Journal of the American Heart Association

EDITORIAL

Balloon Pulmonary Angioplasty for Chronic Thromboembolic Pulmonary Hypertension in Patients With Chronic Obstructive Pulmonary Disease: A Note of Caution

Richard Cheng, MD; Miles Conrad, MD, MPH

In this issue of the *Journal of the American Heart Association* (*JAHA*), Fujii et al. report on 32 patients with chronic obstructive pulmonary disease (COPD) undergoing balloon pulmonary angioplasty (BPA) for chronic thromboembolic pulmonary hypertension (CTEPH).[1] Patients were identified from a larger cohort of 149 patients with CTEPH who underwent BPA over a 10-year-period. COPD was diagnosed based on pulmonary function tests (forced expiratory volume in 1 s [FEV1]/forced vital capacity <70% and FEV1<80% predicted). Compared with patients without COPD, those with COPD had similar improvements in pulmonary vascular resistance and oxygenation. Severe lung injury occurred only 1.6% of the time in the COPD group, numerically less but statistically similar to the non-COPD group (3.0%). These are excellent outcomes in a challenging patient population.

See Article by Fujii.

There is indeed an unmet need for patients with COPD and CTEPH that might be met by BPA. Although surgical pulmonary thromboendarterectomy (PEA) is the preferred approach for patients with CTEPH to reduce pulmonary vascular resistance and improve oxygenation, the presence of COPD has been associated with an increased risk of residual pulmonary hypertension after PEA by an odds ratio of 6.2 and an increased risk of in-hospital mortality by an odds ratio of 4.4.[2] Moreover, in a National Quality Improvement Program database cohort of 468 795 patients, patients with COPD undergoing PEA had increased morbidity (25.8% versus 10.2%) and increased 30-day mortality (6.7% versus 1.4%) as compared with patients without COPD. This association was less profound but still present after logistic regression modeling, with odds ratios of 1.35 and 1.29 for morbidity and mortality, respectively, suggesting that COPD was also a marker of other comorbidities associated with perioperative risk.[3] From the US CTEPH registry, patients who were not offered PEA surgery were twice as likely to have COPD, had worse outcomes, and were more likely to be treated with oxygen, diuretics, or pulmonary hypertension targeted therapies at 1-year.[4]

In this article from Kobe University, the incidence of any COPD in this CTEPH cohort was 32%, and more than mild COPD was 21%. This is consistent with a Russian cohort of 136 patients with CTEPH in patients

Key Words: Editorials ■ balloon pulmonary angioplasty ■ chronic obstructive pulmonary disease ■ chronic thromboembolic pulmonary hypertension

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

Correspondence to: Richard Cheng, MD, FACC, FSCAI Division of Cardiology, Department of Internal Medicine 505 Parnassus Avenue, Room M1178-C San Francisco, CA 94118. Email: richard.cheng@ucsf.edu

For Disclosures, see page 2.

JAHA is available at: www.ahajournals.org/journal/jaha

scheduled for elective PEA that reported the incidence of COPD to be 23%.[2] Of note, patients with mild COPD were excluded from this analysis. Although it is difficult to know for sure the causal relationship between ventilatory impairment and vascular obstruction, it is less likely that patients with CTEPH from, for example, a hypercoagulable state, would subsequently develop ventilatory impairments. More likely, either (1) similar risk factors result independently in both COPD and CTEPH, or (2) ventilator impairment from inflammatory destruction of airways in COPD results in vasoconstriction and vascular involvement. COPD is indeed a risk factor for CTEPH in patients with newly diagnosed acute pulmonary embolism,[5] and in one cohort, improvement in percentage of predicted FEV1 (%FEV1) after PEA surgery was associated with larger mean pulmonary artery pressure improvement.[6]

