EDITORIAL

Renal Sympathetic Denervation and Cardiovascular Disease: Past, Present and Future

The first images of the sympathetic nervous system were published in the 17th century in the Anatomy of the brain and nerves [1,2]. Pourfois du Petit described in 1727 the dilatation of conjunctival vessels after section of cervical sympathetic nerves and later in 1840 Selling concluded that the vasomotor fibers were sympathetic fibers carried from the central nervous system to the blood vessels [3]. The evidence provided by Von Euler that noradrenaline was the sympathetic transmitter contributed significantly to the understanding of the role of the sympathetic system on cardiovascular regulation [4]. From the 1930's, surgical sympathectomy was proved to be life saving in cases of malignant hypertension but it was associated with increased peri-operative morbidity and mortality [5]. Nowadays, transcatheter renal sympathetic denervation presents a major improvement for the treatment of resistant hypertension with several clear advantages over radical sympathectomy [6]. It is a localized procedure, minimally invasive, has no systemic effects and the procedural and recovery time are very short. This special issue of the journal includes papers covering many aspects of the relationship between renal sympathetic denervation and cardiovascular disease.

In the first paper, Philippe van de Borne examined the effects of the sympathetic system on the kidney. The interaction between the sympathetic nervous system and the kidney holds a crucial role for the development of high blood pressure. Especially in essential hypertension, there is a disproportionate increase in renal sympathetic activity compared to other vascular beds. Renal efferent activity augments renin release, increases renal vascular resistance and raises sodium reuptake. Arterial baroreceptors mediate reflex mechanisms that inhibit renal sympathetic activity and thus contribute to natriuresis. Existent afferent renal activity marks the kidney as a sensory organ, and chemoreceptors are likely the stimulus receptors. Afferent renal nerves are important for achieving sodium balance during increased dietary sodium intake. Afferent and efferent nerves are closely related at both an anatomical as well as a functional level, as evident by feedback mechanisms activated by low and high sodium intake. Issues regarding the establishment of complete and effective renal denervation and the fact that afferent denervation may increase the efferent sympathetic drive merit among others further research.

Gino Seravalle and co-workers reviewed the techniques allowing to assess sympathetic activity in humans, highlighting their advantages and limitations. While plasma noradrenaline measurement represents a useful and widely used method to assess sympathetic neural function, new approaches have been developed starting already from the seventies. Direct recording of sympathetic nerve traffic and noradrenaline spillover, have largely supplanted the plasma noradrenaline approach due to the precise estimation of the behavior of regional sympathetic neural function.

Rigas G. Kalaitzidis and co-workers extended further the effects of renal sympathetic innervation/denervation on renal physiology. Not only the sympathetic nervous system has a profound effect on the kidney's ability to regulate blood pressure but, vice versa, the kidney has an important effect on the overall sympathetic tone. It is fairly well established that efferent renal sympathetic nerve activity contributes importantly to homeostatic regulation of renal blood flow, glomerular filtration rate, renal tubular epithelial cell solute and water transport, and hormonal release. The afferent nerves from the kidney activate the central sympathetic nervous system activity, participate in a reflex control system *via* renorenal reflexes, and are involved in cardiovascular regulation and pathogenesis of hypertension in chronic kidney disease patients where kidney ischemia also seems to play a key role. Sympathetic nerve modulation in hypertension had been considered as a therapeutic strategy long before the advent of modern pharmacological therapies.

Dimitrios Petras and co workers focused on the role of sympathetic overactivity in the pathogenesis of kidney injury and chronic kidney disease progression and ellaborated on the effect of renal denervation on these conditions. Renal injury and ischemia, activation of the renin angiotensin system and dysfunction of the nitric oxide system have been implicated in adrenergic activation of the kidney. Conversely, several lines of evidence suggest that sympathetic overactivity, through functional and morphological alterations in renal physiology and structure, may contribute to kidney injury and chronic kidney disease progression. Pharmacologic modulation of sympathetic nervous system activity has been found to have a blood pressure independent renoprotective effect. However, the inadequate normalization of sympathoexcitation by pharmacologic treatment leaves room for novel treatment options.

Costas Thomopoulos and co-workers, addressed the issue of the potential effect of renal nerve ablation on metabolic states associated with resistant hypertension. So far, there is an established pathophysiological background denoting that abnormalities in glucose metabolism especially in obese patients and in those with sleep apnea are constantly accompanied by increased sympathetic firing, as assessed by markers of sympathetic activity. Since resistant hypertension is also characterized by enhanced sympathetic activity, it seems logical and biologically plausible, that renal denervation might favorably influence impaired glucose metabolism, sleep disorders and increased body adiposity beyond blood pressure lowering. Despite the limited evidence from clinical trials, there are promising data suggesting that renal nerve ablation indeed ameliorates glucose metabolism-related measures in resistant hypertension. Well-designed randomized trials recruiting a larger number of patients with hypertension, and focused on metabolic parameters, may refine the role of renal denervation as a potential intervention to cure dysmetabolic states associated with hypertension.

Michalis *et al.*, commented on the unanswered questions for renal nerve ablation efficacy and safety through the published clinical trials. Resistant hypertension is frequently encountered and remains challenging in everyday clinical practice despite the availability of numerous effective antihypertensive drugs. Existing limitations in drug therapy renders renal nerve ablation an attractive alternative for the management of resistant hypertension. Renal nerve ablation has been proven so far both effective and safe in small clinical studies. However, every novel technique raises several questions that need to be answered before the wide application of this approach. Likewise, existing data with renal nerve ablation leave some unanswered questions, which among others include: the heterogeneity in blood pressure response, the identification of response predictors, the extent of renal denervation, the association between office and ambulatory blood pressure reduction, the long-term efficacy and safety of the procedure, the time-course of blood pressure response, and the effects on renal function in the long-term.

Lastly, Tsioufis *et al.* discussed the peri-procedural care of renal nerve ablation candidates. In their review they summarize current recommendations regarding patient selection for renal nerve ablation, focusing on the exclusion of pseudoresistance, and lack of adherence to the antihypertensive drug therapy and suggest a multimodal strategy in order to maximize pharmacological treatment for resistant hypertension. The safety and efficacy of renal nerve ablation are also presented based on published trials. Furthermore, a detailed description of the periprocedural management, the methodology of the renal nerve ablation procedure and appropriate follow-up are provided. Towards improving overall clinical outcome, optimal management of resistant hypertensive patients before and after the renal nerve ablation in specialized and experienced centers is of major importance.

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