renal afferent activity [5–7]. Increased SNA and renal injury in the genesis of hypertension are still considered a sort of “chicken and egg” dilemma. However, regardless of the triggering mechanism, the crucial role of SNA in the maintenance of hypertension has been confirmed both in animal models [9–11] and patients with essential hypertension. These hypertensive models present with an increased efferent renal sympathetic nerve activity [12–14], which has been shown to be under direct control of renal sensory afferent nerve activity that acts through modulation of the posterior hypothalamic activity [15]. This complex interaction translates into an increased renin release [16], increased sodium reabsorption [17], and a reduction of renal blood flow [18–23], thereby turning out into an auto-maintained vicious circle.

An overall increased SNA has also been shown in heart failure patients [24] where increased concentrations of plasma norepinephrine (NE) are associated with a strong negative predictive value on all-cause mortality in an independent way from either glomerular filtration rate or left ventricular ejection fraction [25]. Accordingly, in animal models, renal sympathetic denervation (RSD) of heart failure- and obesity-related hypertension resulted in reduced morbidity and mortality [26,27]. Consequently, while initially used as a physiological tool to elucidate the role of sympathetic activity in pathological states such as hypertension, heart failure, etc., RSD ended up revealing a potential therapeutic strategy [21]. In addition, further support that the denervated kidney reliably sustained electrolyte and volume homeostasis and that nephrectomy of the native kidney resulted in the reduction of systemic vascular resistance became available from human transplant experience [28].

Hot topics

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Evolution of the RSD therapeutic approach

Surgical denervation for blood pressure control is an old concept and was attempted, although unsuccessfully, since early 1950s. Subdiaphragmatic splanchnicectomy in severely hypertensive patients resulted in high perioperative morbidity and mortality, as well as long-term complications, such as bowel and erectile dysfunction and profound postural hypotension [29,30]. These deleterious side effects were principally ascribed to surgical techniques used in the past that did not specifically target the renal nerves. Similarly, given the impossibility of regional action, pharmacologic assault on sympathetic nerve function was also associated with systemic complications. In contrast, more selective animal models of denervation, targeting renal SNA with either surgical stripping or selective infusion of drugs proved to be safer and more effective [31]. Renal sympathetic nerves are derived from numerous spinal ganglia, and arborize throughout the adventitia of the renal artery, therefore representing a difficult surgical target. The first attempt of selective renal nerve ablation with radiofrequency catheter in hypertensive swine resulted in a markedly reduced content of NE (>85%), which was very similar to the effects of direct surgical renal denervation. An important goal for clinical scientists is translation of pathophysiological knowledge into better treatment strategies for patients. Shortly after, transcatheter radio-frequency ablation was in fact adopted into clinical practice with a safety and proof-of-concept human trial [32] and other case reports [33]. In November 2010 the first randomized controlled trial was presented at the American Heart Association Scientific Sessions [34]. In this study, patients were randomized either to traditional medical therapy or traditional medical therapy plus catheter-based radio-frequency ablation. In this approach a catheter is placed in both renal arteries one at a time and circular burns using radio waves are performed in different areas to prevent the formation of a narrowing or an aneurysm in the arteries. There was a significant decrease in blood pressure levels in the treatment group, which was confirmed at six-month follow-up. No serious procedure-related or device-related complications were reported and occurrence of adverse events did not differ between groups.

Unmet needs and clinical prospective

Catheter-based RSD therapy affirms the crucial relevance of renal nerves in the maintenance of elevated blood pressure (BP) levels. While once-and-for-ever treatment represents the ultimate goal, the first natural step after successful renal denervation is a reduction in antihypertensive medicines necessary

to control BP values of hypertensive patients. However, some features of the available data deserve further considerations. Not all patients undergoing catheter-based ablation achieve BP “control,” defined as systolic BP of <140 mm Hg. Of the patients achieving BP control, only a minor fraction are able to reduce the number of drugs they were taking or the dose of those drugs. Moreover, a consistent number of patients undergoing percutaneous RSD experience only a minimal BP drop and are, therefore, considered “nonresponders.”

Finally, concerns related to this new therapeutic approach also appear legitimate. Given the invasive nature of the technique, do these results justify procedural related risks of RSD? How do we interpret the partial benefits in this patient population? Are there any clinical predictors for response? Will catheter-based RSD be an additional arsenal in our therapeutic armamentarium, or just another shooting star?

Theoretically the partial benefits can be explained by two main mechanisms: either the denervation was not successful or nerve traffic to the kidney may not be the only mechanism responsible for “re-resistant” hypertension.

The efficacy of renal denervation can be established by isotope dilution-derived measurement of organ-specific NE release to plasma (regional “NE spillover”). Although catheter-based RSD resulted in a significant mean fall in NE spillover, denervation was proven to be not complete in radiofrequency ablation group [32]. Technical issues in this upcoming interventional area will represent an additional challenge for the amateur cardiologists. However, incomplete RSD does not fully justify the partial benefits for BP control achieved in these studies. The old assumption was that the sympathetic nervous system acted in a global and undifferentiated fashion. However, overall sympathetic nervous system activity is often regionalized in domains such as heart, kidneys and vascular barore-flex system, and may present a varying degree of relative activation and therefore clinical relevance [24–27,35–39]. In line with these considerations, another interventional therapeutic strategy with surgically implantable arterial barostimulator has been proven to be effective in resistant hypertension patients [40,41]. This bilateral implantable device operates by continuous electrical stimulation of the carotid sinus buffer nerves and culminates in reduced circulating NE levels. This effect translates in reduced BP values, hence underscoring the role of a sympathetic, although nonrenal, BP control mechanism [42].

In conclusion, recently published clinical trials have shown very interesting and promising data on radiofrequency, catheter-based, percutaneous RSD. Nevertheless, as traditionally in the history of medicine, a given therapy may not always equally benefit patients with apparently similar pathophysiological

conditions. Whether optimal results are lacking because of technical issues or an incomplete understanding of the role of SNA in essential hypertension remains still to be determined. Therefore, converging efforts from both interventional cardiologists and clinical researchers to improve the potentials of this treatment strategy will be decisive in promoting percutaneous RSD as an established therapeutic option in the near future. ■

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