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Editorial

Patent Foramen Ovale in COPD and Hypoxia: Innocent Bystander or Novel Therapeutic Target?

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Abbreviations: patent foramen ovale, **PFO**; transcranial Doppler ultrasonography, **TCD**; Global initiative for chronic Obstructive Lung Disease, **GOLD**; partial pressure of oxygen, **P_aO₂**; oxygen uptake, **V'O₂**; high-intensity transient signals, **HITS**

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The pathophysiologic origins of hypoxia in COPD involve multiple mechanisms, most notably ventilation perfusion mismatch as a consequence of airflow obstruction and emphysematous capillary bed destruction. However, there is increasing interest in understanding the role of patent foramen ovale (PFO)-mediated right-to-left shunting in hypoxia as a potential therapeutic target. In this issue of *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*, Martolini et al report on their findings regarding the functional significance of PFO in hypoxia and exercise limitation in moderately severe COPD. The authors performed transcranial Doppler ultrasonography (TCD) for identification of PFO during cardiopulmonary

exercise testing in a small cohort of Global initiative for chronic Obstructive Lung Disease (GOLD) stage II individuals. A PFO was identified in 12 of 22 individuals, and PFO presence was itself an independent correlate of partial pressure of oxygen in arterial blood (PaO₂). Furthermore, PFO shunting appeared to increase with elevated respiratory muscle work and intrathoracic pressure swings as assessed by esophageal pressure manometry. However, and most importantly, PFO presence did not associate with markers of exercise performance including oxygen uptake (V'O₂ peak/kg) or 6-minute walk distance. The authors conclude that PFO is unlikely to have a functional impact on exercise capacity in moderately severe COPD.

These findings are provocative and at first glance appear to dispel the notion that PFO shunting, either at rest or with activity, necessarily worsens exercise capacity through a hypoxia-dependent mechanism. On further examination, 2 key points emerge concerning the patients studied. First, the majority of PFO individuals had only mild/Grade I shunt, and the low threshold TCD criteria used may have included some with no PFO. Second, patients in both the PFO and non-PFO cohorts did not have significant resting hypoxia, or for that matter, exertional hypoxia. Thus the patients in the PFO group most likely had incidental PFO's, and it would not be expected that a functional impact on functional capacity would be found. Normoxic COPD populations with mild resting shunt are not the patients in whom the functional impact of a PFO will be manifest.

Other studies have provided some insight but still

fail to adequately address the clinical issue of whether management of hypoxic COPD patients with more substantial shunting present a unique therapeutic opportunity to improve function. Shaikh et al recently evaluated GOLD stage III and stage IV individuals with severe hypoxia ($\text{PaO}_2 < 7.3$ kPa) and less severe hypoxia ($\text{PaO}_2 > 8.0$ kPa). They found no significant difference in PFO prevalence by TCD examination (39% vs. 52%; $P = 0.27$).¹ Furthermore, Kilic et al reported no significant difference in hypoxia in COPD individuals with and without PFO (46.5 ± 13.77 vs. 57.4 ± 6.85 mmHg, respectively), although only 4 individuals with a PFO were included in the study.² The issue is not the prevalence of any PFO but the potential significant contribution to systemic hypoxemia of volumetrically substantial right to left shunting through an anatomically large PFO in some patients. The functional impact of that degree of shunting is difficult to dissect based on exercise testing. A more convincing and active approach to hypothesis testing is to eliminate the intracardiac shunting and then assess whether patients improve or not. Sham procedures might be necessary in a control group if subjective assessments of functional and quality of life changes are included in the study design.

An additional limitation of the present study is the use of TCD to define the presence of a PFO in a COPD cohort. TCD cannot discriminate between intracardiac shunting and intrapulmonary shunting. COPD patients can demonstrate significant intrapulmonary shunting that does not necessarily correlate with airflow, lung volume, or resting blood gas.³ Furthermore, large diameter (>25 - 50 μm) intrapulmonary arteriovenous anastomoses are known to exist under physiologic conditions.⁴ Consistent with prior investigations using TCD in the cryptogenic stroke population, this study defined PFO presence by demonstrating single high-intensity transient signals (HITS) within 25 seconds of saline contrast injection.⁵ However, intrapulmonary shunts can present with <5 HITS and therefore potentially masquerade as a PFO in this study.⁶ Because 66% of PFO patients had 1-10 HITS and the presence of PFO was not confirmed by echocardiography, the potential for concurrent intrapulmonary shunts to confound this study's results cannot be excluded.

This study adds to the growing body of work investigating the role of PFO in hypoxia and human performance. The role of PFO in contributing to hypoxia in diverse conditions such as obstructive

sleep apnea, left ventricular assist device insertion, paralyzed hemidiaphragm, orthodeoxia platypnea, and COPD require a careful approach separating incidental clinically-insignificant PFOs from those that are pathogenic. This study and others argue against a pathologic role for PFO in a significant part of the COPD patient spectrum. However, multiple case series have reported improvement in dyspnea and/or supplemental oxygen use following percutaneous closure in hypoxic populations including those with COPD.^{7,8}

These conflicts in the literature may reflect publication biases but also important differences in patients studied and study designs. PFO closure studies are more likely to include patients with echocardiographically-detected large right-to-left intracardiac shunting. Second, PFO closure studies have been observational studies lacking a control group, randomization, and a standardized methodology of shunt detection, quantification, and assessment of change in functional state. While patient-reported outcomes are important, self-reported endpoints in unblinded participants can be confounded by patients' expectations. Another explanation involves the inclusion of heterogeneous patient cohorts in PFO closure studies that are defined by hypoxia as opposed to a specific pulmonary disease state. If PFOs in some patients do indeed impact systemic oxygenation and/or exercise capacity via right-to-left shunting, one might anticipate that performing PFO closure in a population with severe/disproportionate hypoxia and dyspnea relative to background COPD may be more likely to demonstrate a benefit and support a pathologic role for PFOs.

Other methodological challenges have added to the complexity of this field. The contribution of right-to-left shunting via a PFO to systemic hypoxemia is difficult to quantify. Oxygen saturation of venous blood in all 4 pulmonary veins can be collected as well as the downstream systemic arterial blood after the PFO contribution has been mixed. However, there are uncertainties as to the volume of venous return in each vein, and there is no validated way to calculate the subsequent PFO contribution in clinical studies. Furthermore, studies performed in supine patients may have little relevance to the pathophysiology during exercise.

A well-planned study would also need to assess for concurrent pulmonary hypertension as a driver of PFO shunting. At what level of pulmonary hypertension or pulmonary vascular disease should PFO closure be

contraindicated? The burden of proof may rest upon future percutaneous closure trials with randomization and perhaps patient and investigator blinding. Optimization and stabilization of other therapies for COPD must be achieved prior to randomization. There must be well-documented PFO anatomy and physiology at baseline and at 6-12 months time when closure is considered as complete as possible with detection and quantification of residual shunting that may occur in 10%-25% of patients. The study should

be designed to objectively demonstrate improved oxygenation, functional capacity, and patient-reported outcomes. Finally, the implanted device as well as the implantation procedure must have an extremely low complication rate such that any potential benefit substantially counterbalances the possibility of harm. The time is right for such a multicenter study lead by a multidisciplinary group to more definitively determine if and when a PFO in COPD is an innocent bystander or a novel therapeutic target.

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