Current Cardiology Reports (2019) 21:124
https://doi.org/10.1007/s11886-019-1203-z

INTERVENTIONAL CARDIOLOGY (SR BAILEY, SECTION EDITOR)

Pulmonary Artery Denervation: Update on Clinical Studies

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Abstract

Purpose of Review Sympathetic overactivity plays an important role in the progression of pulmonary arterial hypertension (PAH). The purpose of this review is to illustrate localization of pulmonary arterial sympathetic nerves, the key steps of pulmonary artery denervation (PADN) procedure, and to highlight clinical outcomes.

Recent Findings Sympathetic nerves mostly occurred in the posterior region of the bifurcation and pulmonary trunk. Emerging preclinical data provided the potential of PADN for PAH. PADN, produced at bifurcation area, improved a profound reduction of pulmonary arterial pressure and ameliorated clinical outcomes with an exclusive ablation catheter. The application of PADN in the patients of PAH or combined pre-capillary and post-capillary PH (CpcPH) improved the hemodynamic parameters and increased 6MWD.

Summary Sympathetic overactivity aggravates PAH. PADN is a promising interventional treatment for PAH and CpcPH. Additional clinical trials are warranted to confirm the efficacy of PADN.

Keywords Pulmonary arterial hypertension · Sympathetic nervous · Pulmonary denervation · Ablation · Annular catheter with 10 electrodes · Clinical trial

Introduction

Pulmonary arterial hypertension (PAH) is a fatal disease, characterized by excessive pulmonary vascular remodeling (and/or apoptosis-resistance) with subsequent progressively elevated pulmonary vascular resistance (PVR), leading to right heart failure and premature death [1]. While PAH is mainly classified as group I PAH according to WHO definition, pulmonary hypertension (PH) secondary to different etiologies reflects a wider spectrum of this disease [1, 2]. Mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg and PVR > 3 woods unit at rest measured by right heart catheterization are 2 key criteria for diagnosis of all pre-capillary PH [1, 2]. However, pulmonary capillary wedge pressure (PCWP) or pulmonary arterial occlusive pressure (PAOP) > 15 mmHg is another key criterion for differentiating group II PH (caused by left heart failure) from others [1]. In general, drugs targeting at 3 different signal pathways have dramatically improved clinical outcomes in group I patients. Unfortunately, none of those drugs has been recommended for treatment of group II PH [1]. Moreover, several studies have demonstrated the overexpression of adrenergic receptors on the myocardial cells in failing heart [3] and the overactivation of sympathetic nerves in PH patients [4, 5]. These features trigger the potential of percutaneous pulmonary artery denervation (PADN) for treatment of PAH patients.

Evidence of Sympathetic Overactivation in PAH

The pulmonary vasculature is in totally innervated by 3 different nervous fibers: sympathetic, parasympathetic, and sensory nerve fibers. Vascular tone is mediated by α-adrenoreceptors upon sympathetic nerve stimulation [6]. Noradrenergic fibers are activated by baroreceptors in the pulmonary artery [7]. Chemoreceptors respond to decreased arterial PO_2 levels to increase sympathetic nerve stimulation by the sympathetic chain neurons [6, 8]. Parasympathetic

This article is part of the Topical Collection on *Interventional Cardiology*

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Published online: 05 September 2019

activation via vagal stimulation results in cholinergic-mediated relaxation of pulmonary arteries [9]. Over the last several decades, a body of evidence has showed that overactivated sympathetic nervous system is implicated in the progression of PAH. Patients with PAH have an increased muscle sympathetic nerve activity (MSNA) by microneurography compared to healthy controls [4]. On the other hand, PAH patients also have increased heart rate [4, 5], a risk factor for stratifying the prognosis of this disease [4, 5, 10]. Notably, increased MSNA and heart rate are directly correlated with [4, 10] the presence of pericardial effusion, New York Heart Association class, and 6-min walk distance (6-MWD). Taken together, partial or full destruction of pulmonary arterial sympathetic nerves by percutaneous PADN may be beneficiary for PAH treatment.

