Patent Foramen Ovale Is Not Associated with Hypoxemia in Severe Chronic Obstructive Pulmonary Disease and Does Not Impair Exercise Performance

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Abstract

Rationale: Patent foramen ovale (PFO) may be disadvantageous in chronic obstructive pulmonary disease (COPD). It is unknown whether right-to-left shunting through PFO increases during exercise impairing exercise performance.

Objectives: To determine whether (1) PFO prevalence is greater in hypoxemic versus less hypoxemic patients with COPD, (2) PFO is associated with clinically relevant impairment, and (3) right-to-left shunting increases during exercise and impairs exercise performance.

Methods: Patients with COPD and age-matched control subjects underwent contrast transthoracic echocardiography and transcranial Doppler to identify PFO. Patients with COPD with no shunt and patients with large PFO underwent cardiopulmonary exercise tests with contrast transcranial Doppler, esophageal, and gastric balloon catheters.

Measurements and Main Results: PFO prevalence was similar in 50 patients with COPD and 50 healthy control subjects (46% vs. 30%; $P = 0.15$). Large shunts were more common in patients with COPD (26% vs. 6%; $P = 0.01$). In an expanded COPD cohort, PFO prevalence was similar in 31 hypoxemic ($\text{Pa}_{\text{O}_2} \leq 7.3$ kPa) and 63 less hypoxemic ($\text{Pa}_{\text{O}_2} > 8.0$ kPa) patients with COPD (39% vs. 52%; $P = 0.27$). Patients with intrapulmonary shunting had lower Pa_{O_2} than both patients with PFO and those with no right-to-left shunt (7.7 vs. 8.6 vs. 9.3 kPa, respectively; $P = 0.002$). Shunting significantly increased during exercise in patients with COPD with PFO. Endurance time at 60% $\text{V}_{\text{O}_{2\text{max}}}$ was 574 (178) seconds for patients with PFO and 534 (279) seconds for those without ($P = \text{ns}$).

Conclusions: Hypoxemic patients with COPD do not have a higher prevalence of PFO. Patients with COPD with PFO do not perform less well either on a 6-minute walk or submaximal exercise testing despite increased right-to-left shunting during exercise.

Keywords: patent foramen ovale; chronic obstructive pulmonary disease; right-to-left shunt; hypoxemia; exercise

Among the complications most feared by patients with chronic obstructive pulmonary disease (COPD) is the need to use domiciliary oxygen (1, 2), yet there are clear data to show that when Pa_{O_2} is less than 7.3 kPa, supplemental oxygen extends life (3–5).

One cause of a reduced Pa_{O_2} is right-to-left shunting. Patent foramen ovale (PFO) is a congenital cardiac defect that permits right-to-left shunting and has been reported to be present in at least 25% of the population (6, 7). However, because most

adults are not hypoxemic, PFO *per se* is not expected to cause sufficient right-to-left shunting to elicit hypoxemia.

In patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage III–IV) increased

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At a Glance Commentary

Scientific Knowledge on the

Subject: Prior studies suggested that patent foramen ovale (PFO) is more common in patients with chronic obstructive pulmonary disease (COPD) than control subjects and, when present, is associated with reduced oxygen saturation and impaired exercise tolerance. Because PFO can now be easily and safely closed, PFO represents a potential therapeutic opportunity in COPD.

What This Study Adds to the Field:

We demonstrate that PFO with large shunts is more common in COPD, but we found no relationship between PFO and any adverse phenotypic feature, including 6-minute walk distance, in COPD. Moreover, in a maximal exercise test in which intrathoracic pressure swings were greatly increased, right-to-left shunting increased but patients with PFO did not have impaired exercise performance. We conclude that PFO closure is unlikely to improve exercise performance in COPD.

respiratory load causes significant intrathoracic pressure swings, which can be positive in the expiratory phase (8–10). Additionally, intermittent increases in pulmonary artery pressure during exercise (11) may also increase right atrial pressure further promoting right-to-left shunting.

