Letters to the Editor

Comment on the Management of Resistant Hypertension in a Multidisciplinary Unit of Renal Denervation: Protocol and Results

Comentario al manejo de la hipertensión resistente en una unidad multidisciplinaria de denervación renal: protocolo y resultados

To the Editor,

I have read with great interest the article entitled “Management of Resistant Hypertension in a Multidisciplinary Unit of Renal Denervation: Protocol and Results” (“Manejo de la hipertensión resistente en una unidad multidisciplinaria de denervación renal: protocolo y resultados”), in which the authors report an improvement in arterial blood pressure similar to that observed in previous studies, as well as a more marked reduction in the use of antihypertensive drugs in patients who undergo renal denervation performed within a multidisciplinary program. The reported findings are highly interesting; however, I feel that certain observations could be clinically relevant.

First, the authors consider pseudoresistant hypertension (HT) to be present in patients with mean arterial blood pressure values of less than 140/90 mmHg coinciding with a period of activity occurring during ambulatory blood pressure monitoring (ABPM).

However, in the current recommendations, HT is defined as arterial blood pressure values greater than 130–135/85 mmHg in an ABPM recording during the period of activity. Thus, HT in which the patients have a mean arterial blood pressure in ABPM greater than 130–135/85 mmHg cannot be considered pseudoresistant. This bias in the inclusion of patients with resistant HT may have affected the observed findings.

Secondly, it is noteworthy that, despite the definition of resistant HT as the condition in which the arterial blood pressure values exceed 140/90 mmHg even with the intake of 3 or more drugs, including a diuretic, 10% of the patients in the published report who underwent the procedure were not being treated with diuretics, and the percentage of subjects receiving diuretics after renal denervation is not disclosed. The pharmacological optimization of these patients in later visits may have altered the reported findings.

Finally, the authors administer aldosterone antagonists to counteract possible secondary hyperaldosteronism. However, my attention is drawn to the absence of staging of other secondary forms of HT, especially when it is known that 27% of the population that undergoes the procedure is diagnosed as having obstructive sleep apnea syndrome. In fact, as the authors point out, there could be a placebo effect in the response to the denervation, an occurrence that would not only be related to greater adherence to the treatment or to the low-sodium diet, but to an improvement in the obstructive sleep apnea syndrome with better dietary adherence. Likewise, drug-induced HT was not tested in the study population, a circumstance that could also influence the results obtained.

In agreement with the authors and the Symplicity HTN-2 trial, renal denervation results in a decrease in the arterial blood pressure and a reduction in the drug therapy. However, an exhaustive search for secondary forms of HT and an optimization of drug therapy could avoid the need for the renal denervation procedure which, although it has been shown to be feasible and safe, is not free of complications.

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Comment on the Management of Resistant Hypertension in a Multidisciplinary Unit of Renal Denervation: Protocol and Results. Response

Comentario al manejo de la hipertensión resistente en una unidad multidisciplinaria de denervación renal: protocolo y resultados. Respuesta

To the Editor,

The authors of the article entitled “Management of resistant hypertension in a multidisciplinary renal denervation unit: protocol and results” thank Dr. Bonaque for his interest in our work. The observations made on our study are highly relevant but require some comment.

Indeed, hypertension is defined in current guidelines as arterial blood pressure values ≥130–135/85 mmHg in an ambulatory blood pressure monitoring recording during a period of activity. From a conceptual point of view, establishing this cutoff to select candidates for renal denervation would be as incorrect as including patients with blood pressure of ≥140/90 mmHg in the office setting, the definition of hypertension in the same guidelines. The cut-off to indicate renal denervation should not only include the “presence of hypertension” but also “poor control”. Hence, in the Symplicity-HTN2 trial, the cutoff was an office systolic pressure of 160 mmHg and, in our study, an ambulatory...
blood pressure monitoring value of 140/90 mmHg. Our study cannot therefore be said to have an inclusion bias.

We also agree that the definition of resistant hypertension implies the use of at least 1 diuretic, but this is not always feasible in clinical practice due to intolerance or the adverse effects of these drugs. In addition to being reasonable, a figure of 90% of patients receiving diuretic therapy is almost identical to the population undergoing denervation in Symplicity-HTN2, in which 89% of patients were receiving diuretics.