Therefore, caution should indeed be given to BPA for COPD patients with CTEPH, as ventilatory impairment may lead to vascular obstruction in similar distributions. It is well understood that pulmonary artery thrombosis occurs in areas of the lung as a sequela of severe parenchymal disease such as COPD. Reperfusion to areas with impaired ventilatory elements is expected to lead to worsening ventilation-perfusion mismatch and hypoxia. In fact, in the article, despite excluding patients with mild COPD, the mean %FEV1 in the COPD group was 61%, consistent with moderate COPD, or GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria stage 2 of 4, and whether BPA-treated areas avoided areas of "bad" lung was not clearly stated—it would make sense to avoid BPA of lung segments with the worse perfusion defects by chest computed tomography or ventilation-perfusion scans as it may increase intrapulmonary shunting and worsen hypoxia. A potential signal of this concern: in the article's multivariate analysis, patients with higher vital capacity and higher lung diffusing capacity at baseline had greater improvement in oxygenation. This might suggest that instead of a greater potential for improvement of oxygenation in patients with more severe CTEPH and lower lung diffusing capacity, the expected improvements might have been offset by worsening ventilation-perfusion mismatch.

There may be emerging ways to tease out whether patients with COPD and CTEPH have pulmonary hypertension driven either by both disease processes, or mostly by CTEPH alone; these patients may also happen to have moderately severe COPD. Patients with CTEPH with lower %FEV1 on pulmonary function tests were found in one cohort to have a higher computed tomography angiogram obstructive score.[6] In another cohort, severity of pulmonary hypertension with COPD can be predicted by higher bronchial wall thickness and higher percentage cross-sectional area of pulmonary vessels less than 5 mm^2 normalized by lung area, a relationship not seen in severe CTEPH groups.[7] Magnetic resonance imaging has also been used to quantitate perfusion and ventilation. Mapping with phase-resolved functional lung magnetic resonance imaging shows a pattern of increased ventilation and perfusion time to peak in regions of hypoventilation and decreased perfusion for COPD but only increased perfusion time to peak in regions of hypoperfusion in CTEPH[8,9] and to treatment response after BPA treatment in CTEPH patients or after surgical PEA.[10,11]

As such, diagnosis, evaluation, and treatment of CTEPH remain an interdisciplinary process involving a multidisciplinary team of experts, as consistent with society guidelines, with a multimodality imaging and multimodality treatment approach.[12,13] This might be especially true for treatment of patients with COPD and CTEPH where careful evaluation of available chest imaging and preprocedural planning is needed to avoid revascularization to "bad lung" thereby worsening ventilation-perfusion mismatch and increasing intrapulmonary shunting. With a carefully selected cohort, Fujii et al. have shown us that indeed BPA can be performed safely to reduce pulmonary vascular resistance and improve oxygenation in this difficult-to-treat patient population.

ARTICLE INFORMATION

Affiliations

Division of Cardiology, Department of Internal Medicine, Advanced Heart Failure Comprehensive Care Center, University of California San Francisco, CA, USA (R.C.); and Section of Interventional Radiology, Department of Radiology, University of California San Francisco, CA, USA (M.C.).

Acknowledgments

The authors would like to thank Paul Forfia, MD, and Riyaz Bashir, MD, Temple University CTEPH Program, for collaboration with this editorial.

Disclosures

None.

REFERENCES

1. Fujii H, Taniguchi Y, Yoneda S, Miwa K, Matsuoka Y, Yanaka K, Tsuboi Y, Emoto N, Hirata K. Efficacy and safety of balloon pulmonary angioplasty for patients with chronic thromboembolic pulmonary hypertension and comorbid chronic obstructive pulmonary disease. *J Am Heart Assoc*. 2023;11:e026466. doi: 10.1161/JAHA.122.026466
2. Kamenskaya O, Loginova I, Chernyavskiy A, Edemskiy A, Lomivorotov VV, Karaskov A. Chronic obstructive pulmonary disease in patients with chronic thromboembolic pulmonary hypertension: Prevalence and implications for surgical treatment outcome. *Clin Respir J*. 2018;12:2242–2248. doi: 10.1111/crj.12898
3. Gupta H, Ramanan B, Gupta PK, Fang X, Polich A, Modrykamien A, Schuller D, Morrow LE. Impact of COPD on postoperative outcomes: results from a national database. *Chest*. 2013;143:1599–1606. doi: 10.1378/chest.12-1499
4. Kerr KM, Elliott CG, Chin K, Benza RL, Channick RN, Davis RD, He F, LaCroix A, Madani MM, McLaughlin VV, et al. Results from the United States Chronic Thromboembolic Pulmonary Hypertension Registry: enrollment characteristics and 1-year follow-up. *Chest*. 2021;160:1822–1831. doi: 10.1016/j.chest.2021.05.052