Few data presently exist concerning patients with COPD and PFO, but most of those support the hypothesis that PFO might contribute to hypoxia in COPD. Soliman and colleagues (12) studied 20 GOLD stage III–IV patients and 20 control subjects and reported an increased prevalence of PFO in COPD; furthermore, the presence of a PFO was linked to desaturation during a Valsalva maneuver. Hacievliyagil and coworkers (13) also found a twofold increase in the prevalence of PFO in severe COPD and additionally found that patients with a PFO at rest had lower resting Sa_{O_2} and shorter 6-minute walk (6MW) distances. The difference in mean 6MW distance between patients with COPD who had a PFO and those who did not was 132 m, which substantially exceeds

even the most conservative minimum clinically important difference in this test in COPD (14). Conversely, Kilic and coworkers (15) studied 21 GOLD I and II patients with COPD and concluded that a low Sa_{O_2} was not associated with PFO; however, their population was preselected for the presence of hypoxia. None of these investigators studied right-to-left shunting during exercise.

We therefore conducted a prospective cross-sectional controlled study to determine first whether the prevalence of PFO was greater in patients with COPD who were hypoxemic compared with those who were not. Second, we aimed to determine whether, in COPD, PFO was associated with disadvantage in any clinically relevant parameter. Lastly, to confirm our cross-sectional comparisons in a second exercise study we selected from our COPD patient cohort a smaller group who had large PFO and a control group who did not and measured the magnitude of shunting during exercise as a function of respiratory muscle activity measured from esophageal and gastric balloon catheters.

Methods

Subjects

Patients with COPD were recruited from Royal Brompton Hospital clinics. Inclusion criteria were age older than 40 years and severe COPD (GOLD stage III or higher). Exclusion criteria were clinical evidence of obstructive sleep apnea or obesity-hypoventilation syndrome, active infections, exacerbation in the prior 4 weeks, and cardiac disease (valve disease, cardiomyopathy, left ventricular failure, congenital heart disease). Healthy control subjects were recruited from a departmental database; some data from these control subjects were reported in our study of PFO and obstructive sleep apnea (16). The Brompton and Harefield Ethics Committee approved the study and all patients gave written informed consent.

Cross-Sectional Prevalence

Arterial blood gas tensions (room air), 6MW distance (17), and respiratory function tests (18–22) were performed. The St. George's Respiratory Questionnaire (SGRQ) was completed (23).

Hypoxemic patients with COPD were defined as those with Pa_{O_2} less than or equal

to 7.3 kPa and less hypoxemic as those with Pa_{O_2} greater than 8 kPa breathing room air.

PFO detection. The presence of PFO was evaluated by contrast transthoracic echocardiography (TTE) and contrast transcranial Doppler (TCD). Shunt magnitude was recorded at rest and after a Valsalva maneuver (*see online supplement*).

PFO shunt capacity was graded as small, moderate, or large in accordance with validated criteria (*see online supplement*) (24–26). Using TCD a five-point grading scale was used and shunt magnitude was defined as follows: no shunt = grade 0, small shunt = grade 1–2, moderate shunt = grade 3, large shunt = grade 4–5. Where there was a disagreement between TTE and TCD, the larger detected shunt was recorded.

Pulmonary shunts were identified on TTE if contrast was detected in the left heart five cardiac cycles after contrast had entered the right heart.

For the purposes of analysis, if satisfactory images were obtained using either TTE or TCD then those data were used for analysis.

Right-to-Left Shunting during Exercise

Severe patients with COPD with no significant right-to-left shunt and patients with significant shunts defined on TCD as Spencer grade 3–5 (24) took part. A symptom-limited, incremental work rate cardiopulmonary exercise test was undertaken on a cycle ergometer. Sixty percent of the peak work rate, determined for each individual, was used for the second exercise test.