Localization of Pulmonary Arterial Sympathetic Nerves

The sympathetic nervous system originates from the thoracolumbar region of the spinal cord [11]. Short preganglionic fibers from the T1–L2 segments synapse on paravertebral or prevertebral ganglia, enabling long postganglionic fibers to innervate target organs such as the heart and lungs. Zhang et al. [12] reported that a great abundance of sympathetic nerves occurred in the proximal and distal segments of the bilateral pulmonary arteries in canines, which were mostly located in the posterior region of the bifurcation and pulmonary trunk. Zhou et al. [13] described that nervous bundle originates from 1 to 3 ganglions just above the pulmonary valvular level and runs along the left side of pulmonary trunk in Mongolian dogs. At the proximity of bifurcation, pulmonary nervous trunk divides into left and right branches. Both ranches run into posterior wall of left and right pulmonary arterial branches. Obviously, there are less nervous endings in the anterior region of pulmonary artery in animals, even species difference exists. Unfortunately, there is a scarce of data about the distribution of pulmonary nerves in the human body. As a result, the anatomical study on pulmonary nervous distribution in human is urgently required to facilitate the clinical use of PADN.

Sympathetic Nervous Injury by and Preclinical Study of PADN

Zhou et al. [13] demonstrated for the first time, that the minimal distance from nervous trunk to the vessel lumen localized at the left side of pulmonary arterial bifurcation region and was less 1 mm (Fig. 1a), a desired range of radiofrequency ablation. Three nervous fibers merge soon after taking off (Fig. 1b). Radiofrequency induces severe nervous injury as reflected by the swelling and edema of nerves (solid arrows in Fig. 1b). As the ablation procedure is transluminal performed at three sites, ablation is associated with visible intimal injury (arrows in Fig. 1c). At 1 month follow-up, the intimal healing process is completed (Fig. 1d) without thrombus formation.

The first surgical or medical PADN procedure using surgical longitudinal injury of pulmonary sympathetic nerve or application of specific sympathetic ganglion blocker (6-OMT) on the surface of sympathetic nerve came from an acute PH model developed by Jurastch et al. in 1980 [14]. The study reported that pulmonary artery pressure did not increase after continuous occlusion of blood flow and stretching of pulmonary artery after PADN. Furthermore, this provocative treatment effect was thought to be correlated with the destroying of the baroreceptors localizing at the bifurcated area at the end of the main pulmonary artery. This fundamental study provided the concept of percutaneous PADN for treatment of PAH.

In 2013, Chen et al. [15] tested the efficacy of PADN using their own designed ablation catheter in the animal model. In that study, a complete occlusion at the interlobar branch or bifurcation region but not at basal trunk using a balloon was associated with a significant elevation of pulmonary arterial pressure, suggesting more proximal location of nerves and or baroreceptors. They found that PADN performed at the bifurcation area (5-mm proximal to the orifice of either right or left pulmonary arterial branches, or at the distal bifurcation region) induced a profound reduction of pulmonary arterial pressure. Particularly, no procedural related complication was recorded in this provocative experiment.

Efficacy and feasibility of PADN for chronic PH animal were tested by Zhou et al. [13]. Chronic PH dogs were induced by dehydromonocrotaline after 4 weeks. In that study, the sham group was used in order to minimize the bias. PADN procedure resulted in improvement in hemodynamics as well as pulmonary arterial remodeling and RV functions, which was supported by another experimental study by Rothman et al. [16] who used a renal ablation catheter in porcine and by Zhang et al. [17] in animals with heart failure induced by aortic ligation. Zhou et al. also confirmed the durable reduction in transduction velocity and injury of pulmonary sympathetic nerves by PADN [13].

