

## EFFECTS OF OXYGEN ON EXERCISE-INDUCED INCREASE OF PULMONARY ARTERIAL PRESSURE IN IDIOPATHIC PULMONARY FIBROSIS

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**ABSTRACT.** *Introduction:* Idiopathic pulmonary fibrosis (IPF) is a severe disease with no known effective therapy. Patients with IPF may develop severe increase of pulmonary arterial pressure (PAP) on exercise, the mechanisms of which is not clearly identified. *Objectives:* To determine whether oxygen may correct the increase of PAP developed during exercise in patients with IPF. *Patients and methods:* We performed a prospective study on patients with IPF and no hypoxaemia at rest. The absence of pulmonary hypertension (PH) at rest was confirmed by echocardiography (systolic PAP <35 mmHg). Eight patients underwent echocardiography during exercise in air and with oxygen (to maintain saturation of at least 94%). Right ventricle-right atrium gradient and cardiac output were measured at rest, after each increment and at peak. We then compared the echocardiographic results obtained for air and oxygen. *Results:* All patients developed significant increase of SPAP on exercise ( $73 \pm 14$  mmHg in air). Oxygen did not significantly improve SPAP on exercise (SPAP:  $76 \pm 15$  mmHg). Echocardiographic characteristics were similar between air and oxygen except for exercise tolerance in term of workload ( $p=0.045$ ) and endurance ( $p=0.017$ ). Resting pulmonary function tests did not predict the occurrence of increase of PAP on exercise. *Conclusion:* Our results demonstrate that oxygen does not improve exercise-induced increase of PAP in patients with IPF and support the hypothesis that hypoxic vaso-constriction is not the main mechanism of acute increase of PAP during exercise. (*Sarcoidosis Vasc Diffuse Lung Dis* 2008; 25: 133-139)

**KEY WORDS:** idiopathic pulmonary fibrosis, pulmonary hypertension, exercise, oxygen, echocardiography

### INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a rare disease with a poor prognosis; the median survival of three years after diagnosis is due in part to the absence of any effective treatment. The aetiology of

this disease remains unknown involving complex but yet only incompletely elucidated pathophysiological mechanisms although alveolar epithelial cell injury, dysregulation of fibroblasts vascular injury and aberrant angiogenesis related to vascular remodeling appear as key elements (1).

Pulmonary hypertension (PH) has been described in IPF for different level of severity in patients referred for lung transplantation. Several studies recently reported its prevalence in IPF (3-6) and have shown that exercise induced PH may be particularly detected in IPF patients with a forced vital capacity (FVC) between 50 and 80%, despite a normal resting pulmonary arterial pressure (PAP). It has been proposed that hypoxic vasoconstriction may

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contribute to exercise-induced pulmonary hypertension. Weitzenblum *et al.*, previously reported the increase in mean PAP on exercise, accompanied by a decrease in PaO<sub>2</sub>, in various interstitial lung diseases but did not demonstrate that increase PAP was due to hypoxemia (7). So, the precise mechanism underlying the development of increased SPAP during exercise remains unclear.

Trans-thoracic echocardiography coupled with Doppler, is a non-invasive technique which enables estimation of systolic PAP (SPAP) primarily through flow analyses of tricuspid regurgitation (TR) (8). Measurements of pulmonary acceleration time lower than 90 ms have been shown to provide appropriate evidence of pulmonary hypertension (8) while the right ventricle-right atrium (RV-RA) gradient on continuous Doppler scans by analysis TR flow, subaortic time-velocity integral of flow (subaortic VTI) and inferior vena cava (IVC) collapsibility may be used to estimate RA pressure.

The aim of this study was therefore to examine whether oxygen supplementation during exercise would affect the exercise-induced increase in PAP in IPF using resting and exercise trans-thoracic echocardiography. We hypothesized that in patients with normal PAP at rest, oxygen supplementation would cause a significant decrease in the exercise-induced increase in the SPAP.

## METHODS AND MATERIALS

The inclusion criterion was idiopathic pulmonary fibrosis, as described in the American Thoracic Society/European Respiratory Society consensus definition for IPF (9). Eleven patients were included in this prospective study. Informed consent was obtained from all patients and the protocol was approved by local ethical committee. At time of inclusion, patients were on moderate-dose oral corticosteroid treatment (n=4) and/or subcutaneous interferon- $\gamma$  treatment (n=6). One patient received no treatment.

