Respiratory Medicine (2006) **100**, 903–910

respiratoryMEDICINE

# Prevalence and clinical significance of a patent foramen ovale in patients with chronic obstructive pulmonary disease

**Suleyman Savas Hacievliyagil[a,*], Hakan Gunen[a], Feridun M. Kosar[b], Ibrahim Sahin[c], Talat Kilic[a]**

[a]*The Department of Pulmonary Medicine, Turgut Ozal Research Centre, Inonu University, Malatya 44069, Turkey*
[b]*The Department of Cardiology, Turgut Ozal Research Centre, Inonu University, Malatya, Turkey*
[c]*The Department of Internal Medicine, Turgut Ozal Research Centre, Inonu University, Malatya, Turkey*

Received 17 March 2005; accepted 10 August 2005

**KEYWORDS**
Patent foramen ovale;
COPD;
Prevalence;
Clinical significance

**Summary**
*Background:* A patent foramen ovale (PFO) is not widely recognized as a factor contributing to hypoxemia in patients with chronic obstructive pulmonary disease (COPD). We therefore sought to clarify the prevalence and clinical significance of a PFO in patients with COPD, and to analyze the factors related to its occurrence.
*Methods:* This study included 52 consecutive stable patients with COPD and 50 healthy controls. The demographic and clinical features of the study group were noted. To test for a PFO, standard and contrast transthoracic echocardiographic examinations were performed while resting and during the Valsalva maneuver (VM). Patients performed 6-min walking tests (6 MWT), and the distances traveled were measured.
*Results:* During VM, we detected a PFO in 23 COPD patients and 10 healthy controls ($P<0.01$). A PFO was detected while resting in 11 COPD patients, but in none of the controls ($P=0.001$). Comparison of multiple parameters between COPD patients with and without a PFO during VM did not reveal any clinically significant differences. When we compared COPD patients with and without a PFO during resting, however, we found that the former had longer durations of disease, lower $PaO_2$ and $SaO_2$, higher dyspnea scores, shorter distances walked during 6 MWT and higher desaturation rates ($P<0.05$). Logistic regression analysis showed that longer duration of disease, lower $SaO_2$ and higher systolic pulmonary artery pressure were independent predictors of the occurrence of a PFO in resting COPD patients.

*Corresponding author. Tel.: +90 422 3410660x3807; fax: +90 422 3410728.
*E-mail address:* sshacievliyagil@inonu.edu.tr (S.S. Hacievliyagil).

0954-6111/$ - see front matter 
doi:10.1016/j.rmed.2005.08.015

*Conclusions:* The prevalence of a PFO is higher in patients with COPD than in healthy individuals. The presence of a PFO while resting may contribute significantly to the deterioration of arterial oxygenation and performance status. These findings indicate that a PFO may be a principle cause of hypoxemia in patients with COPD.


## Introduction

A patent foramen ovale (PFO) is detected in about 10–35% of normal individuals.[1–6] In most people, functional closure of the foramen ovale occurs just after birth, when the pulmonary vascular pressure decreases with spontaneous breathing movements, and left atrial pressure exceeds right atrial pressure. However, this functional sealing may not be complete in all individuals, and right to left shunting continues to occur during strenuous activities such as singing, yelling, coughing, straining for bowel movements, and performing spirometry. Clinically important consequences of this right to left shunting through a PFO may include cerebrovascular events due to paradoxical embolism[7,8] and severe arterial hemoglobin-oxygen desaturation in hemodynamically unstable patients.[1,6,9] However, the clinical significance of such transient shunting episodes remains controversial because they are of very short duration and their frequency is too low to generate clinical problems in most individuals.

In exceptional situations, the right to left shunting may become continuous, generating physiologic consequences. Individuals with persistent primary or secondary pulmonary hypertension are at increased risk of shunting; however, to date only one published study has directly addressed the prevalence of a PFO in this population.[6] In that study, which was carried out in a relatively small group of patients ($n = 58$), the prevalence rates of PFO in patients with primary and secondary pulmonary hypertension were found to be 25% and 28%, respectively. Chronic obstructive pulmonary disease (COPD) is one of the main causes of secondary pulmonary hypertension. During the advanced stage of COPD, alveolar hypoventilation frequently leads to pulmonary hypertension of varying degrees. However, only a few studies have examined the prevalence and clinical significance of a PFO in patients with COPD. In the studies performed to date, the Valsalva maneuver (VM) has been utilized as the standard procedure for the detection of a PFO. Using this procedure, Soliman et al. found the prevalence of a PFO to be higher in COPD patients than in normal subjects (70% versus 35%).[9] However, clinicians have not been able to determine the significance of a PFO in these patient populations, making it difficult to determine the clinical importance of its treatment.

