Editorial

Catheter-based Renal Denervation as a Treatment for Pulmonary Hypertension: Hope or Hype?

Denervación renal por catéter como tratamiento para la hipertensión pulmonar: ¿esperanza o espejismo?

Carlos G. Santos-Gallego and Juan José Badimón*

Atherothrombosis Research Unit, Cardiovascular Institute, Mount Sinai School of Medicine, New York, United States

Pulmonary arterial hypertension (PAH) is characterized by a progressive increase in pulmonary vascular resistance (PVR) that causes right ventricular (RV) failure and premature death.[1] This hypertensive condition leads to precapillary pulmonary hypertension, defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg, pulmonary capillary wedge pressure $\leq$ 15 mmHg, and PVR > 3 Wood units at rest. The prevalence of PAH is estimated to range from 15 to 50 patients/million,[1] with a female predominance (men:women, 1:2) and 1-year and 5-year survival rates of 85% and 57%, respectively.[2] During the last 15 years, treatments for PAH have been studied in multiple clinical trials, with approval subsequently granted for 9 distinct drugs belonging to 4 pharmacological families[1,3]: prostanoids (epoprostenol, iloprost, treprostinil), endothelin receptor antagonists (bosentan, ambrisentan, macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), and adenylate cyclase stimulators (riociguat). Despite these therapeutic advances, many patients with PAH show disabling symptoms and an ominous prognosis, underscoring the need for new therapeutic strategies to combat PAH.

The pathophysiology of PAH involves excessive vasoconstriction and vascular remodeling.[1] The increased PVR is initially reversible and is due to an imbalance between vasodilatory and vasoconstrictive agents, but can become permanent in later stages. The vascular remodeling is characterized by intimal thickening and fibrosis and the proliferation and migration of vascular smooth muscle cells, with hypertrophy and fibrosis of the tunica media, inflammation, and in situ thrombosis, which trigger the formation of plexiform and obstructive lesions (the most characteristic finding of PAH), all of which lead to RV remodeling. Given our poor understanding of the pathophysiology of PAH, the development of new preclinical models of PAH[4,5] and their evaluation using appropriate imaging[6] techniques are essential to further our understanding of PAH.

Various studies of PAH patients show a hyperstimulation of the sympathetic nervous system (SNS) that appears to contribute to the development of the condition. This excessive activation of the SNS in PAH is confirmed by both indirect (elevated plasma concentrations of catecholamines[7]) and direct evidence (muscle sympathetic nerve activity via microneurography of the peroneal nerve,[8] heart rate variability,[9] and baroreceptor reflex variability[9]). Additionally, Juratsch et al[10] found that the increases in the mPAP and PVR (induced by distension of the pulmonary artery) were completely abolished by both chemical sympathectomy using 6-hydroxydopamine and denervation of the pulmonary sympathetic plexus, but not by vagotomy or hyperoxygenation. All of these findings indicate that PAH can be mediated, at least partly, by SNS hyperactivation.

Given the involvement of the SNS and the renin-angiotensin-aldosterone system[4,11] in the pathogenesis of PAH, it is tempting to hypothesize that treatments that reduce this neurohormonal activation could be an effective therapeutic strategy for PAH. One of the most noteworthy examples is catheter-based renal denervation (CRD), an intervention that reduces activation of the SNS and the renin-angiotensin-aldosterone system and that was recently studied as a possible treatment for arterial hypertension. In this article of *Revista Española de Cardiología*, Qingyan et al[12] report the first preclinical results of this strategy in a proof-of-concept study that evaluated the efficacy of CRD as a treatment for PAH in a canine experimental model. The authors induced PAH through monocrotaline injection, a universally accepted PAH model. Next, 1 group of dogs underwent CRD (PAH+CRD group), with the remaining dogs serving as the control arm (PAH control group). Compared with the PAH control arm, at the 8-week follow-up, the PAH+CRD group showed better hemodynamic parameters (lower mPAP and PVR), reduced RV remodeling (lower RV and right atrial dilatation by echocardiography, more preserved RV longitudinal strain, and less interstitial fibrosis in the RV myocardium), lower neurohormonal activation (lower plasma and pulmonary tissue concentrations of angiotensin II and endothelin-1, as well as aldosterone and B-type natriuretic peptide [BNP] in the RV), and reduced pulmonary vascular remodeling (less intimal thickening). The authors concluded that CRD is an effective strategy for PAH, because the treatment reduces the elevated pulmonary pressures and adverse remodeling (both of