All patients in our study were attending the Hypertension Unit of our hospital, which is accredited as a Center of Excellence by the European Society of Hypertension. This unit routinely screens for drug-induced hypertension and investigates secondary causes in all patients with poor control. Patients with sleep apnea were included because they continued to be poorly controlled despite specific treatment for the sleep apnea. There was no “pharmacological optimization” in any of the patients after denervation (except for a reduction in the dose and number of drugs), given that drug therapy was optimized before ablation in all patients.

In view of all these considerations, we do not believe that our series included patients with secondary hypertension or drug-induced hypertension or patients receiving suboptimal drug therapy that could have influenced our results.

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**EDITORIALS**

**1. Relationship Between Nighttime Blood Pressure, the Renin-angiotensin System, and Melatonin**

**Relación entre la presión arterial nocturna, el sistema renina-angiotensina y la melatonina**

**To the Editor,**

We have read with great interest the article on nighttime blood pressure (BP) and neurohormonal activation in patients with idiopathic atrial fibrillation in the Revista Española de Cardiología. According to the authors, nighttime BP values are directly associated with left atrial size and atrial and brain natriuretic peptides in patients with idiopathic atrial fibrillation. We think it may be of interest to discuss a number of issues related to nighttime BP and neurohormonal activation.

First, the authors do not mention the effect of another neurohormone, melatonin, on BP. Oscillations in physiological functions that occur over a 24-h period are known as circadian rhythms. During sleep, there is a decrease in BP in the cardiovascular system. Melatonin is one of the main hormones serving as an endocrine signal in the circadian rhythm. Its secretion is mainly controlled by light via the suprachiasmatic nucleus (biological clock), such that darkness stimulates its secretion and light inhibits it. Recently, our group demonstrated an association between an abnormal pattern of melatonin secretion and alterations in BP in healthy subjects.

Second, the authors discuss from a physiological point of view the important role of nighttime BP in remodeling and growth of the left atrium, possibly mediated by activation of the renin-angiotensin system (RAS). Several articles have been published on the association between the RAS and melatonin. Angiotensinogen is the precursor of the RAS and has been identified in pineal glial cells and the receptors type AT1b in pinealocytes. Angiotensin II, as part of the RAS, acts on receptors type AT1b in pinealocytes to influence the synthesis and activity of tryptophan hydroxylase, an enzyme that limits melatonin production. The demonstration of a functional pineal RAS interfering with melatonin synthesis indicates that this may affect the modulation of circadian rhythms. In fact, the majority of published studies suggest that the relationship between angiotensin and melatonin synthesis in cardiovascular disease is antagonistic.

Finally, the administration of low pharmacologic doses of melatonin (1 mg) reduces BP as a consequence of various mechanisms, such as a direct hypothalamic effect, a lowering of catecholamine levels, the relaxation of the smooth muscle wall and, above all, as a result of its antioxidant properties. There is evidence suggesting that melatonin may have a hypotensive effect, especially in non-dipper hypertensive patients. Thus, the interaction between the RAS and melatonin in relation to BP should be taken into account. From a clinical standpoint, more research is needed on the interaction between angiotensin and melatonin to further our understanding of the pathophysiology of cardiovascular disease, with a possible impact on chronotherapeutic strategies.

Alberto Domínguez-Rodríguez and Pedro Abreu-Gonzalez

**2. The Endocrine Nucleus and the Left Ventricular Hypertrophy Associated with Stress**

The endocrine system is associated with cardiovascular hypertension, a known physiological consequence of stress. The presence of a multiplicity of hormones in the heart has been recently supported, as they are involved in both the pathogenesis and the treatment of the disease. The endocrine system is associated with cardiovascular hypertension, a known physiological consequence of stress. The presence of a multiplicity of hormones in the heart has been recently supported, as they are involved in both the pathogenesis and the treatment of the disease. The endocrine system is associated with cardiovascular hypertension, a known physiological consequence of stress. The presence of a multiplicity of hormones in the heart has been recently supported, as they are involved in both the pathogenesis and the treatment of the disease. The endocrine system is associated with cardiovascular hypertension, a known physiological consequence of stress. The presence of a multiplicity of hormones in the heart has been recently supported, as they are involved in both the pathogenesis and the treatment of the disease. The endocrine system is associated with cardiovascular hypertension, a known physiological consequence of stress. The presence of a multiplicity of hormones in the heart has been recently supported, as they are involved in both the pathogenesis and the treatment of the disease.