We therefore sought to clarify the prevalence and clinical significance of a PFO in patients with stable COPD. We measured the effect of a PFO on arterial oxygenation and analyzed the correlation of several clinical parameters with the presence of a PFO. In addition to determining the incidence of a PFO in response to VM, we also measured the incidence of a PFO in patients during normal breathing and exercise testing.

## Patients and methods

The study was performed at the Turgut Ozal Research Center of Inonu University, Malatya, Turkey. The study protocol was approved by the ethics committee of the center, and informed written consent was obtained from all subjects prior to entry into the study. We prospectively enrolled 74 consecutive patients with stable COPD who had been admitted to our center's outpatient clinics for their scheduled visits for COPD, most on a 3–6 month basis. Diagnosis of COPD was made according to the criteria set by the American Thoracic Society (ATS).[10] Patients were excluded from the study if they had had an acute attack within 1 month prior to enrollment, or if they had been diagnosed with primary or secondary cardiac disorders not related to COPD that could affect arterial oxygenation or cause right to left shunting. Subjects not enrolled or excluded after enrollment included those with hypoventilation syndromes (obstructive sleep apnea syndrome, or obesity-hypoventilation syndrome or primary hypoventilation) or primary or secondary cardiac or pulmonary diseases, based on their medical histories, past medical records and results of a detailed physical examination.

As a control group, we enrolled 50 healthy subjects over 40 years of age. These control subjects were recruited from patients admitted to the outpatient clinics of the cardiology department of our center due to suspicious cardiological symptoms, but who were diagnosed as normal after detailed examination.

Complete medical histories were recorded for all patients, including age, disease duration, and smoking load (pack-years). Clinical examinations included detailed hemograms, and biochemical, spirometric and arterial blood gas analysis. Disease duration was measured from the date of first visit to a doctor for chronic cough, dyspnea or sputum production. This information was obtained by reviewing personal and official medical documents and by asking the patients multiple cross questions. Severity of dyspnea was assessed according to the Modified Medical Research Council (MMRC) scale, which ranged from 0 (not being troubled by shortness of breath except with strenuous exercise) to 5 (being too breathless to leave the house or breathless when dressing or undressing).[11]

## Study protocol

(1) After noting age and disease duration, we took standard PA chest films for all patients and controls. Patients with results that were not normal for COPD, including those with hyperinflation, increased radiolucency, diaphragmatic flattening, and increased diameter of pulmonary arteries, were excluded from the study.
(2) A spirometric examination was performed on all patients, according to standard ATS procedures,[12] using a Vmax 20c spirometer (SensorMedics Corp., Yorba Linda, CA, USA).
(3) Arterial blood gas analysis was performed in all patients while they were breathing room air at rest.
(4) All patients and controls underwent detailed transthoracic color flow and pulsed Doppler echocardiographic examination, with and without injection of agitated physiologic saline as contrast material. The same cardiologist performed all the transthoracic echocardiography (TTE) examinations, and all measurements were performed using the same machine and its related equipment (ATLHDI 5000 CV, Mechatronics, Seattle, WA, USA). The peak velocity of tricuspid regurgitant flow was recorded, and the systolic pulmonary artery pressure ($PAP_S$) was measured using the modified Bernoulli equation, as described previously.[13] The contrast echocardiograpic examination was performed to assess flow patterns across the foramen ovale. Boluses of agitated physiologic saline were rapidly infused into the right antecubital vein, until the images of these echogenic microbubbles were clearly visualized in the right atrium. A PFO was deemed to be present if the microbubbles clearly traversed the interatrial septum from right to left, or if six or more microbubbles were detected in the left atrium within three cardiac cycles after total opacification of the right atrium. This procedure was repeated several times, both during normal breathing and VM. Interatrial septal defects were differentiated by both color and spectral Doppler. Only data from patients with good to excellent echocardiographic images were assessed further. These patients were monitored by finger pulse oxymetry during echocardiography, and changes in hemoglobin oxygen saturation during VM were noted. The echocardiographic technique used and its reliability are described in detail elsewhere.[14,15]
(5) A standard 6-min walking test (6 MWT) in a 50 m long corridor was performed in all patients, and the distance walked by each patient was measured.

