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REVIEW ARTICLE

Renal denervation in the treatment of resistant hypertension: Dead, alive or surviving?

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Abstract Hypertension is one of the most common chronic clinical problems encountered by physicians. The prevalence of resistant hypertension is estimated at 9% in the US. Patients with resistant hypertension have been shown to be at higher risk for adverse cardiovascular events, hence the need for greater efforts in improving the treatment of hypertension. The renal sympathetic nerves play an important role in the development of hypertension, mediated via sodium and water retention, increased renin release and alterations in renal blood flow. The proximity of the afferent and efferent renal sympathetic nerves to the adventitia of the renal arteries suggested the feasibility of an endovascular, selective, minimally invasive approach to renal denervation; a potential treatment option for resistant hypertension. While the RAPID, Reduce-HTN, EnligHTN, DENERHTN and Symplicity HTN-1 and -2 studies showed significant benefit of renal denervation in the treatment of resistant hypertension, the results of Oslo RDN, Prague-15 and Symplicity HTN-3 were not so favorable. Future well-designed clinical trials are needed to ascertain the benefits or otherwise of renal denervation in treatment-resistant hypertension.

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

Desnervação renal no tratamento da hipertensão arterial resistente: morta, viva ou sobrevivendo?

Resumo A hipertensão arterial é um dos problemas clínicos crónicos mais frequentes. Nos EUA a prevalência de hipertensão arterial resistente está estimada em 9%. Os doentes com hipertensão resistente têm um maior risco de eventos cardiovasculares adversos, o que justifica maiores esforços na melhoria do tratamento da hipertensão. A inervação simpática renal tem um papel

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importante no desenvolvimento da hipertensão, mediada através da retenção de sódio e água, com aumento da libertação de renina e de alterações do fluxo sanguíneo renal. A anatomia da inervação simpática renal, com os seus nervos aferentes e eferentes em relação de proximidade com a adventícia, permite uma abordagem endovascular, seletiva e minimamente invasiva para a desnervação renal, e constitui uma opção de tratamento potencial para a hipertensão arterial resistente. Enquanto os estudos RAPID, *Reduce*-HTN, EngliHTN, DENERHTN e *Simplicity* HTN 1,2 mostraram um benefício significativo da desnervação renal no tratamento da hipertensão arterial resistente, os resultados dos estudos Oslo-RDN, *Prague*-15 e *Simplicity* HTN 3 não foram tão favoráveis. Serão necessários ensaios clínicos bem estruturados para confirmar ou infirmar os potenciais benefícios da desnervação renal no tratamento da hipertensão arterial resistente.

Introduction

Hypertension is one of the most common chronic clinical problems encountered by physicians. Resistant hypertension is defined as systolic blood pressure (BP) ≥160 mmHg or (≥150 mmHg in patients with type 2 diabetes mellitus) refractory to medical treatment despite the use of optimal doses of three or more different drug types including a diuretic.[1] The prevalence of resistant hypertension is estimated at 9% in the US.[2] In a study of 205 750 treated hypertensive patients, 1 in 50 developed resistant hypertension within a median of 1.5 years from the initial treatment.[3] In the same study, patients with resistant hypertension were shown to be at higher risk for adverse cardiovascular events.[3] The increased morbidity and mortality associated with this condition supports greater efforts to improve treatment options.

Historical perspective

After a link was established between the sympathetic nervous system and the development of resistant hypertension, surgical sympathectomy was introduced in the 1930s, but was abandoned shortly afterwards due to multiple side effects such as postural hypotension, tachycardia, bladder, bowel and erectile dysfunction, and high periprocedural mortality.[4] The proximity of the afferent and efferent renal sympathetic nerves to the adventitia of the renal arteries suggested the feasibility of an endovascular, selective, minimally invasive approach to renal denervation (RDN). In the endovascular approach, a treatment catheter is introduced through a guiding catheter into the renal arteries. The catheter is placed in close proximity to the vessel wall to ensure stable contact. Low-energy radiofrequency ablations are then applied moving the catheter from distal to proximal locations in the renal arteries.[5]

Anatomical and physiological effects of renal denervation

The renal nerves arise from T10-L2 and follow the course of the renal artery lying in the adventitia. Renal sympathetic nerves play an important role in the development of hypertension, mediated via sodium and water retention, increased renin release, and alterations in renal blood flow.[5]

Experimental studies established the important concept that sub-vasoconstrictor levels of renal sympathetic activity can increase renin secretion and renal sodium retention without changing renal hemodynamics.[6] Assessment of regional overflow of norepinephrine (NE) from the kidneys to plasma has demonstrated that renal NE spillover rates can be markedly elevated in patients with essential hypertension and are associated with hypertensive end-organ damage.[5,31] Measurement of NE excretion in the urine, now largely obsolete, was performed in order to quantify sympathetic nervous system activity in humans.[6] In the light of these findings, RDN therapy was considered a logical therapeutic approach in the treatment of hypertension.

The sympathetic nervous system and cardiovascular disease[7]

Surgical sympathectomy was first introduced in the 1930s and was effective in lowering high BP in patients with severe hypertension.[8,9] However, the side effects associated with the procedure and the introduction of ganglionic blockers made it obsolete.[10] For a long time, it was difficult to study and assess the role of the sympathetic nervous system (SNS) in the pathogenesis of hypertension, due not to uncertainty concerning the relation between the two, but rather to the difficulty of testing and assessing that relation. Previous techniques included the measurement of serum and urinary excretion of NE and its derivatives, yielding a rough estimate of SNS activity in the whole body.[11] Hagbarth and Vallbo reported microneurography as a newer tool to study SNS nerve firing in subcutaneous tissues and skeletal muscles.[12] The NE spillover technique was first used by Esler et al.,[13] measuring organ-specific NE release in its efferent veins as an indirect measurement of SNS nerve fiber firing in an individual organ,[14] and that technique was later used to demonstrate that heart failure caused SNS overactivity.[15] Accumulated evidence underlines the role of sustained chronic SNS activity in many diseases including ischemic heart disease,[16] heart failure,[17,18] hypertension,[19–21] kidney disease,[22] type