The exclusion criteria were hypoxaemia (PaO<sub>2</sub> < 70 mmHg) or PH (SPAP > 35 mmHg) at rest, left ventricular systolic dysfunction at rest (LVEF $\leq$ 45%) and non-analysable regurgitation tricuspid flow. Thus 3 of the 11 IPF patients were excluded from the study: One had PH at rest (SPAP: 50 mmHg),

one had ischaemic cardiopathy with left ventricular dysfunction and third had no regurgitation tricuspid flow for analysis during exercise.

### *Pulmonary function tests and baseline characteristics*

All patients underwent evaluation of respiratory function at rest, including lung volume measurements using plethysmography, determination of expiratory flow and lung diffusion capacity (DLCO) (*Jaeger-Masterlab*<sup>®</sup> plethysmograph). Reference values used were those of the Official Statement of the European Respiratory Society (10, 11). Resting arterial blood samples were taken for determination of arterial gas partial pressures and patients completed a six-minute walking test with determination of resting oxygen saturation and lowest saturation during the walk using digital oxymetry (Respironics, Carlsbad, CA).

### Determination of oxygen supplementation requirement

On the same day the patients were submitted to an incremental peak exercise test on cycle ergometer with continuous determination of SaO<sub>2</sub>, to determine the oxygen flow required to maintain SaO<sub>2</sub> > 94% during exercise. The exercise protocol initiated during ambient air breathing was started at 25 watts, with 20-watt increments every two minutes until SaO<sub>2</sub> values 94% or less started appearing. As soon as oxygen saturation had decreased, oxygen was administered via a face mask. Flow rate was adjusted to ensure that oxygen saturation remained at or above 94% throughout the examination. In such conditions oxygen flow was 5  $\pm$  2 l/min. Exercise was stopped upon appearance of symptoms of dyspnea or voluntary exhaustion.

### *Transthoracic echocardiography and cardiac Doppler at rest and during exercise*

A transthoracic echocardiography was performed at rest, with the patient lying on the left side. Resting measurements included left ventricular diameter and volume as well as left ventricular ejection fraction using the biplane Simpson method. Characteristics of the right ventricle (RV) were also assessed namely, the RV end-diastolic diameter and

shortening fraction, tricuspid annular plane systolic excursion (TAPSE), and tricuspid S-waves on Doppler tissue imaging also provided an appreciation of the RV systolic function. We also analysed pulmonary acceleration time, the right ventricle-right atrium (RV-RA) gradient on continuous Doppler scans by analysis TR flow, subaortic time-velocity integral of flow (subaortic VTI) and inferior vena cava (IVC) collapsibility to estimate pressure in the RA.

Echocardiography was carried out during an incremental exercise test, with a workload beginning at 25 watts and increasing by 20 watts every two minutes. We stopped exercise for symptoms (dyspnea or exhaustion). During the last minute of each incremental stage, measurements were performed. In addition, VTI, the diameter (d) of the outflow chamber of the left ventricle (OCLV), and heart rate (HR), was calculated as follows:  $Q_C = (\Pi d^2/4) * VTI * HR$ .

SPAP is considered equal to right ventricular systolic pressure (RVSP) in the absence of pulmonary valve stenosis. Right ventricular systolic pressure, and so SPAP, can be estimated using continuous wave Doppler.

#### Treatment of data

Right ventricle to right atrial (RV-RA) systolic gradient was calculated using the modified Bernoulli equation ( $4V^2$ , V is the velocity of tricuspid regurgitation flow) (8). RVSP was estimated by adding right atrial pressure (RAP) to the RV-RA gradient with RAP being estimated using echocardiographic characteristics of inferior vena cava (12).

For each patient, echocardiographic studies at rest and with exercise were performed by a single sonographer. Learning bias was avoided by carrying out a first exercise test in air and a second test with oxygen for the first four patients and carrying out the tests in reverse order for the last four patients.

#### Statistical analysis

Results are presented as mean  $\pm$  standard deviation. All statistical analysis was carried out with Statview® software. A two-way ANOVA for repeated measures on the last factor was carried out for main effects of exercise intensity and oxygen supple-

mentation on all resting and exercise echocardiographic measurements. Post-hoc analyses were achieved using Wilcoxon tests. Correlations were analysed using Spearman's rank correlation test. Values of  $p < 0.05$  were considered significant.