A second cardiopulmonary exercise test on a cycle ergometer with oximetry was performed. Esophageal and gastric balloon catheters were inserted for measurement of esophageal and gastric pressures (P_{oes} and P_{gas}) (8, 27). P_{oes} and P_{gas} were recorded throughout the test. The protocol comprised 2 minutes rest, 2 minutes unloaded cycling, and then continuous exercise at 60% peak work rate. Agitated saline contrast was injected at 2-minute intervals during the protocol. Earlobe capillary blood samples were taken before and at the end of exercise. Inspiratory effort was measured as the difference between end-expiratory esophageal pressure and the P_{oes} nadir; expiratory effort was measured

Figure 1. Recruitment flow charts for (a) chronic obstructive pulmonary disease (COPD) cross-sectional study and (b) COPD exercise protocol. *5: unable to take oxygen off to take blood gas, 2: asthma, 1: tuberculosis, 1: diaphragm paralysis, 1: obliterative bronchiolitis, 1: asbestosis, 2: lung transplant. **5: $\text{Pa}_{\text{O}_2} > 8$ kPa and group had reached target, 1: arterial blood gas phobia. CCF = congestive cardiac failure; GOLD = Global Initiative for Chronic Obstructive Lung Disease; OHS = obesity-hypoventilation syndrome; OSA = obstructive sleep apnea; PFO = patent foramen ovale; RLS = right-to-left shunt; TCD = transcranial Doppler.

as the difference between end-inspiratory P_{gas} and peak expiratory P_{gas} . The values observed in the eight breaths after contrast injection were averaged to obtain data for analysis.

Statistical Analysis

Full details of statistical analysis, including the sample size calculation, are in the online supplement. Statistical significance was defined as P less than 0.05.

Results

Two-hundred and seven severe patients with COPD were approached from which 113 were studied and 50 healthy control subjects; technically adequate data were obtained in 105 of the 118 patients and these were used for analysis. To compare prevalence of PFO between patients and control subjects we used the youngest 50 patients with COPD only because PFO prevalence is age related (6). Patient recruitment is shown in Figure 1.

In regard to imaging of the PFO, technically adequate data were obtained with both TCD and TTE in 100 patients with COPD and all 50 control subjects. For patients with COPD agreement between TCD and TTE showed a kappa statistic for measurements at rest was of 0.53 indicating moderate agreement between TCD and TTE; during Valsalva kappa was 0.79 indicating substantial or good agreement between TCD and TTE. In the healthy control subjects the kappa statistic for measurements at rest was 0.82 indicating good agreement between TCD and TTE; during Valsalva kappa was 0.83 again indicating good agreement (see Table E1 in the online supplement).

Cross-Sectional Prevalence

Patients with COPD versus control subjects.

The demographics of 50 control subjects and 50 youngest patients with COPD are shown in Table 1. As expected the patients with COPD had a lower Pa_{O_2} at rest (but not higher Pa_{CO_2}) and a reduced 6MW distance ($P < 0.0001$ for both). Statistical significance was not tested for FEV₁ because this variable was used to divide the groups.

The prevalence of a PFO (of any size) did not differ between COPD and control groups at rest (26% [13 of 50] vs. 12% [6 of

Table 1: Baseline Characteristics of Patients with COPD and Healthy Control Subjects

	COPD (n = 50)	Healthy Control Subjects (n = 50)	P Value
Age, yr	55 (5)	52 (11)	0.07
Sex, male/female	27/23	42/8	0.002
FEV ₁ , % predicted	29.4 (11.4)	101.4 (13.4)	
FVC, % predicted	81.0 (19.9)	104.2 (13.4)	
FEV ₁ /FVC	28.6 (8.0)	78.8 (6.4)	
Body mass index, kg/m ²	24.3 (4.4)	24.3 (2.7)	0.98
Pa_{O_2} , kPa	8.4 (1.7)	12.3 (1.4)	<0.001
Pa_{CO_2} , kPa	5.6 (1.3)	5.6 (0.5)	0.58

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

Values are expressed as mean (SD). Chi-square test was used to calculate P value for sex. Student t test was used to calculate P value for remaining parameters.