the pulmonary vasculature and the RV) caused by lower neurohormonal activation. These fascinating results must be cautiously analyzed in light of the many limitations of the study.

The authors must be congratulated for the major new development of the study, which is the use of CRD (initially developed for arterial hypertension) to treat PAH by alleviating neurohormonal activation. Catheter-based renal denervation is an interventional procedure that aims to destroy the sympathetic nerve fibers of the renal periarterial nerve plexus via radio-frequency ablation using a catheter that heats the tissue. After the positive results of the SIMPLICITY-2[13] clinical trial on the treatment of arterial hypertension, researchers began to study the use of CRD to reduce the neurohormonal activation of the SNS in other cardiovascular diseases, such as heart failure[14] and atrial fibrillation.[15] Indeed, a similar approach to that of Qingyan et al[12] for PAH treatment is to reduce the activation of the SNS specifically in the lung via catheter-based pulmonary artery denervation. As described above, Juratsch et al[10] found increases in the mPAP and PVR in response to balloon distension of the pulmonary artery; these increases were completely abolished by surgical denervation of the pulmonary artery bifurcation and chemical sympathectomy. These results indicated that the efferent branch of this pulmo-pulmonary reflex is mediated by the SNS. In a study in dogs,[16] balloon occlusion of the left interlobar pulmonary artery increased the mPAP and PVR, which normalized following catheter-based denervation of the pulmonary artery. In a subsequent study in patients with PAH,[17] catheter-based denervation of the pulmonary artery induced immediate reductions in systolic and mean pulmonary pressures (from 86 ± 8 to 72 ± 5 mmHg and from 55 ± 5 to 39 ± 7 mmHg, respectively) and PVR, as well as improvements in the 6-minute walking test (from 324 ± 21 to 491 ± 38 m) and in the tricuspid excursion index (from 0.7 ± 0.04 to 0.50 ± 0.041). Importantly, however, this first clinical study included only 21 patients who were not randomized and were followed-up for only 3 months. The composition of the population was also unusual (there was no elevation of right atrial pressure, suggesting that the PAH in these patients was relatively mild).

One of the problems prior to the present study[12] is our lack of understanding of the specific effect of the SNS on pulmonary hypertension. A recent study[18] showed that the drug nebivolol—an antagonist of β1 adrenergic receptors but an agonist of β2 and β3 adrenoceptors—reduces pulmonary vascular remodeling and induces nitric oxide-mediated vasodilation in the pulmonary artery, thereby attenuating the hemodynamic severity of pulmonary hypertension and mitigating RV remodeling. The effects of nebivolol seem to be derived from activation of a particular beta receptor, because the selective beta-blocker metoprolol lacks these beneficial effects. Thus, the effect of each specific adrenoceptor on pulmonary hypertension must be elucidated before modulating the entire SNS using CRD.

The most evident limitation of the Qingyan et al[12] study is its experimental design, because the authors performed the CRD immediately after the injection of monocrotaline, that is, before the PAH had been established and before the mPAP had begun to increase. This experimental design supports the involvement of the sympathetic system in the pathophysiology of PAH but fails to probe the effectiveness of CRD or to reflect the clinical situation (where patients receive treatment after years of chronically elevated pulmonary pressure). A more suitable design would have been induction of PAH with monocrotaline at the beginning of the study, with CRD performed once the mPAP is elevated and established (eg, 2-3 months after monocrotaline injection); the final evaluation of therapeutic efficacy would occur at the end of the study (2-3 months after CRD or 4-6 months after PAH induction). This new alternative design adequately reflects clinical practice, where patients with PAH only receive treatment once

PAH is established. In contrast, in the original design of Qingyan et al,[12] CRD is used as prophylaxis to avoid later PAH development (a setting that markedly differs from clinical reality).