## RESULTS

### *Clinical and functional characteristics*

Patient characteristics are summarised in table 1. All had moderate ventilatory restriction, with altered DLCO. Resting PaO<sub>2</sub> was normal, but the alveolar-arterial oxygen gradient was slightly increased. Performance on the 6-minute walk test was  $442 \pm 56$  meters ( $81\% \pm 0.07$ ) with a significant decrease in SaO<sub>2</sub> ( $>4\%$ ) from baseline ( $> 96\%$ ).

### *Resting echocardiographic data*

The results are summarised in tables 2 and 3. SPAP and cardiac output were normal at rest. With oxygen supplementation, The basal RV-RA gradient was  $25 \pm 5$  mmHg, so an estimated SPAP of  $30 \pm 5$  mmHg. Cardiac output was not significantly different ( $4.8$  l/min).

**Table 1.** Clinical and functional characteristics

Characteristics	Mean $\pm$ standard deviation
Age (years)	68 $\pm$ 6.9
Sex ratio (M/F)	6 / 2
FEV <sub>1</sub> (%)	70.2 $\pm$ 3.9
FVC (%)	71.9 $\pm$ 9.7
TLC (%)	77.2 $\pm$ 18.0
DLCO (%)	44.1 $\pm$ 7.8
DLCO/AV (%)	75 $\pm$ 16.1
pH	7.41 $\pm$ 0.02
PaO <sub>2</sub> (mmHg)	80.9 $\pm$ 7.4
PaCO <sub>2</sub> (mmHg)	38.4 $\pm$ 7.5
D (A-a)O <sub>2</sub> (mmHg)	21.1 $\pm$ 10
Distance (meters)	442 $\pm$ 56
Resting SaO <sub>2</sub> (%)	96.2 $\pm$ 0.4

FEV<sub>1</sub>: forced expiratory volume in one second

FVC: forced vital capacity

TLC: total lung capacity

DLCO: diffusing capacity of the lung for carbon monoxide

DLCO/AV: diffusing capacity of the lung for CO/alveolar ventilation

PaO<sub>2</sub>: arterial partial pressure of oxygen

PaCO<sub>2</sub>: arterial partial pressure of carbon dioxide

D (A-a)O<sub>2</sub>: alveolar-arterial pressure difference for oxygen

Distance: during the six-minute walk test

SaO<sub>2</sub>: transcutaneous oxygen saturation

**Table 2.** Echocardiographic characteristics at rest

Characteristic	Mean $\pm$ standard deviation
LVEF (%)	57.2 $\pm$ 4.5
RVEDD (mm)	29 $\pm$ 4.1
TDDRV/RDDGV ratio	0.65 $\pm$ 0.08
RV SF (%)	35 $\pm$ 7.4
TAPSE (mm)	21.8 $\pm$ 7.4
S wave DTI (cm/s)	13.9 $\pm$ 4.8
Visual estimation of the RVEF	Abnormal in 50% of patients

LVEF: left ventricular ejection fraction.

RVEDD: Right ventricular end-diastolic diameter

RV SF: Right ventricular shortening fraction

TAPSE: tricuspid annular plane systolic excursion.

S wave DTI: velocity of the S wave on Doppler tissue imaging at the level of tricuspid annulars.

RVEF: right ventricular ejection fraction

### *Exercise performance and echocardiographic data*

The whole results for the eight patients tested are summarised in table 3 and figure 1. In air, at peak exercise, SPAP was high (>45 mmHg) in all patients and cardiac output increased to 8.9 l/min at peak. Only four patients achieved 85 watt workload and no patient achieved 105 watt.

With O<sub>2</sub> supplementation, six patients achieved 85 watt and 3 achieved 105 watt. At peak, the mean RV-RA gradient was 67  $\pm$  15 mmHg, so an estimated SPAP of 76  $\pm$  15 mmHg. Mean cardiac output increased to 10.9 l/min at peak. Heart rate, cardiac output and SPAP increased with increasing power outputs but did not differ significantly between tests with and without oxygen. Indeed, no significant improvement in the RV-RA gradient was observed

with exercise tests plus oxygen versus tests in air (Fig. 1). The difference in cardiac output at peak between tests with and without oxygen was not significant. Because all the 8 patients achieved 65 watt workload both in air and oxygen, we also compared echographic characteristics at 25, 45 and 65 watt: SPAP and Q<sub>c</sub> did not differ between air and oxygen.