## Statistical analysis

All variables were reported as mean $\pm$ SD. The $\chi^2$ test was used to compare differences in PFO prevalence between patients with COPD and normal controls. These differences were calculated during both normal breathing and VM. The patients with COPD were subsequently divided into three groups: those without a PFO (Group I), those with a PFO only during VM (Group II), and those with a PFO during normal breathing (Group III). Demographic and clinical data obtained from spirometric examination, echocardiographic evaluation and 6 MWT were compared among these three groups. Subsequently, Groups I and II were combined and compared with Group III, and Groups II and III were combined and compared with Group I. To determine the independent parameters predicting a PFO, we used the Mann–Whitney *U* test. Sensitivity and specificity analysis for predicting a PFO was performed for all statistically significant parameters using the ROC curve method.

To better analyze the relationship between multiple variables and the occurrence of a PFO, we used the logistic regression method, with the presence or absence of a PFO as the dependent variable. Two types of model were used for this analysis. In the first, we analyzed the effect of independent variables on the occurrence of all PFO cases (29 patients in Group I versus 23 in Groups II plus III). In the second model, we analyzed the effect of independent variables on the occurrence of a PFO during normal breathing (41 patients in Groups I plus II versus 11 in Group III). Both models

included the same independent variables (age, duration of the disease, cigarette load, $PaO_2$, $SaO_2$, $FEV_1$ and $PAP_S$). A *P*-value of less than 0.05 was considered statistically significant.

## Results

Of the starting cohort of 74 patients, 52 (47 males, 5 females) completed the study. The data from the other 22 patients were not assessed further due to poor echogenicity during TTE. No patients or control subjects were removed from the study on the basis of results of PA chest films and spirometric measurements. In the control group, the TTE findings were evaluated as normal. Table 1 lists the general characteristics of the patients with COPD.

A PFO was detected in 23 COPD patients (44%) and 10 controls (20%) during VM ($P = 0.009$). Of the former, 11 patients also had a PFO during normal breathing, compared with none of the control subjects ($P = 0.001$). Table 2 lists the general characteristics and the comparison results of the patients in Groups I–III. No significant differences were observed between Groups I and II with respect to the relevant parameters, except for desaturation rate during VM ($P = 0.001$). Differences between Groups I and III were statistically significant for parameters such as disease duration ($P = 0.007$), $PaO_2$ ($P = 0.006$), $SaO_2$ ($P = 0.002$), MMRC scale ($P = 0.043$), $PAP_S$ ($P = 0.008$), distance traveled during 6 MWT ($p = 0.012$) and desaturation rate during VM ($P < 0.001$). Differences between Groups II and III were statistically significant for parameters such as disease duration ($P = 0.036$), $SaO_2$ ($P = 0.012$), MMRC scale ($P = 0.005$), distance traveled during 6 MWT ($P = 0.028$), and desaturation rate during VM ($P = 0.001$).

**Table 1** The general characteristics of the patients.

| Characteristics | Total ($n = 52$) |
|---|---|
| Age (year) | 65.6±8.8 |
| Disease duration (year) | 11.6±7.1 |
| Cigarette load (pack-years) | 46.3±28.9 |
| pH | 7.46±0.04 |
| $PaO_2$ (mmHg) | 59.8±11.8 |
| $PaCO_2$ (mmHg) | 43.5±9.6 |
| $SaO_2$ (%) | 89.9±6.4 |
| FVC (%predicted) | 72.7±20.2 |
| $FEV_1$ (%predicted) | 44.7±13.4 |
| $FEV_1$/FVC | 49.8±13.5 |
| MMRC dyspnea scale | 2.94±0.94 |
| Hematocrit (%) | 47.6±6.5 |
| Albumin (g/dL) | 3.6±0.5 |
| BMI ($kg/m^2$) | 22.8±3.9 |
| $PAP_S$ (mmHg) | 51.4±18.9 |
| 6 MWT (m) | 354±154 |
| Desaturation rates during valsalva maneuver | −0.94±1.35 |

MMRC: Modified Medical Research Council.