Second, the biological plausibility of CRD is not fully evident. This acute experimental model cannot be considered representative of the PVR increase in patients with chronic PAH. Vasoconstriction is only one of the pathophysiological mechanisms involved in PAH; in fact, in patients with PAH who fail to respond to a vasoreactivity test, the main mechanism of PVR is vascular remodeling due to obstructive and fixed lesions and proliferation of vascular smooth muscle cells. Thus, theoretically, CRD could abolish functional vasoconstriction, but it is doubtful that the intervention could induce inverse remodeling of severe and obstructive lesions in distal pulmonary arteries. CRD might be effective in initial stages, when PAH is being established, but not in the more advanced stages (when PAH is already chronically established), and the present study is unable to provide information on the effectiveness of CRD in such advanced stages. This limitation is vitally important because, given that CRD is neither noninvasive nor risk free, it will surely not be applied in early stages of PAH, but in more advanced stages.

Third, another limitation of the study by Qingyan et al[12] is the lack of understanding of the perirenal plexus nerve lesions produced by CRD. The authors of the article failed to study the degree of nerve damage after CRD application in this experimental model or to determine whether a greater percentage of destroyed nerves correlated with lower PVR or lower plasma concentrations of catecholamines or angiotensin II. Perhaps the authors can still take advantage of some of the immunohistochemical stains frequently used to study the plexus nerves[19–21]: the presence of intact and functional sympathetic axons within the nerve fascicles can be identified using immunohistochemistry for tyrosine hydroxylase—a functional marker of norepinephrine synthesis—, the nerve damage in stromal elements (nerve fascicles) can be assessed with immunohistochemistry for S-100, and the afferent fibers can be marked with CGRP (calcitonin gene-related peptide). This is a topical issue, given that one of the possible reasons for the neutral results of the SIMPLICITY-3[22] study is that CRD incompletely injures the renal plexus; consequently, if an incomplete renal denervation is unable to improve arterial hypertension, such a denervation approach is perhaps unlikely to be effective for PAH.

Crucially, the authors have not performed a long-term study of the model (only 8 weeks from the CRD). A recent study[21] showed that nerve injury (evaluated using immunohistochemistry for tyrosine hydroxylase) following CRD was highest in the acute phase, but this damage began to mitigate from 60 days, and there was even focal nerve regeneration in the long-term, indicating a gradual recovery. This nerve regeneration would theoretically limit the benefits of CRD in the long term, precisely the duration that was not studied by the authors.

An additional limitation of the study by Qingyan et al[12] is the lack of a simulation (sham) group, because the HAP+control group underwent HAP induction without catheter insertion. One of the possible reasons for the difference between the success of the SIMPLICITY-2[13] trial and the neutral results of the SIMPLICITY-3[22] study is that the former trial lacked a sham group (with the placebo effect possibly explaining the mPAP reduction seen in the control group); in contrast, the SIMPLICITY-3 trial included a sham group. Although the placebo effect does appear to be much more important in humans, there may still be some effect associated with the insertion of the catheter into the renal arteries.

In summary, Qingyan et al[12] should be congratulated for the novelty of the study and its promising and appealing results on the potential use of CRD as a therapeutic strategy for the treatment of PAH. However, the study should only be considered a hypothesis generator. Thus, additional carefully designed and exhaustively

evaluated preclinical experiments (which include a chronic model of PAH) should confirm these results and answer questions about the safety and efficacy of denervation before the procedure can advance to the clinical trial phase (which would include an appropriate control/sham group). Hence, the title of this editorial: much is promised by these results (hope), but care must be taken to avoid the generation of unrealistic expectations (hype).

CONFLICTS OF INTEREST

None declared.

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