By contrast, oxygen allowed a slight but significant improvement in exercise tolerance in terms of workload (p=0.045) and endurance (p=0.017).

Correlation between echocardiographic data and baseline characteristics

The SPAP at peak was not correlated with FEV<sub>1</sub> (r=0.08, p=0.8), FVC (r=0.07, p=0.85), TLC (r=0.32, p=0.44), DLCO (r=0.43, p=0.27), PaO<sub>2</sub> (r=0.62, p=0.09), alveolar-arterial oxygen gradient (r=0.13, p=0.75), distance walked during the six-minute walk test (r=0.51, p=0.19) or the lowest oxygen saturation recorded during the walking test (r=0.22, p=0.6). We also found that SPAP at peak did not correlate with cardiac output at peak (r=0.29, p=0.52).

## DISCUSSION

IPF patients displaying oxygen desaturation during the six minutes walk test also developed increased PAP during exercise. To our knowledge this is the first study demonstrating that oxygen did not significantly improve the RV-RA gradient and pul-

**Table 3.** Echocardiographic results for exercise tests in air (A) and with oxygen (O<sub>2</sub>) at rest and at peak

	Rest		Peak effort	
	Air	O <sub>2</sub>	Air	O <sub>2</sub>
HR (bpm)	78.9 $\pm$ 12.9	77.1 $\pm$ 11.6	116.7 $\pm$ 12.8	121.2 $\pm$ 16.3
SAP (mmHg)	132.9 $\pm$ 9.9	137.8 $\pm$ 17.9	165.9 $\pm$ 15.5	169.6 $\pm$ 24.7
DAP (mmHg)	78.4 $\pm$ 9.1	80.9 $\pm$ 12.6	88.4 $\pm$ 13.2	91.9 $\pm$ 8.0
RV-RA gradient (mmHg)	23 $\pm$ 6	25 $\pm$ 5	61 $\pm$ 16	67 $\pm$ 15
SPAP (mmHg)	28 $\pm$ 6	30 $\pm$ 5	73 $\pm$ 14	76 $\pm$ 15
Cardiac output (l/min)	4.8 $\pm$ 1.5	4.8 $\pm$ 1.6	8.9 $\pm$ 4.5	10.9 $\pm$ 2.8
Exercise duration (min)			6.9 $\pm$ 1	7.8 $\pm$ 1.6 (p=0.017)
Workload (watts)			78	88 (p=0.045)

The values reported are means  $\pm$  standard deviation

HR: heart rate

SAP: systolic arterial pressure

DAP: diastolic arterial pressure

SPAP: systolic pulmonary artery pressure

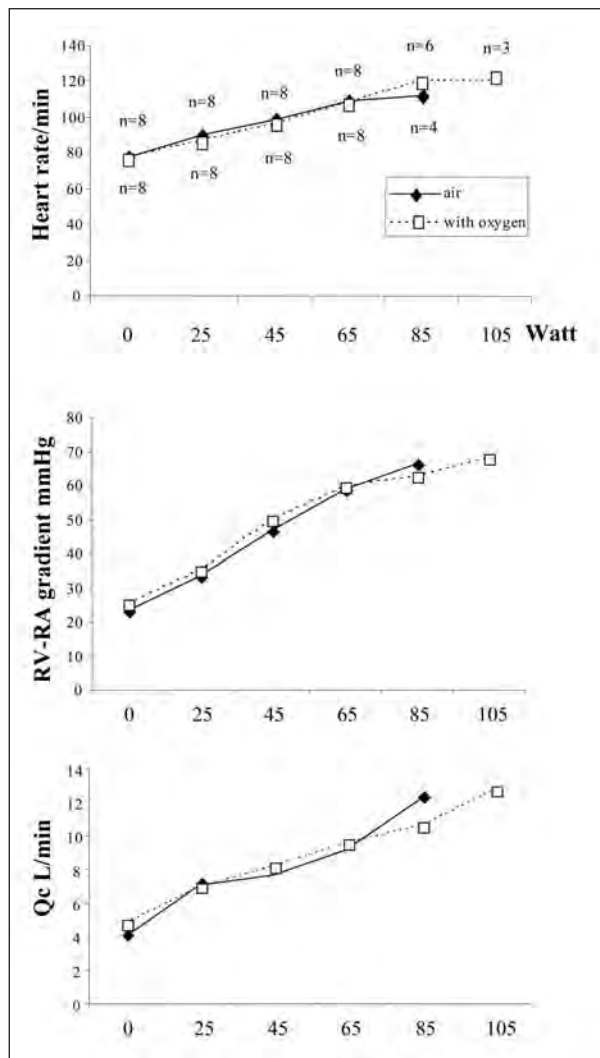


Fig. 1. Heart rate, RV-RA gradient and cardiac output in air and with oxygen. Number of patients is indicated for each increment in workload (n)

monary pressure for successive increments or at peak in IPF patients.

