Editor's Page

# Management of Arterial Hypertension: From No Treatment to Renal Denervation

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On April 12, 1945, President Franklin Roosevelt died suddenly at Warm Springs, Georgia, with a diagnosis of a massive cerebral hemorrhage. According to his personal physician at that time his death "came out of the clear sky".[1] However, his death was not unexpected, since President Roosevelt suffered from malignant hypertension and congestive heart failure. His treatment consisted of digitalis for heart failure and dietary measurements, including salt restriction and weight loss, for blood pressure control.

Up to 1940, elevated arterial blood pressure was considered as a normal consequence of aging and no or limited pharmacologic treatment was applied. In the late 1930s, surgical sympathectomy was used for the treatment of severe hypertension, but the accompanying serious side effects discouraged the wide implementation of the procedure.[2] The adverse prognostic role of arterial hypertension was highlighted in the following years by the Framingham Heart Study, conducted in 1948, the first large epidemiological study to show that arterial hypertension is a major risk factor for cardiovascular disease.[3] Progress in the pharmaceutical treatment of arterial hypertension began in 1958, the year of introduction of thiazides and thiazide-like diuretics. These compounds were meant to be the cornerstone of antihypertensive treatment and their use has continued until today.[4,5] The identification of calcium channel blockers in 1964 and the introduction of renin–angiotensin–aldosterone system inhibitors in the 1980s were the next major achievements in the pharmaceutical treatment of arterial hypertension, contributing to an improvement in the cardiovascular prognosis of hypertensive patients.[5]

Despite the significant advances in the effective treatment of arterial hypertension, approximately 5-10% of patients exhibit resistant hypertension, i.e. inadequately controlled blood pressure, despite the use of more than 3 antihypertensive agents, including a diuretic, at maximum doses.[5] Renal denervation has emerged as an appealing interventional approach for the treatment of resistant hypertension. Although arterial hypertension is a multifactorial disease, there is compelling evidence to suggest that the renal sympathetic nervous system plays an important role in its complex pathophysiology. Indeed, kidney injury induced by ischemia, hypoxia or other stimuli results in the activation of renal afferent nerves, which in turn stimulate the central sympathetic nervous system, leading to the release of renal efferent nerves. These latter promote activation of the renin–angiotensin–aldosterone system and induction of sodium and water retention, a decrease in renal blood flow, and vasoconstriction, thus contributing to the development and maintenance of arterial hypertension.[6,7] To further reinforce this knowledge, in experimental models, renal denervation prevented the development or attenuated the magnitude of arterial hypertension.[8]

In recent years, catheter-based radiofrequency ablation of the renal sympathetic nervous system has raised expectations for the treatment of resistant hypertension. The first clinical studies demonstrated a significant decrease in office blood pressure at 6 and 24 months, respectively, without major adverse events.[9,10] However, when a sham-controlled group was included in a well designed randomized prospective trial and the change in 24-hour blood pressure was the efficacy endpoint, renal denervation failed to achieve its goal, since no difference in the blood pressure change

was observed between the denervation and the sham-controlled groups.[11] The initial disappointment soon turned into skepticism about the possible pathophysiological, clinical or technical considerations that might have been neglected, thus leading to the procedure's failure. Indeed, considering the complexity of the pathophysiology of arterial hypertension, the selection of patients with true resistant hypertension who may benefit from renal denervation should be based on definite criteria of renal sympathetic nervous system overdrive that, up to now, cannot feasibly be applied. Furthermore, the procedure itself may have limitations regarding the effectiveness of renal sympathetic nerve interruption. The introduction of technically advanced energy delivery systems[12,13] or alternative methods, such as chemical ablation, which achieve a circumferential distribution of lesions[14,15] may show more prominent results. The increasing learning curve and the establishment of biochemical or imaging markers of a successful denervation will further enhance the effectiveness of the procedure.

Cardiovascular disease remains the leading cause of death worldwide and arterial hypertension is among its main contributors. Reaching a prevalence of 30% with rates expected to increase in the coming years, arterial hypertension is becoming an epidemic that warrants urgent and effective treatment. Although there has been outstanding progress leading from no treatment to renal denervation, there are still gaps in our knowledge. Researchers should focus on the complex genetic and pathophysiological mechanisms underlying arterial hypertension, but more importantly, physicians should focus on patients by identifying the true resistant hypertensive patients after excluding secondary forms of hypertension, ensuring compliance with pharmacological treatment and encouraging lifestyle modifications.

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