Pulmonary arterial hypertension (PAH) includes a series of clinical conditions characterized by progressive increase of pulmonary vascular resistance (PVR) leading to right heart failure and premature death (1). In the past 15 years, multiple randomized controlled studies (RCT) have been performed in this field resulting in the regulatory approval of 8 drugs of 3 pharmacological classes: endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostanoids (1). Meta-analyses of RCTs with approved drugs, utilized either as monotherapy (2) or in combination (3), have shown improvements in all-cause mortality or clinical worsening, respectively. Despite these important progresses in medical therapy, many patients with PAH remain with relevant symptoms and poor outcome. Interventional resources such as lung transplantation are effective when medical therapy fails, but the shortage of organ donors limits the number of such procedures.

In this issue of the Journal, Chen et al. (4) present their experience with pulmonary artery denervation (PADN) in 13 patients with idiopathic PAH. PADN is an interventional procedure aimed to obliterate the nerve fibers into the vessel wall of the main pulmonary arteries by a dedicated 7.5-F multiple-function (temperature sensor and radiofrequency ablation) catheter positioned through a peripheral vein (patent application in progress). The authors apparently observed after 3 months from the PADN a significant reduction of mean pulmonary arterial pressure (PAP), and improvement of the 6-min walk distance and of the Tei index in the 13 patients treated as compared with the 8 who refused the procedure. These unexpectedly favorable results need to be analyzed together with the relevant and multiple limitations of the study.

Firstly, the biological plausibility of these effects is not clear. In fact, in idiopathic PAH patients who are “nonresponders” to the acute vasoreactivity test (such as those enrolled in this study), the main mechanism for the increase of the PAP and the PVR is related to the fixed proliferative and obstructive lesions of the distal pulmonary arteries and not to functional and potentially reversible vasoconstriction (1). In this setting, a hypothetical “pulmo-pulmonary baroreceptor reflex” that originates in the large pulmonary arteries has never been demonstrated. Theoretically, PADN may abolish a functional vasoconstriction but may hardly induce a reverse remodeling of the severe, fixed obstructive lesions in the distal pulmonary arteries.

The same authors have recently published a study on an animal model (Mongolian dogs) in which they were able to acutely induce an increase in PAP and PVR by occlusion of the left pulmonary interlobar artery (5). After PADN, the increase was no longer reproduced. However, this acute model cannot be considered representative of the chronic increase in PAP and PVR observed in idiopathic PAH patients that do not respond to the vasoreactivity test.

The characteristics of the patient population of the Chen et al. study (4) are unusual for a group who carry the diagnosis of idiopathic PAH. In fact, 13 of 21 patients (62%) were men (men are not more than 30% to 35% of the population in most idiopathic PAH series), all patients were on long-term oxygen therapy (utilized by no more than 30% of patients in most idiopathic PAH series), and the interval between initial symptoms and PADN was on average about 6.8 years (long-term survivors?) It is also highly unusual that a patient population of idiopathic PAH defined in the methods as “not responding optimally to current medical therapy” have normal right atrial pressures at rest. In addition, 5 of 8 patients (63%) who refused PADN (control group) were hospitalized after 1 week of follow-up (see Table 4 of Chen et al. [1]). All these discrepancies raise questions concerning the correctness of the diagnosis of idiopathic PAH and the nature of the control group.

As acknowledged by the authors, the methodology was limited because the control group was not randomized but rather consisted of the patients who decided not to accept PADN. Surprisingly, also for the small size of the 2 groups, the baseline characteristics ended up to be perfectly comparable. It is not clear why patients who underwent PADN were withdrawn abruptly from the approved medical therapy (but not oxygen therapy). In fact, PADN should have been performed in addition to the current medical treatment to match the medical treatment of the control group.
Last, but not the least, the safety of PADN cannot be established with this 3-month study: 1 patient died of sepsis, and the possible detrimental effect of the ablation procedure on the pulmonary vessel wall potentially leading to aneurysmal dilation cannot be excluded (6). It is also not clear whether the patients were able to withdraw oxygen therapy after PADN or had to up-titrate it. In fact, PADN may theoretically blunt the hypoxic vasoconstrictive reflex that is important for the appropriate ventilation to perfusion matching of the lungs.

The search for additional treatment resources for PAH has resulted in ultimate failures even if the initial efficacy and safety experience in single centers was very encouraging.

Inhaled vasoactive intestinal peptide was shown to markedly improve hemodynamics and exercise capacity in idiopathic PAH patients in a single-center study (7), but this was not confirmed in a formal and relatively large multicenter RCT (8). Very innovative treatments such as stem cell therapy were also proposed in the past, and initial experience in humans appeared quite promising (9). However, after 6 years, no additional information was available from the authors of this apparently revolutionary paper, nor have other groups been able to obtain similar results. Reproducibility of results is one of the basic points of the scientific method, and this is even more important if clinical data are provided from a single-center experience.

Failures have also been observed when an appropriate development plan was followed. For example, the endothelin receptor antagonist sitaxsentan was withdrawn from the market after several cases of death due to severe liver toxicity that was not properly identified in the phase II and III studies (10). The tyrosine kinase inhibitor imatinib was recently withdrawn from the regulatory approval process for idiopathic PAH patients (11). Proper safety evaluation requires a long-term follow-up and an appropriate number of patients.

The challenging paper of Chen et al. (4) should be considered as a very preliminary proof-of-principle study that requires a formal and large multicenter RCT to appropriately evaluate a possible new area for the treatment of PAH patients. Strict diagnostic inclusion and exclusion criteria need to be applied. The authors report that the specific PADN catheter is going to be patented, and we imagine that programs for commercialization are also ongoing. Surprisingly, new catheters can be sold and utilized based only on general technical safety requirements, even if they have not been tested in formal clinical trials as required for experimental drugs. The expertise for ablating arrhythmias and for renal denervation in resistant hypertension is quite prevalent in clinical practice, and the risk for the application of PADN in clinical practice before clear evidence of efficacy and safety is available is unfortunately high. This would not be the good clinical practice that is required by our patients. We should be sure that we can provide them with established hope, and avoid any potential hype.

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