When we compared Group I with the rest of the patients, we observed significant differences in the variances of $PaO_2$ ($P = 0.016$) and $SaO_2$ ($P = 0.041$), and in the desaturation rate during VM ($P < 0.001$) (Table 3). Similarly, when we compared Group III with the rest of the patients, we observed statistically significant differences in disease duration ($P = 0.006$), $PaO_2$ ($P = 0.012$), $SaO_2$ ($P = 0.001$), MMRC scale ($P = 0.015$), $PAP_S$ ($P = 0.01$), distance traveled during 6 MWT ($P = 0.008$) and desaturation rate during VM ($P < 0.001$). Lower resting hemoglobin-oxygen saturation, except for the comparison between Groups I and II, and higher desaturation rates during VM revealed statistically significant results in all comparisons. None of these statistically significant parameters, however, yielded clinically important sensitivity and specificity values that would predict a PFO on the ROC curve method.

When we used logistic regression analysis to determine the important factors associated with the occurrence of a PFO, both during normal breathing and VM, we found that age, duration of disease, cigarette load, $PaO_2$, $SaO_2$, $FEV_1$ and $PAP_S$ did not show a significant association with occurrence of a PFO (Table 4). According to this model, the negative predictive power was 82.8% and the positive predictive power was 69.6%, whereas the overall predictive power was 76.9%. Using the same method of analysis to determine the factors associated with the occurrence of a PFO only during normal breathing ($n = 11$) showed that this condition was associated with disease duration ($P = 0.032$), $SaO_2$ ($P = 0.034$) and $PAP_S$ ($P = 0.034$) (Table 5). Thus, the negative predictive power of this model was 95.1% and the positive predictive power was 72.7%, whereas the overall predictive power was 90.4%.

## Discussion

In this study, we sought to determine the prevalence and clinical significance of a PFO in patients with COPD. Our results strongly support previous findings that the prevalence of a PFO

**Table 2** The comparison of the patients in Groups I–III.

| Characteristics | COPD patients without PFO (Group I) ($n = 29$) | COPD patients with PFO only during valsalva maneuver (Group II) ($n = 12$) | COPD patients with PFO during resting (Group III) ($n = 11$) |
|---|---|---|---|
| Age (year) | 65.6±8.5 | 65.3±10.2 | 66.1±9.0 |
| Disease duration (year) | **10.3±5.9$^{\#}$** | **11.2±10.0*** | **15.4±5.4$^{*,\#}$** |
| Cigarette load (pack-years) | 44.8±29.8 | 51.4±29.2 | 44.7±28.6 |
| pH | 7.46±0.05 | 7.46±0.04 | 7.45±0.05 |
| $PaO_2$ (mmHg) | **63.3±11.5$^{\#}$** | 59.2±11.7 | **51.1±8.6$^{\#}$** |
| $PaCO_2$ (mmHg) | 43.9±10.2 | 40.4±6.9 | 45.9±10.5 |
| $SaO_2$ (%) | **91.7±5.6$^{\#}$** | **91.1±6.1$^{\#}$** | **84.1±6.0$^{\#,\#}$** |
| FVC (%predicted) | 70.4±21.3 | 78.3±18.7 | 72.7±19.2 |
| $FEV_1$ (%predicted) | 45.5±14.8 | 46.3±13.9 | 41.0±8.9 |
| $FEV_1/FVC$ | 52.5±15.0 | 46.3±9.9 | 46.5±12.0 |
| MMRC dyspnea scale | **2.86±0.99*** | **2.58±0.79$^{\#}$** | **3.55±0.68$^{*,\#}$** |
| Hematocrit (%) | 46.7±7.2 | 48.7±5.9 | 49.1±5.4 |
| Albumin (g/dL) | 3.6±0.4 | 3.6±0.5 | 3.6±0.9 |
| BMI ($kg/m^2$) | 22.4±3.5 | 24.3±4.8 | 21.9±3.7 |
| $PAP_S$ (mmHg) | **46.6±13.8$^{\#}$** | 51.5±18.9 | **64.2±25.5$^{\#}$** |
| 6 MWT (m) | **386±156$^{\#}$** | **378±139*** | **246±127$^{\#,*}$** |
| Desaturation rates during valsalva maneuver | **−0.14±0.52$^{\#,\beta}$** | **−1.1±1.0$^{\#,\#}$** | **−2.91±1.14$^{\beta,\#}$** |

