JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 2, 2024

EDITORIAL COMMENT

Radiation to Illuminate the Path of Neuromodulation for Pulmonary Hypertension*

Karl-Philipp Rommel, MD,[a,b] Lukas Hobohm, MD,[c,d] Alexander M.K. Rothman, MD,[d,e] Philipp Lurz, MD, PhD[c]

Pulmonary hypertension (PH) poses a significant global health challenge, impacting approximately 1% of the population. Etiologically, the condition can be categorized into 5 distinct groups, each characterized by varying pathologic drivers, prevalence rates, and therapeutic options. Although pulmonary arterial hypertension (PAH), or World Health Organization Group 1 PH, is relatively uncommon and amenable to medical therapies, the heterogeneous therapeutic responses with limiting side effects and persistent progression of the disease contribute to substantial morbidity, mortality, and quality of life. Consequently, there is a pressing need for additional treatment targets.[1]

A growing body of evidence indicates that the autonomic nervous system may be a viable target for therapeutic intervention. Sympathomimetics such as methamphetamine and related diet suppressants including aminorex, fenfluramine derivatives, and benfluorex increase sympathetic activity and cause PAH.[2] In patients with PAH (not associated with drug use), autonomic activity has shown correlations with clinical deterioration, 6-minute walk distances, right atrial dimensions, neurohumoral activation, and adverse remodeling of the right ventricle, characterized by fibrosis, hypertrophy, and capillary vasculopathy.[1]

Consequently, the concept of pulmonary artery denervation (PADN) has emerged, with demonstrated feasibility using various techniques such as surgery, endovascular radiofrequency ablation, and ultrasound ablation. Key observations from these interventions include a reduction in pulmonary artery pressures, an increase in cardiac output, and a decrease in pulmonary vascular resistance (PVR), coupled with improvements in 6-minute walk tests. Notably, recent applications of these interventional procedures to patients with group 2 and 3 PH have yielded promising results, marking an exciting new therapeutic avenue for an expanding patient population.[3,4]

The technical principle underlying this intervention revolves around the destruction of nerve fibers along the pulmonary arteries. Preclinical studies have unveiled variations in the distances, sizes, and distributions of these nerve fibers along the main stem and branches of the pulmonary artery. This diversity underscores potential challenges and uncertainties in terms of ablation localization and tissue penetration, particularly when using an endovascular approach.[4]

Stereotactic body radiotherapy (SBRT) is an advanced technique designed to deliver precise, high doses of radiation to specific targets in the body, minimizing exposure to surrounding normal tissue. Initially developed for intracranial, orbital, and base of skull tumors, SBRT has evolved to address a diverse range of targets. Its potential application in the cardiovascular system, particularly the concept of "radioablation" for ventricular tachycardia patients, has attracted significant interest.[5] Observational case series involving patients with refractory ventricular

*Editorials published in *JACC: Basic to Translational Science* reflect the views of the authors and do not necessarily represent the views of *JACC: Basic to Translational Science* or the American College of Cardiology.

From the [a]Department of Cardiology, Heart Center at University of Leipzig and Leipzig Heart Institute, Leipzig, Germany; [b]Cardiovascular Research Foundation, New York, New York, USA; [c]Department of Cardiology, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [d]Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; and the [e]Division of Clinical Medicine, University of Sheffield, Sheffield, United Kingdom.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2023.11.010

JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 2, 2024
FEBRUARY 2024:257–259

arrhythmias have demonstrated the efficacy of SBRT in reducing arrhythmic events. The technique's success is attributed to its ability to deliver energy efficiently to challenging areas, often inaccessible with traditional endo- or epicardial ablation catheters. In addition, SBRT achieves this with high precision and homogeneous distribution within the myocardium, creating fully transmural ablation lines. Furthermore, SBRT offers the potential for a fully noninvasive procedure, thereby potentially reducing the risk of interventional complications.[5] The application of SBRT has also been explored preclinically in ablation procedures involving the pulmonary veins and renal arteries.[6]

In this issue of *JACC: Basic to Translational Science*, Xu et al[7] present a study proposing that the benefits of SRBT could also be leveraged for PADN. The authors used a canine model, inducing acute PAH in 20 beagles through infusion of a thromboxane A2 agonist, resulting in a dose-dependent increase in pulmonary artery pressures, which was reversible within 15 minutes on discontinuation of the infusion. Subsequently, half of the dogs underwent PADN using SRBT with a relatively high radiation dose of 45 Gy and an average procedure time of nearly one and a half hours.

In repeated hemodynamic challenges with thromboxane A2 at 1 and 6 months, the SBRT group exhibited attenuated increases in systolic and mean pulmonary artery pressures compared with baseline and the control group. To a lesser extent, PVR was reduced at 6 months in the SBRT group compared with baseline, and cardiac output increased over time in the SBRT group, although without statistical significance. The authors also provide evidence, both histologic and serologic, indicating effective reduction of neuronal activity in the pulmonary arteries.

The authors should be commended for integrating the concepts of PADN and SRBT to enhance the thoroughness of PADN, potentially improving procedural success and mitigating interventional complications.

The fundamental objective of PADN is to achieve effective perivascular nerve destruction, a critical aspect given the challenges posed by large vascular dimensions, high blood flow, and variable distribution and distances of nerve fibers from the lumen. Drawing from experiences with renal denervation and the limited data available in the PADN domain, it becomes evident that interventional techniques may differ in their potential to fully destroy sympathetic fibers circumferentially along the pulmonary artery.[8] Radiofrequency approaches are generally acknowledged to be safe and effective but have limitations in terms of penetration depth and circumferential coverage. Additionally, they share the potential for adverse endothelial lesions with intravascular ultrasound approaches, which itself are limited by vascular dimensions and the need for high energy delivery. Surgical methods, although deemed to be the most comprehensive in denervating the pulmonary artery, are highly invasive. Consequently, SRBT theoretically poses an attractive alternative that could optimize the completeness of denervation.