Evidence of Improvement in Clinical Outcome by PADN

Emerging preclinical data provided the potential of PADN for both PAH and PH. Accordingly, we designed our first-in-man study [18] in 2013 which included 13 patients with idiopathic PAH who were refractory to maximal medications, with another 8 same patients severing as control group. The results showed that the reduction in mPAP was 20 % immediately

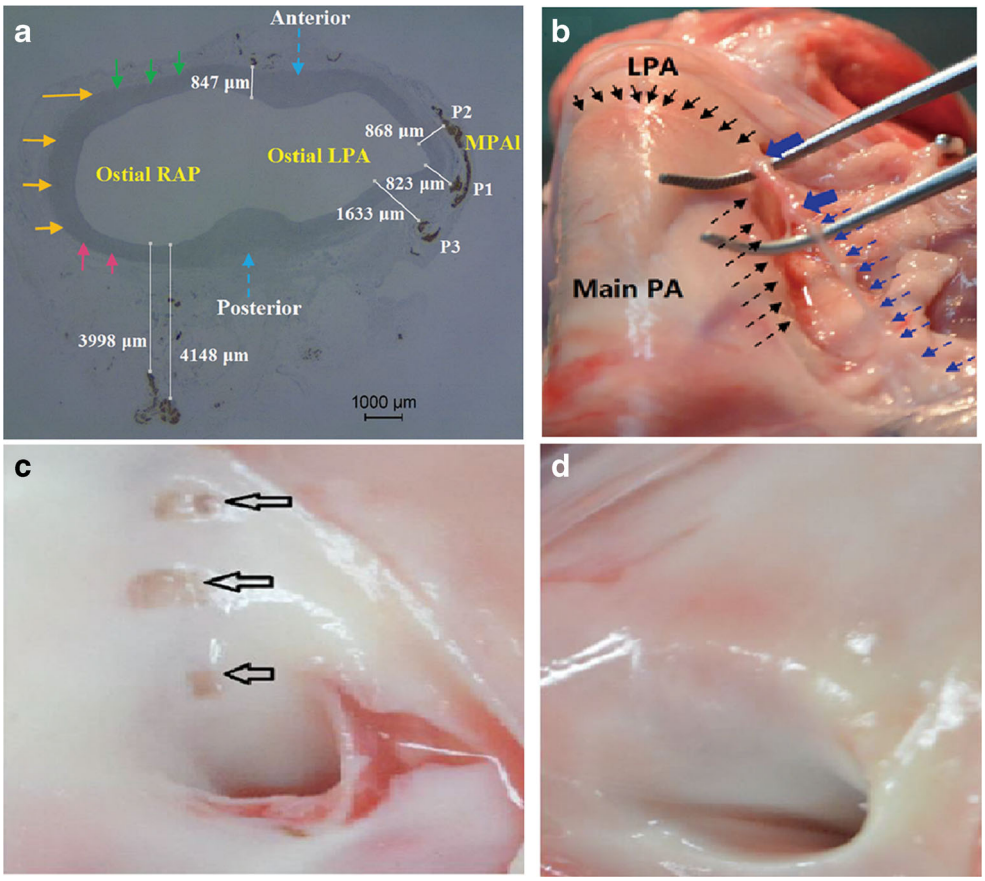

Fig. 1 Location and ablation of pulmonary nerves. **a** The shortest distance (823 mm) between the nerve endings and the PA lumen at the distal PA. **b** Sympathetic nerves localized in the groove (*dashed black arrows*) are parallel to the left lateral wall of the distal MPA up to the orifice of the LPA (*solid black arrows*); when the nerves were removed from this groove, the injured segment induced by PADN (*solid blue arrows*) became swollen. **c** Immediately after PADN, an intimal injury was very clearly visualized (*black arrow*) and was replaced by **d** scarring. (Reprinted from: Zhou L, et al. JACC Cardiovasc Interv. 2015, 8(15):2013–2023. https://doi.org/10.1016/j.jcin.2015.09.015, with permission from Elsevier) [13]

after the procedure and 35 % at 3 months follow-up, accompanied by reduction of NT-pro BNP and improvement of RV functions. 6-MWD increased almost 92 m in the PADN group over 3 months follow-up. Similar to experimental study, no procedure-related complication was found.