COPD: Chronic Obstructive Pulmonary Disease.
PFO: Patent Foramen Ovale.
MMRC: Modified Medical Research Council.
*$0.01 \leqslant P < 0.05$; $^{\#}0.001 \leqslant P < 0.01$; $^{\beta}P < 0.001$.

during VM is significantly greater in COPD patients than in normal subjects. In contrast to previous findings, however, we observed that about 20% of COPD patients with a PFO suffer from right to left shunting even at rest, and the negative impact of this condition on exercise capacity is clinically significant in this subgroup. The occurrence of a PFO while resting was related to disease duration, arterial oxygen content, and $PAP_S$. In contrast, we found no correlation between the presence of a PFO only during VM and any of the demographic and clinical parameters, indicating that the presence a PFO solely during VM does not have clinical significance.

Hypoxemia in COPD is related to multiple factors, among the most important of which are disturbances in ventilation–perfusion ratio, decreased diffusing capacity, increased dead space, and respiratory muscle fatigue.[16] Other factors include deterioration of performance status, increased closing volume, fibrosis, loss of alveolar capillary bed and genetic variations in the ventilatory drive.[16] It is well known that hypoxemia in patients with COPD is due to a combination of factors rather than a single factor. A clinically important hypoxemic state ($PaO_2 \leqslant 60$ mmHg) has been found to develop during the advanced stages of COPD, and in COPD patients with $FEV_1$ less than 50% of the predicted value.[16,17] Right to left shunting through the foramen ovale is not recognized as contributing to hypoxemia in COPD. Although the prevalence of a PFO during VM has been reported for a group of patients with severe COPD, that study did not determine right to left shunting during resting, nor did it address the clinical importance of a PFO.[9] The foramen ovale permits the passage of blood from right to left in some normal individuals, and the same should be true for patients with COPD. Although the clinical impact of this shunting is negligible in normal individuals, this is probably not the case in all COPD patients. Our results suggest that assessing individuals for the presence of a PFO only during strenuous effort gives misleading information, and does not completely reflect its clinical effects. The most important subgroup of patients in whom a PFO has some clinical significance is those who are shunt positive both during VM and while resting. The assessment of MMRC scales and response to 6 MWT in COPD patients exhibiting shunting only during VM was similar to that of COPD patients without shunting. The desaturation rate during VM was found to be higher

**Table 3** The comparison analysis of different combinations of the patients in Group I–III.

| Characteristics | COPD patients without PFO (Group I) ($n = 29$) | All patients with PFO (Group II and Group III) ($n = 23$) | COPD patients without PFO and with PFO only during Valsalva maneuver (Groups I and II) ($n = 41$) | COPD patients with PFO during resting (Group III) ($n = 11$) |
|---|---|---|---|---|
| Age (year) | 65.6±8.5 | 65.7±9.4 | 65.5±8.9 | 66.1±9.0 |
| Disease duration (year) | 10.3±5.9 | 13.2±8.2 | **10.6±7.2** | **15.4±5.4**$^{\#}$ |
| Cigarette smoking (pack-years) | 44.8±29.8 | 48.2±28.5 | 46.7±29.4 | 44.7±28.6 |
| pH | 7.46±0.05 | 7.46±0.04 | 7.46±0.04 | 7.45±0.05 |
| $PaO_2$ (mmHg) | **63.3±11.5** | **55.3±10.9*** | **62.1±11.6** | **51.1±8.6**$^{\#}$ |
| $PaCO_2$ (mmHg) | 43.9±10.2 | 43.0±9.0 | 42.9±9.4 | 45.9±10.5 |
| $SaO_2$ (%) | **91.7±5.6** | **87.7±6.9*** | **91.5±5.7** | **84.1±6.0**$^{\#}$ |
| FVC (%predicted) | 70.4±21.3 | 75.7±18.7 | 72.7±20.7 | 72.7±19.2 |
| $FEV_1$ (%predicted) | 45.5±14.8 | 43.7±11.8 | 45.7±14.3 | 41.0±8.9 |
| $FEV_1/FVC$ | 52.5±15.0 | 46.4±10.7 | 50.7±13.9 | 46.5±12.0 |
| MMRC dyspnea scale | 2.86±0.99 | 3.04±0.88 | **2.78±0.93** | **3.55±0.68*** |
| Hematocrit (%) | 46.7±7.2 | 48.9±5.5 | 47.3±6.8 | 49.1±5.4 |
| Albumin (g/dL) | 3.6±0.4 | 3.6±0.7 | 3.6±0.4 | 3.6±0.9 |
| BMI ($kg/m^2$) | 22.4±3.5 | 23.1±4.3 | 23.0±3.9 | 21.9±3.7 |
| $PAP_S$ (mmHg) | 46.6±13.8 | 57.6±22.7 | **48.0±15.4** | **64.2±25.5**$^{\#}$ |
| 6 MWT (meters) | 386±156 | 315±147 | **384±149** | **246±127**$^{\#}$ |
| Desaturation rates during valsalva maneuver | **−0.14±0.52** | **−1.96±1.4**$^{\beta}$ | **−0.41±0.81** | **−2.91±1.14**$^{\beta}$ |