50]; $P = 0.12$), or after a Valsalva maneuver (46% [23 of 50] vs. 30% [15 of 50]; $P = 0.15$). However, if the analysis was confined to large shunts the prevalence following Valsalva was significantly higher in patients with COPD compared with healthy control subjects (26% [13 of 50] vs. 6% [3 of 50]; $P = 0.01$). The prevalence of pulmonary shunt in patients with COPD was not significantly different from healthy control subjects (24% [12 of 50] vs. 12% [6 of 50]; $P = 0.19$). Data for the comparison of the entire group against control subjects are provided in the online supplement.

Hypoxemic versus less hypoxemic patients with COPD. The baseline characteristics of the hypoxemic and less hypoxemic group are given in Table 2. There was no difference in the prevalence of PFO or the magnitude of associated shunt between the hypoxemic and less

hypoxemic groups at rest (29% [9 of 31] vs. 27% [17 of 63], respectively; $P = 0.99$) or after Valsalva (39% [12 of 31] vs. 52% [33 of 63], respectively; $P = 0.27$). Pulmonary shunts were more common in the hypoxemic compared with the less hypoxemic group (48% [15 of 31] vs. 24% [15 of 63], respectively; $P = 0.02$).

Analysis of the entire COPD population. The resting Pa_{O_2} did not differ between patients with COPD with a PFO and those without (8.6 vs. 8.5 kPa; $P = 0.87$) or between control subjects with a PFO and those without (12.6 vs. 12.3; $P = 0.45$).

In control subjects 6MW was not different between participants with a PFO and those without (631 vs. 625 m; $P = 0.78$), but, unexpectedly, patients with COPD with a PFO had a greater 6MW distance than those without (312 vs. 243 m; $P = 0.01$).

Table 2: Baseline Characteristics of Patients with Chronic Obstructive Pulmonary Disease with $Pa_{O_2} \leq 7.3$ kPa and > 8 kPa

Characteristic	$Pa_{O_2} \leq 7.3$ kPa (n = 31)	$Pa_{O_2} > 8$ kPa (n = 63)	P Value
Age, yr	63 (8)	62 (9)	0.42
Sex, male/female	21/10	39/24	0.65
FEV ₁ , % predicted	27.8 (11.9)	30.8 (9.1)	0.23
FVC, % predicted	77.0 (21.9)	85.7 (19.4)	0.07
FEV ₁ /FVC	28.4 (7.5)	28.0 (7.9)	0.80
TLC _{OC} , % predicted	24.6 (12.7)	34.4 (11.5)	0.001
KCO _C , % predicted	35.5 (15.3)	44.3 (14.2)	0.02
TLC, % predicted	127.3 (16.3)	130.6 (16.4)	0.40
RV, % predicted	217.3 (50.9)	214.7 (50.0)	0.83
RV/TLC	67.7 (27.3)	60.0 (9.3)	0.18
FRC, % predicted	187.1 (35.5)	184.6 (32.2)	0.75
Body mass index, kg/m ²	25.3 (4.5)	24.0 (4.3)	0.22
Pa_{O_2} , kPa	6.5 (0.7)	9.7 (1.0)	
Pa_{CO_2} , kPa	6.6 (1.4)	5.2 (0.7)	

Definition of abbreviation: RV = residual volume.

Values are expressed as mean (SD). Chi-square test was used to calculate P value for sex. Student t test was used to calculate P value for remaining parameters.

Figure 2. Resting PaO_2 according to shunt status within the chronic obstructive pulmonary disease (COPD) group. Patients without right-to-left shunts (RLS) had a higher PaO_2 than patients with RLS when considered as a group but this failed to achieve significance when patients with patent foramen ovale (PFO) were considered without those with intrapulmonary shunting. The horizontal dashed line represents the level (7.3 kPa) where domiciliary oxygen has been shown to be beneficial. IP = intrapulmonary.