With understanding the limitations of a FIM study, a consecutive registry study with 66 patients was conducted in Chinese centers. We found [19•] that the average reduction of mPAP post-PADN was around 10 %–15 %, a criterion of optimal PADN procedure in our subsequent studies. Over 1 year follow-up, the maximal improvement of mPAP, PVR, and RV functions was monitored at 3 months after the procedures. Between 3 and 12 months, there was no obvious deterioration of hemodynamics. Among those 66 patients who did not responded well to target drugs, 4 patients were defined as non-responders to PADN treatment because the reduction in mPAP was less 10 % post-PADN. During 1 year follow-up, PAH-related mortality was reported in less 15 % of 66 patients with such severe disease. The treatment effect of PADN on patients was also in another before and after designed study (data not shown). While pericardial effusion is one of the variables reflecting the severity of PAH, we also found that pericardial fluid > 1 cm in depth was an independent factor for the non-responder of PADN procedure. Fortunately, pericardial fluid gradually decreased over the 1 year follow-up duration after PADN treatment. The current PADN-CFDA study is a multi-centered, randomized, sham-operated controlled study to further verify the effectiveness and safety of PADN (NCT03282266).

Heart failure (HF) is a common final stage of most cardiovascular diseases [20]. The backward transmission of increased left ventricular filling pressure results in elevated pulmonary venous pressure, a status known as passive or isolated post-capillary (Ipc) pulmonary hypertension (PH), without an elevation of pulmonary vascular resistance (PVR) or diastolic pressure gradient (DPG) [21–23]. Fayyaz et al. [24] reported that PH is associated with global pulmonary vascular remodeling, leading to reactive or combined pre-capillary and post-capillary PH (CpcPH), which is defined as a DPG of ≥ 7 mmHg, or a PVR of > 3 wood units (WU), or both [22, 23]. Although the presence of PH is a hallmark of poor clinical outcomes in patients with HF [2, 20], controversy exists regarding the routine treatment of CpcPH with drugs targeting pulmonary arterial hypertension [25, 26]. Our preclinical study [17] has confirmed the overexpression of α-adrenergic receptor on smooth muscle cells in HF animals with PH, a finding indicating the possible benefit of PADN for group II PH patients. Thus far, we designed multicenter, randomized,

sham-controlled PADN-V trials [27••] including 98 combined pre- and post-capillary PH. At the 6-month follow-up, the mean increases in the 6-MWD were 83 m in the PADN group and 15 m in the sildenafil group. 1-SD decrease in 6-MWD was strongly correlated with clinical worsening ($p = 0.04$). PADN treatment was associated with significant reduction (29.8 %) in PVR and less rate (16.7 %) of clinical worsening, compared with 3.4 % ($p < 0.001$) and 40 % ($p = 0.014$) in the sildenafil group. At the end of the study, there were 7 all-cause deaths and 2 embolisms. In that study, a right atrial pressure measured by the right heart catheterization was unchanged during 6 months follow-up in the PADN group, possible explanation would be the shorter (only 6 months) follow-up duration. Otherwise, a small sample size might be another reason for not achieving positive result in the right atrial pressure.

Additionally, the application of PADN in the treatment of 16 PAH patients significantly improved the hemodynamic parameters and increased 6-MWD in another study from Russia [28]. Similarly, stimulating the pulmonary artery trunk and its bifurcation to identify the target site correlated with slowing of heart rate or decreasing blood pressure came from another small study by a Japanese team [29]. In this study, investigators did not find the actual reduction of mPAP and PVR, but the significant improvement in hemodynamic occurred at 4 months after PADN procedure. Low-dose radiation induced reduction of pulmonary arterial pressure was reported in one patient who had a chest cancer [30].