COPD: Chronic Obstructive Pulmonary Disease.
PFO: Patent Foramen Ovale.
MMRC: Modified Medical Research Council.
$^{*}$ $0.01 \leqslant P < 0.05$; $^{\#}0.001 \leqslant P < 0.01$; $^{\beta}P < 0.001$

**Table 4** The results of logistic regression analysis for the relationship of all PFO cases with independent variables.

| Variables | *B* | Exp (*B*) | %95 CI | *P* |
|---|---|---|---|---|
| Age (year) | −0.006 | 0.994 | 0.914–1.080 | 0.881 |
| Disease duration (year) | 0.050 | 1.045 | 0.956–1.142 | 0.332 |
| Cigarette smoking (pack-years) | 0.009 | 1.010 | 0.986–1.034 | 0.434 |
| $PaO_2$ (mmHg) | −0.035 | 0.965 | 0.893–1.044 | 0.380 |
| $SaO_2$ (%) | −0.052 | 0.949 | 0.832–1.082 | 0.435 |
| $FEV_1$ (%predicted) | −0.011 | 0.989 | 0.938–1.043 | 0.685 |
| PAPs (mmHg) | 0.038 | 1.039 | 0.993–1.087 | 0.101 |
| Constant | 4.501 | | | |

PFO: Patent Foramen Ovale.

in the former group (Group II). However, since the difference between the mean desaturation rates of Groups I and II was less than 1%, this difference was evaluated as an expected physiologic finding of no consequence.

Longer duration of disease showed the highest statistical significance among the factors that could influence the occurrence of a PFO at rest. This is reasonable, because exposure to alveolar hypoventilation for longer periods of time may lead to higher pulmonary artery pressures, resulting in permanent functional opening of the foramen ovale. COPD patients with a PFO both during VM and while at rest had higher MMRC scales, higher

**Table 5** The results of logistic regression analysis for the relationship of PFO cases during resting with independent variables.

| Variables | *B* | Exp (*B*) | %95 CI | *P* |
|---|---|---|---|---|
| Age (year) | 0.120 | 1.127 | 0.906–1.402 | 0.284 |
| Disease duration (year) | 0.186 | 1.205 | 1.016–1.428 | **0.032** |
| Cigarette smoking (pack-years) | 0.039 | 1.040 | 0.995–1.087 | 0.085 |
| $PaO_2$ (mmHg) | −0.024 | 0.976 | 0.862–1.106 | 0.709 |
| $SaO_2$ (%) | −0.484 | 0.616 | 0.391–0.971 | **0.034** |
| $FEV_1$ (%predicted) | −0.228 | 0.796 | 0.598–1.059 | 0.118 |
| $PAP_S$ (mmHg) | 0.114 | 1.121 | 1.009–1.245 | **0.034** |
| Constant | 33.085 | | | |

PFO: Patent Foramen Ovale.

desaturation rates during VM, and walked shorter distances during 6 MWT, when compared with patients with a PFO only during VM. Similar results were obtained when COPD patients with a PFO both during VM and while at rest were compared with COPD patients without a PFO under all conditions.

