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Renal denervation for treatment of drug-resistant hypertension

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ABSTRACT

At the seven-year anniversary of the first catheter-based renal denervation procedure for resistant hypertension, it is timely to reflect on the past, present, and future of the development and clinical application of this treatment. Unresolved procedural and technical questions are central: How much renal denervation is optimal? How can this level of denervation be achieved? What test for denervation can be applied in renal denervation trials? Will renal denervation show a "class effect," with the different energy forms now used for renal nerve ablation producing equivalent blood pressure lowering? When I have assessed renal denervation efficacy, using measurements of the spillover of norepinephrine from the renal sympathetic nerves to plasma, the only test validated to this point, denervation was found to be incomplete and non-uniform between patients. It is probable that the degree of denervation has commonly been suboptimal in renal denervation trials; this criticism applying with special force to the Symplicity HTN-3 trial, where the proceduralists, although expert interventional cardiologists, had no prior experience with the renal denervation technique. Recently presented results from the Symplicity HTN-3 trial confirm that renal denervation was not achieved effectively or consistently. Given this, and other difficulties in the execution of the trial relating to drug adherence, an idea mooted is that the US pivotal trial of the future may be in younger, untreated patients.

A brief history of the "pressor nerves"

Electrical stimulation of the sympathetic nerves by Claude Bernard and Charles Brown-Sequard, through the attendant vasoconstrictor and blood pressure responses, led to their designation as the "pressor nerves" [1]. By the first years of the 20th century, this information, and his own clinical observations, led Geisbock [2] to propose that human hypertension was caused by the influence of the brain on the sympathetic nervous system.

No treatment of hypertension was available in this era or, in fact, thought by many to be needed. This situation changed with the introduction of surgical sympathectomy for the treatment of severe hypertension [3]. The aim, in what was an extensive range of surgical techniques [3–5], was to surgically sever the sympathetic chain and all accessible sympathetic nerves of the thorax and abdomen, cutting as many "pressor nerves" as possible to remove their systemic vasoconstrictor influence. Selective renal sympathectomy was not performed, as no theory existed to suggest importance of the sympathetic nerves of the kidneys in the pathogenesis of hypertension. Surgical sympathectomy, applied as a treatment for hypertension in the years 1935–1960 [3–5], demonstrably prolonged the life of patients with severe and malignant hypertension but at the cost of disabling side effects, most notably postural and postprandial hypotension and syncope and sexual dysfunction.

Ganglionic blocking drugs, discovered by Paton and Zaimis [6], ended the period of surgical sympathectomy for

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hypertension and ushered in an era of antiadrenergic drugs. Ganglion blockers constituted the first antiadrenergic pharmacotherapy for hypertension and could achieve what the sympathectomy surgery achieved minus surgical risk but with complications that were almost identical with those of sympathectomy and equally disabling. But a new principle for hypertension drug development had been established, and neuron-blocking drugs such as guanethidine, centrally acting sympathetic nervous inhibitors including methyldopa and clonidine, beta-adrenergic receptor blocking drugs, and alpha-adrenergic receptor blockers followed in quick succession, with ganglion blockers rapidly becoming a footnote to history [7]. These antiadrenergic drugs, combined with diuretics and direct-acting vasodilators such as hydralazine, were the preferred antihypertensive therapy from 1960 to 1990 [7].

Drug-resistant hypertension

In the modern era, drugs antagonizing the renin–angiotensin system have become the dominant antihypertensive therapy. ACE-inhibitor drugs and angiotensin receptor blocking drugs gradually replaced antiadrenergic drugs as preferred antihypertensive agents; they were equally efficacious, at least, and better tolerated. Subsequently joined by dihydropyridine calcium channel blocking drugs, the anti-renin drugs, calcium channel blockers, and diuretics came to be the preferred agents in national and international hypertension guidelines [8]. In concert, antiadrenergic antihypertensive drugs moved progressively toward the bottom of the lists. The sympathetic nervous system lost its earlier prominence in discussions of essential hypertension pathogenesis and treatment and came to be considered as passé, almost irrelevant to hypertension care.