5. Kanwar MK, Cole M, Gauthier-Loiselle M, Manceur AM, Tsang Y, Lefebvre P, Panjabi S, Benza RL. Development and validation of a claims-based model to identify patients at risk of chronic thromboembolic pulmonary hypertension following acute pulmonary embolism. *Curr Med Res Opin*. 2021;37:1483–1491. doi: 10.1080/03007995.2021.1947215
6. Yanagisawa A, Naito A, Jujo-Sanada T, Tanabe N, Ishida K, Matsumiya G, Suda R, Kasai H, Sekine A, Sugiura T, et al. Vascular involvement in chronic thromboembolic pulmonary hypertension is associated with spirometry obstructive impairment. *BMC Pulm Med*. 2021;21:407. doi: 10.1186/s12890-021-01779-x
7. Coste F, Benlala I, Dournes G, Dromer C, Blanchard E, Girodet PO, Montaudon M, Baldacci F, Picard F, Marthan R, et al. Quantitative CT assessment of bronchial and vascular alterations in severe precapillary pulmonary hypertension. *Int J Chron Obstruct Pulmon Dis*. 2019;14:381–389. doi: 10.2147/COPD.S177638
8. Kaireit TF, Voskrebenzev A, Gutberlet M, Freise J, Jobst B, Kauczor HU, Welte T, Wacker F, Vogel-Claussen J. Comparison of quantitative regional perfusion-weighted phase resolved functional lung (PREFUL) MRI with dynamic gadolinium-enhanced regional pulmonary perfusion MRI in COPD patients. *J Magn Reson Imaging*. 2019;49:1122–1132. doi: 10.1002/jmri.26342
9. Voskrebenzev A, Gutberlet M, Klimes F, Kaireit TF, Schonfeld C, Rotarmel A, Wacker F, Vogel-Claussen J. Feasibility of quantitative regional ventilation and perfusion mapping with phase-resolved functional lung (PREFUL) MRI in healthy volunteers and COPD, CTEPH, and CF patients. *Magn Reson Med*. 2018;79:2306–2314. doi: 10.1002/mrm.26893
10. Czerner CP, Schoenfeld C, Cebotari S, Renne J, Kaireit TF, Winther HB, Pohler GH, Olsson KM, Hoeper MM, Wacker F, et al. Perioperative CTEPH patient monitoring with 2D phase-contrast MRI reflects clinical, cardiac and pulmonary perfusion changes after pulmonary endarterectomy. *PLoS One*. 2020;15:e0238171. doi: 10.1371/journal.pone.0238171
11. Schoenfeld C, Hinrichs JB, Olsson KM, Kuettner MA, Renne J, Kaireit T, Czerner C, Wacker F, Hoeper MM, Meyer BC, et al. Cardio-pulmonary MRI for detection of treatment response after a single BPA treatment session in CTEPH patients. *Eur Radiol*. 2019;29:1693–1702. doi: 10.1007/s00330-018-5696-4
12. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–3731. doi: 10.1093/eurheartj/ehac237
13. Siennicka A, Darocha S, Banaszkiewicz M, Kedzierski P, Dobosiewicz A, Blaszczak P, Peregud-Pogorzelska M, Kasprzak JD, Tomaszewski M, et al. Treatment of chronic thromboembolic pulmonary hypertension in a multidisciplinary team. *Ther Adv Respir Dis*. 2019;13:1753466619891529. doi: 10.1177/1753466619891529