When we combined Groups I and II, we found that the average desaturation rate in this combined group was 2.5% less than that in Group III. Similarly, the average MMRC scale was 0.77 point lower for the combined group than for Group III. The 6 MWT is a standard method for measuring the performance status of patients with COPD and for monitoring the progression of the disease.[18,19] In addition, the 6 MWT results of COPD patients correlate well with disease severity. Although the mean age and the staging of the disease according to $FEV_1$ did not differ between the Group III patients and the other patients, the former walked 140 and 132 m less than the patients in Groups I and II, respectively. This was important, because the similarity of these 2 key parameters (mean age and the staging of the disease) in all groups made the results of the comparisons more powerful and the differences more meaningful. The results obtained by comparing Group III with all other patients (Groups I and II combined) were the same as for the comparisons between Group III and Groups I and II individually.

To our knowledge, this study is first to show that a PFO has clinical significance in COPD patients, as well as being the first to show differences between having a PFO at rest and having a PFO only during VM. In particular, the present results indicate that a PFO has clinically important consequences in 20% of patients with COPD, with regard to arterial oxygen content and performance status.

The models we developed to determine the relationship between multiple independent variables and either all PFO cases (Groups II and III) or only those with a PFO at rest (Group III) gave good overall predictive power (76.9% and 90.4%, respectively). It is clear that the superior overall predictive power of the second model is more important clinically. We also found that the negative predictive powers of both models were stronger than the positive predictive values. None of the variables included in the first model, however, reached statistical significance. This was likely a consequence of combining Groups II and III. Specifically, the results of Group II were similar to those of Group I, and hence mixing the Group II and III data may have interfered with the model. In previous studies, patients were tested for a PFO only during VM. This may be why previous investigators reported no clinical impact of a PFO. In the second model, we combined Groups I and II, which appeared to overcome the deficiencies of the first model. The second model revealed several factors related to the occurrence of a PFO, including disease duration, $SaO_2$ and $PAP_S$.

A PFO has been suggested to protect patients with pulmonary hypertension against further elevation of pulmonary artery pressure and against further deterioration of cardiac function.[20] However, this finding could not be confirmed, and no difference in survival was observed between patients with and without pulmonary hypertension.[9,21,22] A PFO may contribute to the deterioration of arterial oxygen content by further increasing pulmonary artery pressure, which will increase the right to left shunting of deoxygenated blood. As a result of this vicious circle, the progression of the disease will be accelerated. We found that $PAP_S$ was significantly different between Groups I and III, and between Groups I plus II and Group III. Although the mean $PAP_S$ values were similar in Groups II and III, exercise capacity was significantly lower in Group III. This condition suggests a limited role of pulmonary artery pressure in reducing exercise capacity. Regardless of

the initial arterial oxygen saturation and $PAP_S$, the desaturation rate was significantly higher during VM in COPD patients with a permanent PFO (Group III). This may be regarded as direct evidence for the negative contribution of a PFO to pulmonary mechanics and exercise capacity. These findings, however, do not necessarily mean that increased pulmonary artery pressure has no influence on the permanent patency of the foramen ovale, but rather that the relationship is somewhat nonlinear.

One possible criticism of our study is that we used TTE rather than transesophageal echocardiography (TEE), the method favored by most investigators due to its better echogenicity. However, the new generation of echocardiography machines and their related equipment has much better resolution and echogenicity than older machines. A meta-analysis revealed only a slight difference between TTE and TEE in regard to their ability to detect a PFO (9.3% versus 11.2%, respectively).[23] In addition, we only included patients with good to excellent echogenicity on TTE in our study, excluding data from 22 patients with unsatisfactory images. Thus, we do not believe that our use of TTE had any significant influence on our results.

In conclusion, we have shown here that a PFO, if present during resting, may contribute significantly to arterial deoxygenation and has a negative effect on performance status of patients with COPD. Our findings indicate that detection of a PFO only during strenuous exercise may be insufficient to identify truly affected patients, and that a PFO should also be demonstrated during resting periods. Our results suggest that a PFO may be one of the main factors contributing to hypoxemia in patients with COPD, and that hypoxemic patients should be tested for it.

