

## Effect of Carvedilol on Blood Pressure Variability

### *Efecto del carvedilol sobre la variabilidad de la presión arterial*

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Hypertension is currently one of the chronic diseases most frequently encountered in clinical practice, affecting a growing number of people worldwide. According to the World Health Organization, the prevalence of hypertension in people over 25 years is approximately 40%, with one billion patients being considered as uncontrolled hypertensives in 2008. Hypertension is also associated with increased cardiovascular events including acute myocardial infarction, stroke, chronic renal failure and finally death. At present there are ample pharmacological tools to manage hypertension including beta blockers, diuretics, calcium channel blockers, angiotensin converting enzymes inhibitor and angiotensin receptor inhibitor, among other agents. Although blood pressure is similarly reduced by these antihypertensive drugs, the long term benefits and the type of adverse events are not the same. As an example, beta blockers were considered a first-line treatment for this disease; however, in the last hypertension clinical guideline published in the United States, the JNC-8 (1) as well as in other clinical guidelines such as NICE in the United Kingdom, (2) this family of drugs was excluded as one of the initial therapies for hypertension. This decision was based on the increased incidence of cardiovascular events, such as cardiac death, acute myocardial infarction and stroke associated with the use of beta blockers, compared with other antihypertensive agents. Of note, these issues regarding the safety of beta blockers are mainly derived from studies with atenolol (3) and metoprolol. (4) Unfortunately, there is no similar evidence from clinical trials on the novel beta blockers with more powerful vasodilatory effect, such as carvedilol and nebivolol, which in addition have a lower risk of developing diabetes compared with classical beta blockers.

The mechanism by which hypertension produces organ injury has not been clearly established. The hypothesis of mean blood pressure has been the most plausible; however, it only partially explains the pathophysiology of organ injury caused by hypertension. Subsequent studies have identified blood pres-

sure variability as an independent predictor factor of stroke and vascular injury in hypertensive patients, (5) which might eventually explain some of the damage caused by this disease, and most importantly, this could be targeted with the use of drugs.

Consistent with the hypothesis of mean arterial pressure, treatment of hypertension is largely aimed at lowering blood pressure, which has been shown to decrease the incidence of the already mentioned adverse cardiovascular events. However, part of the protective effect achieved with some antihypertensive treatments apparently results from this could be targeted with the blood pressure variability rather than from mean blood pressure reduction. For example, with a similar mean blood pressure fall obtained by using amlodipine or diuretics, the reduction of blood pressure variability and stroke is more pronounced than with other families of antihypertensive agents. (6)

Humans or other hypertensive animals, spontaneously develop increased blood pressure variability. (7, 8) Although it is true that sinoaortic denervation in rats can induce mild increase in blood pressure, this experimental model mainly allows the study of blood pressure variability. (9) Interestingly, these rats show target organ injury similar to that in humans with hypertension, e.g, aortic hypertrophy, left ventricular hypertrophy, kidney damage and blood vessel remodeling. (10, 11) Firstly, these findings confirm the importance of blood pressure variability in the pathophysiology of hypertension and secondly they turn sinoaortic denervation rats into an excellent model to study blood pressure variability.

The article published in this issue of the Journal by Julieta de Mauro et al. (12) shows that in the sinoaortic-denervation rat model, chronic administration of high carvedilol doses (30 mg/kg/day) reduces intraday blood pressure variability. They also showed subjective decrease in interstitial and perivascular fibrosis in the histological analysis, as well as lower aortic and ventricular TGF- $\beta$  expression, a recognized fibrosis and remodeling stimulator. Despite this sig-

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nificant reduction in blood pressure variability and ventricular and aortic remodeling markers, rats treated with carvedilol showed no reduction in aortic or ventricular hypertrophy compared to placebo-treated animals. There are two important aspects to discuss about these results. The first is that although this research team has been able to reproduce this experimental model in a previous study, (13) unfortunately a “sham” group was not included in the present work. The importance of this experimental group as a reference for normality would ensure the successful reproduction of the sinoaortic denervation model and would also allow understanding the magnitude of blood pressure variability reduction with carvedilol. The second aspect that could also be clarified with the presence of a “sham” group is that the lack of difference between rats treated with the drug and with placebo could represent, rather than the real absence of drug effect, no remodeling in this animal model at 8-week follow-up, since these macroscopic changes usually occur at later stages. Effectively, previous studies published by other groups usually perform this type of morphometric measurements at around 16 weeks after surgical denervation. (10, 14)

Although it is true that this study has some weaknesses, it should be noted that in general it is novel and relevant both from scientific and clinical points of view. This research shows preliminary results of blood pressure variability and target organ injury reduction with the use of carvedilol in an experimental model in rats. These findings could be easily corroborated in clinical trials and then transferred to the daily clinical practice.

In this article new questions also remain open, as, for example, what is the effect on blood pressure variability and target organ injury of low versus high carvedilol doses and longer follow-up, as for example 20 weeks, when compared with placebo and also other beta blockers as nebivolol or even classic beta blockers such as metoprolol or atenolol, as well as other proved antihypertensive drugs with greater capacity to reduce blood pressure variability, as calcium channel inhibitors. It would also be interesting to see the effect of carvedilol on a model of hypertension and blood pressure variability using spontaneously hypertensive rats with sinoaortic denervation and the relationship with other types of target organ injury, as the development of arterial stiffness, another independent risk factor of cardiovascular disease. (15, 16) Moreover, another question still unanswered is what is the molecular mechanism leading to increased fibrosis of these organs, since understanding this mechanism could also open new therapeutic approaches to prevent complications resulting from hypertension and blood pressure variability.

### Conflicts of interest

None declared

(See author's conflicts of interest forms in the web / Supplementary Material).

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