However, there was a problem. Despite the widespread prescribing of ACE-inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers, in a substantial minority of patients with essential hypertension, perhaps 10% [9,10], goal blood pressures were not achieved. In these drug-resistant hypertensives, a new strategy was needed, and in fact, was devised. This materialized in the development of device-based therapies targeting the sympathetic nervous system, the surgically implanted barostimulator device [11] and catheter-based renal denervation [12,13], the latter being the subject of this review.

Catheter-based renal denervation: Theoretical origins, patents, and early development

Central to the development of radiofrequency renal denervation was knowledge of the physiology of the renal sympathetic nerves and their pathophysiology in experimental and human hypertension. In untreated essential hypertensive patients, the application of regional noradrenaline isotope dilution methodology [14], to measure the outward flux of the transmitter from renal sympathetic nerves to plasma (renal noradrenaline spillover), demonstrated that a high level of activation of the renal sympathetic outflow was present [15] (Fig. 1). The sympathetic nervous outflow is commonly activated also to the heart, shown with selective cardiac noradrenaline spillover measurements [15], and to the skeletal muscle vasculature, demonstrated with microneurography recording [16–18], but it is the renal sympathetic activation that is central to hypertension pathogenesis [19].

In experimental studies, the renal nerves have been demonstrated to stimulate secretion of renin from the juxtaglomerular apparatus, to promote renal tubular reabsorption of sodium, and to cause renal vasoconstriction, reducing renal blood flow, all potentially blood pressure-elevating responses [20,21]. The renal tubules receive a dense sympathetic innervation, at all tubular levels. A specific and important relation of the renal sympathetic nerves to renal tubular sodium reabsorption, key to hypertension pathogenesis, concerns pressure–natriuresis, the normal capacity of the kidneys to excrete sodium at higher arterial perfusion pressures [23].

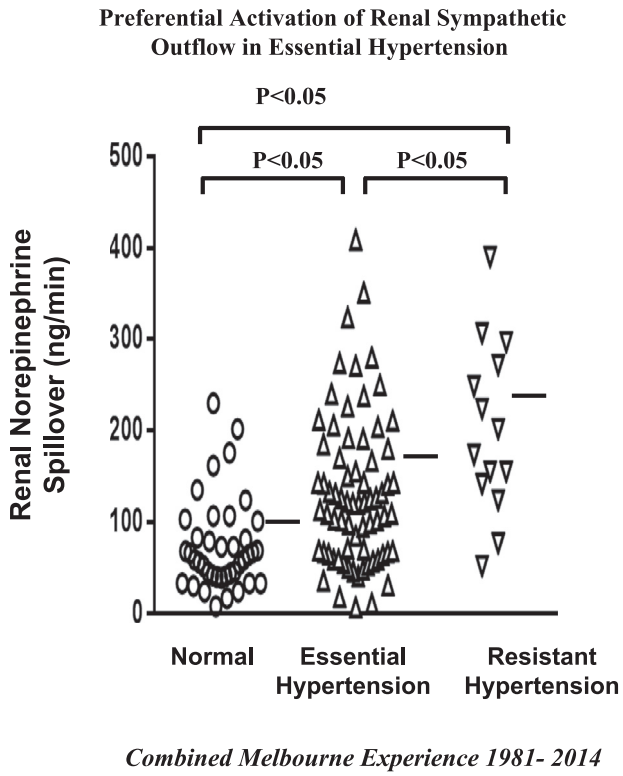

Fig. 1 – Sympathetic activity in the kidneys, assessed using isotope dilution measurements of renal norepinephrine spillover to plasma, in healthy volunteers and patients with arterial hypertension, where renal sympathetic activation was evident in many. In untreated patients with mild-moderately severe essential hypertension (middle column), renal norepinephrine spillover was increased overall, and elevated in approximately 50%. In drug-resistant hypertension, with patients administered on average five antihypertensive drug classes, renal norepinephrine spillover was higher again, attributable to their hypertension, and its treatment; vasodilators, dihydropyridine calcium channel blockers, and diuretics stimulate the sympathetic nervous system. (From unpublished results of the author, Markus Schlaich, Gavin Lambert, and Dagmara Hering.)