Phenotypic aspects of patients with COPD with or without a PFO are shown in Table E2. The patients with a right-to-left shunt (considering PFO and intrapulmonary shunts together) had a lower PaO_2 than those without (8.3 vs. 9.3 kPa; $P = 0.007$), although they had a tendency to a lower FEV_1 and a higher SGRQ. When the

cohort was considered as three groups (i.e., no right-to-left shunt, intrapulmonary shunting, and PFO), it is apparent that patients with an intrapulmonary shunt had a lower PaO_2 than patients with PFO (Figure 2). Patients with PFO retained a lower SGRQ and greater 6MW in the three-way analysis (Figure 3).

Figure 3. Six-minute walk (6MW) distance (top) and St. George's Respiratory Questionnaire (SGRQ) total score (bottom) expressed both as a function of right-to-left shunting (RLS) considered irrespective of cause (left) and split into patent foramen ovale (PFO) and intrapulmonary shunt (right). Patients with a PFO had longer 6MW distances and lower SGRQ scores. IP = intrapulmonary.

Right-to-Left Shunting during Exercise

The demographics of the exercise participants are shown in Table 3, and their selection in Figure 1b. The groups were well matched in essential respects. Their performance on an incremental exercise test is shown in Table 4.

In the PFO group there was a significant increase in shunt size during submaximal exercise from minute 1 to 3 (grade 1 [1] to grade 2 [2]; $P = 0.008$), from minute 1 to 5 (grade 1 [1] to grade 3 [2]; $P = 0.001$), and from minute 3 to 5 (2 [2] to 3 [2]; $P = 0.023$) (see Figure E1a). Shunt size peaked in the fifth minute and reached a plateau for the remaining duration of exercise. There was no significant difference between shunt size during the final stage of exercise and the first minute of recovery ($P = 0.59$).

In the group without evidence of right-to-left shunting at baseline there was no increase in shunting beyond an insignificant, grade 1 shunt during exercise in seven out of nine patients, which persisted into recovery in three patients. Shunt size was not significantly different from baseline to exercise to recovery (see Figure E1b).

Ventilation at peak exercise in the submaximal exercise test was 33.6 (8.8) L/min for patients without a PFO and 31.2 (9.5) L/min for those with PFO ($P = 0.72$). The mean (SD) endurance time (T_{Lim}) was 574 (178) seconds in patients with a PFO and 534 (239) seconds in those without ($P = \text{ns}$). Individual data for both groups are graphically represented Figure E2.

As expected, the exercise was sufficient to induce significant respiratory muscle activity in PFO and non-PFO groups (Figure 4; see Table E3). The maximum pressures observed during the submaximal exercise test did not differ between patients with and without a PFO. Mean (SD) peak values were P_{oes} 42.1 (25.6) versus 32.8 (7.2) cm H_2O , P_{ga} 23.5 (25.5) versus 18.0 (13.1) cm H_2O , and P_{di} 33.5 (12.0) versus 32.1 (12.1) cm H_2O .

Discussion

This study shows that in patients with severe COPD, PFO prevalence was similar but intrapulmonary shunts were more prevalent in patients with hypoxemia compared with those with higher PaO_2 . PFO was not more common in severe COPD than healthy adults, in contrast to prior studies in this

Table 3: Baseline Characteristics of No Significant Right-to-Left Shunt and PFO Groups Participating in the Exercise Substudy

Characteristic	No Significant Right-to-Left Shunt (n = 9)	PFO (n = 90)	P Value
Age, yr	61 (6)	65 (9)	0.29
Sex, male/female	6/3	4/5	0.64
FEV ₁ , % predicted	32.8 (14.1)	34.8 (10.6)	0.75
FEV ₁ , L	0.95 (0.29)	0.9 (0.31)	
FVC, % predicted	94.0 (12.9)	90.8 (16.6)	0.66
FEV ₁ /FVC	26.9 (8.9)	30.2 (8.6)	0.44
TLCoc, % predicted	40.2 (14.1)	40.3 (10.5)	0.99
KCoc, % predicted	49.0 (15.3)	51.9 (18.3)	0.72
TLC, % predicted	131.4 (18.1)	126.0 (18.6)	0.54
RV, % predicted	212.3 (62.4)	190.8 (46.1)	0.42
RV/TLC	56.1 (7.6)	57.4 (7.6)	0.74
FRC, % predicted	184.4 (47.6)	170.8 (36.3)	0.51
Body mass index, kg/m ²	27.1 (5.4)	26.6 (6.5)	0.85
Pa _{O₂} , kPa	9.7 (1.0)	9.6 (1.3)	0.90
Pa _{CO₂} , kPa	5.1 (0.4)	5.2 (0.4)	0.50

