

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,<sup>4</sup> 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,<sup>3</sup> 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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## 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*.<sup>1</sup> 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.<sup>2</sup> 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.<sup>2</sup> Its secretion is mainly controlled by light via the suprachiasmatic nucleus (biological clock), such that darkness stimulates its secretion and light inhibits it.<sup>3</sup> Recently, our group demonstrated an association between an abnormal pattern of melatonin secretion and alterations in BP in healthy subjects.<sup>4</sup>

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).<sup>1</sup> Several articles have been published on the association between the RAS and melatonin.<sup>5-7</sup> Angiotensinogen is the precursor of the RAS and has been identified in pineal glial cells and the receptors type AT1b in pinealocytes.<sup>5</sup> 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.<sup>7</sup> 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.<sup>7</sup>

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,<sup>8</sup> especially in non-dipper hypertensive patients.<sup>9</sup> 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.

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### Relationship Between Nighttime Blood Pressure, the Renin-angiotensin System and Melatonin. Response

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

#### To the Editor,

We appreciate the interest of Drs. Dominguez-Rodríguez and Abreu-Gonzalez in our article, as well as their comments, given their extensive experience in the role of melatonin in arterial blood pressure.

Although numerous epidemiological studies have demonstrated that the arterial blood pressure is the most important risk factor for atrial fibrillation,<sup>1,2</sup> the underlying pathophysiological mechanisms are still unknown. As we indicate in our article, it has been suggested that, among other effects, the activation of the renin-angiotensin system induces changes in cardiac structure, such as left ventricular hypertrophy and/or increase in left atrial size, that act as an ideal substrate for the neurohormonal activation implicated in atrial fibrillation.<sup>3–5</sup>

The objective of our study was to evaluate the hypothesis that the arterial blood pressure values obtained by means of 24-h blood pressure monitoring are associated with structural changes in left atrium and with the neurohormonal markers involved in the development of idiopathic atrial fibrillation (IAF). Thus, said results should be encompassed in the context in which the study was carried out, in the attempt to search for new pathophysiological mechanisms that help to shed light on as yet unidentified causes of IAF.

In this respect, the contributions of Dominguez-Rodríguez and Abreu-Gonzalez are highly interesting, as is the recent review by Campos et al.,<sup>6</sup> which summarizes the accumulated evidence on the important role of angiotensin II and melatonin in the modulation of circadian rhythm, and their implication in cardiovascular disease. Undoubtedly, and in view of the results of our study, the analysis of the possible interaction of the renin-angiotensin system and the melatonin concentration with nocturnal arterial blood pressure values in individuals with IAF could contribute to the elucidation of another new pathophysiological mechanism implicated in the development of IAF. Unfortunately, in the design of the pilot study

and the subsequent case-control study,<sup>7</sup> we did not consider analyzing the melatonin concentration. Thus, with the present data, we are unable to respond to this unquestionably new and interesting pathophysiological hypothesis concerning the genesis of IAF.

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