Key Technical Points of PADN

Hemodynamic measurements are required before, during, and post-PADN procedure. This can be done via a Swan-Ganz catheter from a jugular vein approach. For some patients who cannot hold their breath which can result in inaccurate measurement of PCWP, a left ventricular end-diastolic pressure is measured by a pig-tail catheter from left ventricle. After that, PADN can be done in an easy way as described in below:

Step 1: Pulmonary arterial angiography (PAA, Fig. 2). Even CT angiograph also can provide some important information about the exclusion of thrombus, vessel diameter, and location of pulmonary arterial bifurcation, PAA through femoral vein approach is still the standard as usual [18, 19•, 27••]. We recommend 2 views of injection (anterior-posterior 20°and cranial 20°view) to maximally separate the right from the left branch of the pulmonary artery.

Step 2: Identifying the ablation sites. As showed in Fig. 2 II, the red line represents the lateral wall of the main pulmonary artery (MPA), the blue line represents the anterior wall of the left pulmonary artery (LPA), and the point where the 2 lines intersect is point A; the intersection of the yellow (posterior wall of the LPA) and red lines is point B, which is 1 to 2 mm posterior to point A; the green line starts from the inferior wall of the right pulmonary artery (RPA) and ends at point A, and point C localizes at this level and 1 to 2 mm anterior to point A.

Step 3: PADN procedure. An 8-F long sheath is inserted and advanced to the main PA. A PADN catheter with 10 electrodes is positioned along the long sheath at the distal MPA, with electrodes A, B, and C at points A, B, and C, respectively. PA ablation is performed only in the peri-conjunctional area between the distal main trunk and the ostial left branch (points A, B, and C). The following ablation parameters are programmed at each point: temperature ≥ 45 °C, energy ≤ 20 W, and time 120 s (for point C) or 240 s (for points A and B). The procedure could be interrupted for 10 s if the patient reports severe chest pain.

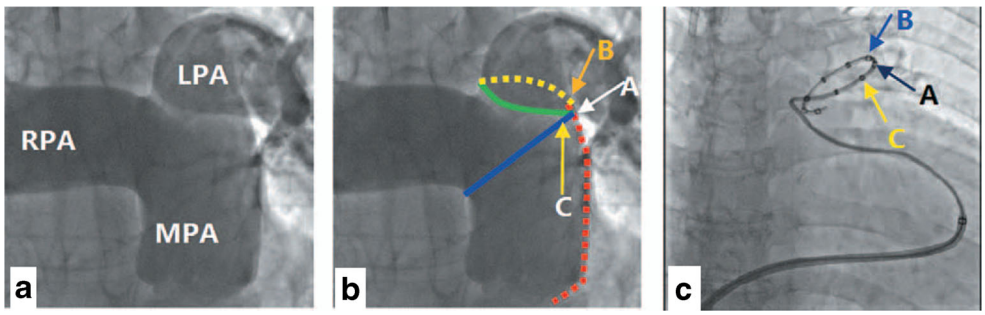

Fig. 2 Pulmonary angiography and PADN procedure. **a** Anterior-posterior 20° and cranial 20° view of the pulmonary arterial angiograph. **b** The *red line* indicates the lateral wall of the main pulmonary artery(MPA), the *blue line* represents the anterior wall of the left pulmonary artery (LPA), and the point where the 2 lines intersect is point A; the intersection of the *yellow* (posterior wall of the LPA) and *red lines* is point B, which is 1 to 2 mm posterior to point A; the *green line* starts from the inferior wall of the right pulmonary artery (RPA) and ends at point A, and point C localizes at this level and 1 to 2 mm anterior to point A. **c** A pulmonary artery denervation catheter with 10 electrodes is positioned at the distal MPA, with electrodes A, B, and C at points A, B, and C, respectively. (From: Chen SL, Circ Cardiovasc Interv. 2015, 8(11):e2837. https://doi.org/10.1161/CIRCINTERVENTIONS.115.002837, with permission from Wolters Kluwer Health, Inc.) [19•]

Conclusion

In conclusion, sympathetic hyperactivity plays an important role in the progression of PAH/PH and is an independent predictor of clinical prognosis. PADN is a promising interventional treatment for this disease. Further studies are warranted before PADN is recommended for routine treatment of PAH.

Compliance with Ethical Standards

Conflict of Interest Hang Zhang and Shao-Liang Chen declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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