Definition of abbreviations: PFO = patent foramen ovale; RV = residual volume.

Values are expressed as mean (SD). Chi-squared test was used to calculate *P* value for sex. Student *t* test was used to calculate *P* value for remaining parameters.

field. However, large shunts through PFO were found to be more prevalent in severe COPD. This study also shows that when right-to-left shunting from all causes was considered patients with a right-to-left shunt from all causes were more hypoxic, over a range that encompassed the threshold for long-term oxygen therapy. Even so their SGRQ scores were lower and their 6MW distances not different from patients without a right-to-left shunt. In a subset of patients studied during exercise we confirmed that when inspiratory and expiratory muscle activity is increased, right-to-left shunting also increases, but this was not reflected in greater desaturation during a maximal incremental exercise test, reduced peak $\dot{V}O_2$, or impaired exercise performance. The present data do not support a case for closure of PFO, although they should not preclude patients with COPD having PFO closed for other indications, such as paradoxical embolus.

Strengths and Limitations of the Study

One strength of the present study is its size; our cohort is bigger than all three previous studies combined (12, 13, 15). We also did not select patients on the grounds of oxygenation or functional capacity. Patients were not well matched with control subjects with regard to sex; however, sex was not thought by Hagen and colleagues (6), after almost 1,000 autopsies, to influence the

prevalence of PFO, although clinical events after PFO, such as stroke caused by paradoxical embolus (*vide infra*), do seem potentially to be influenced by sex (28, 29).

A further strength of our study is that we confirmed by direct experiment that the presence of PFO is not associated with reduced exercise performance, at least at submaximal intensities. The strongest confirmation of this claim, because of the size of the cohort, comes from the 6MW data. However, additional support comes from the exercise substudy, which even though it was conducted at 60% of $\dot{V}O_{2\max}$ required our patients to reach approximately 85% predicted maximal voluntary ventilation (30, 31) and elicited increased right-to-left shunting documented by TCD. We acknowledge

that understanding the pathophysiology of right-to-left shunt would have been enhanced had we also measured cardiac output simultaneously but permission to place a right heart catheter was refused by our ethics committee. Boerrigter and colleagues (32) have recently provided data regarding the interaction of respiratory muscle pressure generation and right atrial pressure; their data show that pulmonary arterial pressures are greatly influenced by the phase of respiration, but that transmural pressure, which should determine the likelihood of shunting, is relatively unchanged during the respiratory cycle.

It might be argued that higher exercise intensity (e.g., 75% or 80%) might produce a greater increase in pulmonary arterial and right atrial pressure, uncovering a greater right-to-left shunt. However, our patients exercised to the limit of tolerance at 60% peak power suggesting that peak $\dot{V}O_2$ and cardiac output was approached toward the end of the constant exercise test. Nevertheless, we acknowledge that the present data cannot exclude that patients with COPD with PFO experience limitation because of an increased shunt fraction when approaching $\dot{V}O_{2\max}$.

