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REVIEW ARTICLE

Renal denervation for resistant hypertension

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Abstract There is a marked contrast between the high prevalence of hypertension and the low rates of adequate control. A subset of patients with suboptimal blood pressure control have drug-resistant hypertension, in the pathophysiology of which chronic sympathetic hyperactivation is significantly involved. Sympathetic renal denervation has recently emerged as a device-based treatment for resistant hypertension. In this review, the pathophysiological mechanisms linking the sympathetic nervous system and cardiovascular disease are reviewed, focusing on resistant hypertension and the role of sympathetic renal denervation. An update on experimental and clinical results is provided, along with potential future indications for this device-based technique in other cardiovascular diseases.

PALAVRAS-CHAVE
Hipertensão arterial;
Sistema nervoso simpático;
Desnervação renal

Desnervação renal para hipertensão arterial resistente

Resumo A elevada prevalência da hipertensão está em claro contraste com a sua ainda insuficiente taxa de controlo. Um importante subgrupo destes doentes apresenta uma hipertensão resistente aos fármacos, na qual a hiperativação crónica do sistema nervoso simpático tem importantes implicações fisiopatológicas. Recentemente, a desnervação simpática renal emergiu como um tratamento de intervenção para a hipertensão arterial resistente. No presente artigo, são revistos os mecanismos fisiopatológicos subjacentes à interação entre o sistema nervoso simpático e as doenças cardiovasculares, com particular enfâse na hipertensão

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arterial resistente e no papel da desnervação simpática renal. É igualmente feita uma atualização dos resultados de estudos experimentais e clínicos, bem como de potenciais futuras indicações desta técnica de intervenção noutras doenças do foro cardiovascular.

List of abbreviations

BP	blood pressure
CI	confidence interval
eGFR	estimated glomerular filtration rate
SNS	sympathetic nervous system
RAAS	renin-angiotensin-aldosterone system
RDN	renal denervation
RF	radiofrequency

Introduction

Hypertension is the leading global risk factor for cardiovascular mortality, accounting for more than nine million deaths worldwide in 2010.[1] Its close association with myocardial infarction, heart failure, stroke, end-stage renal disease and cardiovascular death is well established, with 54% of stroke and 47% of ischemic heart disease worldwide attributable to high blood pressure (BP).[2] Effective BP lowering has consistently been shown to reduce overall cardiovascular risk,[3] but rates of adequate BP control remain suboptimal, despite the wide range of antihypertensive drugs available and strong evidence supporting their use. A recently published study confirmed that rates of BP control in European countries are low, with only 37% of treated hypertensive patients achieving recommended BP values.[4]

The blame for such low rates cannot be attributed only to poor treatment. Resistant hypertension has a prevalence ranging from 15% to 30% of treated hypertensive patients,[5] and is an important cause of failure of BP control. Most importantly, these patients exhibit a worse prognosis, with a higher risk for cardiovascular events, compared to hypertensive patients without resistant hypertension.[6]

In recent decades, the renin-angiotensin-aldosterone system (RAAS) has been the central focus of hypertension treatment and management. The availability of safe, effective and evidence-based drugs that block this system has meant that the role of other systems, particularly the autonomic nervous system, has been neglected.

The sympathetic nervous system (SNS) and its possible role in the pathogenesis of hypertension is receiving increasing attention. The aim of this review is to provide an update on the current understanding of the role of the SNS in blood pressure control and its implications for sympathetic renal denervation (RDN).

The sympathetic nervous system and cardiovascular disease

The development of open surgical sympathectomy in the 1930s highlighted the role of the SNS in severe hypertension, since it appeared to be effective in lowering high BP in patients with severe hypertension.[7,8] However, the procedure was abandoned due to its poorly tolerated side effects and high surgical risk, especially after the appearance of ganglionic blockers, the first effective antihypertensive drug class.[9]

The recent development of a new device-based approach to treat severe resistant hypertension, through RDN, focused attention on the already well-known role of the SNS in initiating and maintaining high BP in patients with essential hypertension.[10,11]

Assessment of the sympathetic nervous system in humans

The major reason that the SNS has been so neglected is not because there are doubts concerning its critical role in the pathogenesis of hypertension and other cardiovascular diseases, but because it has been difficult to study and test this relation, due to the complex and clinically impractical methods used for assessing the SNS in humans. Until the early 1970s, the most common techniques were measurements of blood levels and urine excretion rates of norepinephrine and its derivatives, which provide a gross estimate of whole-body sympathetic activity at best.[12] Since then, new methods have emerged for measuring sympathetic nerve firing rates in subcutaneous nerves and for assaying plasma concentrations of sympathetic transmitters.

Microneurography, a technique reported first by Hagbarth and Vallbo,[13] provided a tool to study nerve firing in subcutaneous sympathetic nerves in skin and skeletal muscle vessels. It is based on recording bursts of nerve activity, synchronous with the heartbeat, generated in skeletal muscle vascular efferent nerves, through tungsten electrodes inserted in the skin. It is highly reproducible and closely related to sympathetic traffic directed to other structures and can be repeated over time, allowing assessment of the effects of interventions, direct quantification of sympathetic nerve traffic regulating vasomotor tone, and study of instantaneous reactions to rapid stimuli.

The spillover technique for measurement of norepinephrine release, first applied by Esler et al,[14] is an