On reflection on procedural safety, however, the purported advantages of SRBT may not be as evident, especially considering the well-established safety profiles of both renal artery denervation and PADN. Contrary to the authors' assertion, clinically relevant restenosis rates after renal artery denervation are infrequent and have not been described after PADN. Additionally, these procedures can be conducted in routine cathlab settings with minimal preprocedural imaging and short procedure times.[8] In contrast, SRBT demands substantial logistical efforts, involving extensive preprocedural imaging and treatment in dedicated and specialized oncologic institutions. Although the procedure appears to be relatively safe in the current study, the authors did note minimal texture changes and inflammatory cell infiltration in tissue adjacent to the ablation sites. This underscores the point that the use of radiation in SRBT is not entirely devoid of side effects.

When extrapolating from preclinical findings to clinical practice, it is essential to consider the specific experimental model used. In this study, the authors used a canine model with repeated induction of PH through the infusion of a thromboxane A2 agonist, consistent with a previous study on PADN.[4] Thromboxane A2, an endogenous eicosanoid, induces platelet aggregation and vasoconstriction, and elevated levels have been implicated in experimental and clinical PAH. Although vasoconstriction is a key mediator of PH pathology, it is important to note that the thromboxane A2 model does not fully replicate the small pulmonary artery vasculopathy responsible for the progressively increasing PVR observed in patients with PAH. Notably, PH in this model is entirely reversible after discontinuation of the infusion, highlighting that the hemodynamic effects of PADN are not mediated by its impact on small-vessel structural changes.

Although the exact mechanisms of action of PADN remain unclear, the study by Xu et al[7] and previous research indicate that pulmonary hemodynamics in PH are indeed influenced by sympathetic tone. PH is associated with an early and progressive decrease in pulmonary artery compliance, leading to an increase

in pulsatile afterload through pathologic wave reflections from the distal pulmonary circulation.[9] Pulmonary artery compliance is dynamic and is affected by instantaneous hemodynamics like pulmonary artery pressure, cardiac output, and left atrial pressures.[9] Although the nonlinear elasticity of arteries contributes to this phenomenon, the discussed observations suggest that aspects related to pulmonary arterial compliance could be positively influenced by PADN. This again supports the modulation of sympathetic tone as a potential therapeutic avenue in PH.

In conclusion, the study by Xu et al[7] combines 2 emerging and appealing approaches in cardiovascular medicine, namely, pulmonary neuromodulation to treat PH and precision ablation by SBRT. The work corroborates the concept of pulmonary vascular nerve destruction to improve pulmonary hemodynamics, stresses the need for comprehensive and complete ablation, and provides some mechanistic insights. However, whether SBRT will prove superior to new iterations of endovascular PADN devices able to achieve enhanced tissue penetration and circumferential ablation safely and in a timely manner will need to be established. Similarly, further insights into exact mechanisms by which pulmonary neuromodulation causes improvement in hemodynamics are needed to facilitate future patient selection and maximize procedural benefits of PADN, in particular when expanding the procedure to the large, more heterogeneous population of group 2 PH patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Karl-Philipp Rommel, Heart Center at the University of Leipzig, Department of Cardiology, Strümpellstrasse, Leipzig, Saxony 04289, Germany. E-mail: Karl_Ph_Rommel@web.de.

REFERENCES

1. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–3731.

2. Ramirez RL 3rd, Perez VJ, Zamanian RT. Methamphetamine and the risk of pulmonary arterial hypertension. *Curr Opin Pulm Med*. 2018;24:416–424.

3. Salazar AM, Al-Asad KS, Prasad RM, Panama G, Banga S, Wilcox M. Pulmonary artery denervation as a new therapeutic option for pulmonary hypertension: a systematic review and meta-analysis. *Curr Probl Cardiol*. 2023;48:101776.

4. Rothman AM, Arnold ND, Chang W, et al. Pulmonary artery denervation reduces pulmonary artery pressure and induces histological changes in an acute porcine model of pulmonary hypertension. *Circ Cardiovasc Interv*. 2015;8:e002569.

5. Cuculich PS, Schill MR, Kashani R, et al. Noninvasive cardiac radiation for ablation of ventricular tachycardia. *N Engl J Med*. 2017;377:2325–2336.

6. Cai X, Shen Y, Yang Y, et al. Renal denervation by noninvasive stereotactic radiotherapy induces persistent reduction of sympathetic activity in a hypertensive swine model. *J Am Heart Assoc*. 2021;10:e020068.

7. Xu W, Wang D-y, Chen Z-y, et al. Noninvasive stereotactic radiotherapy for PADN in an acute canine model of pulmonary arterial hypertension. *J Am Coll Cardiol Basic Trans Science*. 2024;9(2):244–256.

8. Fengler K, Rommel KP, Blazek S, et al. A three-arm randomized trial of different renal denervation devices and techniques in patients with resistant hypertension (RADIOSOUND-HTN). *Circulation*. 2019;139:590–600.

9. Thenappan T, Prins KW, Pritzker MR, Scandurra J, Volmers K, Weir EK. The critical role of pulmonary arterial compliance in pulmonary hypertension. *Ann Am Thorac Soc*. 2016;13:276–284.

KEY WORDS noninvasive stereotactic body radiotherapy, pulmonary arterial hypertension, pulmonary artery, pulmonary artery denervation