Significance of the Findings

Hypoxia is a common problem in COPD and PFO closure is now a routine daycase procedure; thus, for the COPD community knowing whether to embark on a program of PFO closure is extremely timely. Our data, although showing that PFO is indeed common in COPD, suggest that at least in patients with GOLD III–IV disease the presence of a PFO is not associated with hypoxemia or reduced exercise performance. Indeed, if the factors known to be of prognostic significance in COPD

Table 4: Performance of Patients with Chronic Obstructive Pulmonary Disease in the Incremental Exercise Test

	No Significant RLS (n = 9)		RLS (n = 9)	
	Baseline	Peak Exercise	Baseline	Peak Exercise
Pa _{O₂} , kPa	9.7 (1.0)	9.4 (1.8)	9.6 (1.3)	8.9 (1.8)
Pa _{CO₂} , kPa	5.1 (0.4)	4.6 (1.0)	5.2 (0.4)	5.2 (0.8)
Sa _{O₂} , %	95 (2)	90 (5)	95 (2)	90 (4)
VE, L/min	14.3 (5.5)	33.6 (8.8)	10.1 (3.0)	31.2 (9.5)
Heart rate, per min	89 (13)	113 (15)	90 (14)	116 (14)
$\dot{V}O_2$, ml/min/kg	3.7 (1.6)	12.9 (2.1)	3.7 (1.3)	13.0 (3.4)
Peak load, W		33 (12)		26 (10)

Definition of abbreviation: RLS = right-to-left shunt. Values are expressed as mean (SD).

Figure 4. Grade of shunt (right), inspiratory effort measured as the amplitude between end-expiratory P_{oes} and the P_{oes} nadir (middle), and expiratory effort measured as the amplitude between end-inspiratory P_{gas} and the P_{gas} peak (left). Mean data for the first four injections are shown. Varying exercise times thereafter render means unrepresentative. PFO = patent foramen ovale.

are evaluated including FEV₁ (33), carbon monoxide transfer (34), hyperinflation (35), and 6MW distance (36) no differences were observed between patients with and without PFO. These data are consistent with the observation that oxygen, except in high doses, does not extend exercise performance in COPD (37, 38).

An unexpected finding of our study was the greatly increased prevalence of intrapulmonary shunts. Intrapulmonary shunts are uncommon in normal lungs (39). The functionality of intrapulmonary shunts in healthy lung is oxygen dependent (40) and this may explain the observed increased prevalence in COPD. We also note that intrapulmonary shunts develop in healthy adults during exercise (41), and it could be that the increased pressures generated by the respiratory muscles in patients with COPD, even at rest (8), are sufficient to elicit them. We speculate that both intrapulmonary shunts and PFO may serve a useful purpose in patients with more severe COPD by offloading right heart pressure, but the current data set does not permit further exploration of this proposition except to note that when the entire COPD population were compared with control subjects (see online

supplement) PFO was more common in patients with COPD, whereas one might have expected, because the patients with COPD were older, that PFO prevalence would be reduced. We tentatively speculate that this observation could represent a “reverse survivor” effect in that patients who are unable to open a PFO may have a worse prognosis by virtue of pulmonary hypertension.

Although we found no relation between the presence of a PFO and any functional parameter, our data do not exclude the possibility that PFO may be relevant through the mechanism of paradoxical embolus; indeed, we believe further studies should be undertaken to address this question. Our data show that right-to-left shunting, in patients with PFO, rises with increasing respiratory muscle recruitment. Thromboembolic disease occurs in up to 25% of patients with acute exacerbation of COPD without evidence of acute infection (42, 43) and there is recognized to be an increased incidence of myocardial infarction and stroke in the first week after acute exacerbation of COPD (44). Because this is also a time of increased respiratory muscle recruitment (45, 46) it is conceivable that some of the increased incidence is explained by paradoxical passage

of thrombus from the right side of the circulation, although systemic inflammatory effects also are likely to play a role.

In conclusion, we show that in patients with severe COPD, PFO prevalence is similar in patients with hypoxemia compared with those with higher Pa_{O_2} . Large PFO are more common in patients with COPD than healthy control subjects. Stable patients with COPD with PFO are not disadvantaged and do not perform less well on formal exercise testing despite an observed increased in right-to-left shunting through the PFO. Thus, in severe patients with COPD, we do not presently recommend PFO closure. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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