## References


1. Shanoudy H, Soliman A, Raggi P, et al. Prevalence of patient foramen ovale and its contrubition to hypoxemia in patients with obstructive sleep apnea. *Chest* 1998;**113**:91–6.
2. Hagen PT, Scholz DG, Edwars WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc* 1984; **59**:17–20.
3. Movsowitz C, Podolsky LA, Meyerowitz CB, et al. Patent foramen ovale: a nonfunctional embryological remnant or a potential cause of significant pathology? *J Am Soc Echocardiogr* 1992;**5**:259–70.
4. Lynch JJ, Schuchard GH, Gross CM, et al. Prevalence of right to left atrial shunting in a healthy population: detection by Valsalva maneuver contrast echocardiography. *Am J Cardiol* 1984;**53**:1478–80.
5. Sardesi SH, Marshall RJ, Mourant AJ. Paradoxical systemic embolization through a patent foramen ovale. *Lancet* 1989;**1**:732–3.
6. Nootens MT, Berarducci LA, Kaufmann E, et al. The prevalence and significance of a patent foramen ovale in pulmonary hypertension. *Chest* 1993;**104**:1673–5.
7. Arquizan C, Coste J, Touboul PJ, Mas JL. Is patent foramen ovale a family trait? A Transcranial Doppler sonographic study. *Stroke* 2001;**32**:1563–6.
8. Schuchlenz H, Weihs W, Beitzke A, et al. Transesophageal echocardiography for quantifying size of patent foramen ovale in patients with cryptogenic cerebrovascular events. *Stroke* 2002;**33**:293–6.
9. Soliman A, Shanoudy H, Liu J, et al. Increased prevalence of patent foramen ovale in patients with severe chronic obstructive pulmonary disease. *J Am Soc Echocardiogr* 1999;**12**:99–105.
10. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1995;**152**:S77–S121.
11. Sahebjami H, Sathianpitayakul E. Influence of body weight on the severity of dyspnea in COPD. *Am J Respir Crit Care Med* 2000;**161**:886–90.
12. ATS Statement. Standardization of spirometry—1994 update. *Am J Respir Crit Care Med* 1995;**152**:1107–36.
13. Battle R, Davitt MA, Cooper SM, et al. Prevalence of pulmonary hypertension in limited and diffuse scleroderma. *Chest* 1996;**110**:1515–9.
14. Lynch JJ, Schuchard GH, Gross CM, et al. Prevalence of right to left shunting in a healthy population: detection by Valsalva maneuver and contrast echocardiography. *Am J Cardiol* 1984;**53**:1478–80.
15. Mulvagh SL, DeMaria AN, Feinstein SB, et al. Contrast echocardiography: current and future applications. *J Am Soc Echocardiogr* 2000;**13**:331–42.
16. Gunen H, Kosar F. Spirometric predictors for the exclusion of severe hypoxemia in chronic obstructive pulmonary disease. *Can Respir J* 2001;**8**:245–9.
17. Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO global initiative for chronic obstructive lung disease (GOLD) workshop summary. *Am J Respir Crit Care Med* 2001;**163**:1256–76.
18. Marin JM, Carrizo SJ, Gascon M, et al. Inspiratory capacity, dynamic hyperinflation, breathlessness, and exercise performance during 6-min-walk test in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**163**: 1395–9.
19. Mak VHF, Bugler JR, Roberts CM, Spiro SG. Effect of arterial oxygen desaturation on six minute walk distance, perceived effort, and perceived breathlessness in patients with airflow limitation. *Thorax* 1993;**48**:33–8.
20. Rozkovec A, Montanes P, Oakley C. Factors that influence the outcome of primary pulmonary hypertension. *Br Hearth J* 1986;**55**:449–58.
21. Okubo S, Naito M, Nakanishi N, et al. Prognosis of primary pulmonary hypertension and its determinants. *J Cardiol* 1988;**18**:1097–107.
22. Glanville AR, Burke CM, Theodore J, Robin ED. Primary pulmonary hypertension: length of survival in patients referred for hearth-lung transplantation. *Chest* 1987;**91**: 675–81.
23. Fisher DC, Fisher EA, Budd JH, et al. The incidence of patent foramen ovale in 1000 consecutive patients. A contrast transesophageal echocardiography study. *Chest* 1995;**107**: 1504–9.