An important limitation of this study could be of relying exclusively on echocardiogram to assess pulmonary artery pressures and changes in pulmonary artery pressure with exercise, especially in patients with advanced lung disease, i.e. the lack of right-heart catheterization to confirm the presence and degree of PH (13). However it was beyond the scope of our study to precisely determine whether or not the patient had PH. While right heart catheter-

ization presents the distinct advantage of providing a direct assessment of pulmonary artery pressure, positioning of a pulmonary artery catheter may affect the patients' dispositions for exercise performance and limit the ability to trigger and capture the exercise-induced increase in SPAP. Clearly the main purpose of our study was to contrast an oxygen supplementation intervention and not to validate the use of a non-invasive technique against right heart catheterization. The SPAP values estimated by echocardiography combined with Doppler scans at rest correlated well with the values measured in patients with a right cardiac catheter (13, 14), even for patients with chronic respiratory failure (15-19). However we must point out that some authors reported various ranges of disagreement between echocardiography and right cardiac catheter which may lead to over- or underestimation of SPAP of as much as  $7.5 \pm 14$  mmHg, with limits of agreement of  $-35$  to  $+20$  mmHg (21, 22).

Care must be taken to align the Doppler beam with the direction of flow or underestimation of the pulmonary artery pressure may result. With these caveats, Doppler echocardiography is a convenient, noninvasive, and relatively accurate tool for evaluating PH (20). So our results showing no beneficial effect of oxygen on SPAP remain valid. In our study, SPAP at peak in air or with oxygen ( $73 \pm 14$  mmHg in air,  $76 \pm 15$  mmHg with oxygen) was much higher than the previously published studies which have reported values from 45 (15, 19) to 54 mmHg (20).

Note, however, that SPAP estimated by echocardiography at rest or with exercise in a semi-supine position is not the same as the SPAP presented by the patient in a standing position. Indeed, in theory, taking hydrostatic pressure into account, a correction of 1 mmHg is required for a vertical displacement of 13.6 cm (23). For echocardiography performed in a semi-supine position with the shoulders displaced 8 to 10 cm from the vertical, the correction required should be less than 1 mmHg. For this reason, we did not make this adjustment to our data.

Exercise leads to the development of increased PAP, decreasing the exercise tolerance of patients with IPF (6). Furthermore, exercise leads to oxygen desaturation, clearly evident in the six-minute walking test (24, 25). The fact that PH with exercise was associated with hypoxaemia in patients with IPF was

previously suggested and investigated by Weitzenblum et al., who observed that the increase in mean pulmonary arterial pressure on exercise was accompanied by a decrease in PaO<sub>2</sub>, without identifying a causal relationship (7). In Weitzenblum's study, the mean PAP measured with right heart catheterization increased from 23.6 mmHg at rest to 45.3 mmHg with exercise, whereas PaO<sub>2</sub> fell from 69.6 mmHg to 56 mmHg. Hypoxic vasoconstriction cannot be ruled out as a contributory factor but the study did not demonstrate that increase PAP was due to hypoxemia. In our study, oxygen administration did not improve SPAP but improved tolerance of exercise. Improved exercise endurance with oxygen has been demonstrated in patients with chronic obstructive pulmonary disease (COPD) and has been attributed to a combination of several factors: decrease in dyspnea alleviation, reduced ventilatory demand and improved operational lung volumes (26).

The initial development of increased PAP only during exercise results from alteration of the pulmonary vascular bed, due in part to the destruction of pulmonary capillaries by fibrotic lesions and to presence of disseminated microthrombi in pulmonary capillaries. A recent study has provided support for this view: increased plasma D-dimer level and beneficial effects on survival of long-term anticoagulant treatment in patients with IPF suggest a state of hypercoagulability (27). In addition, autopsies on several patients who died due to exacerbation of the disease revealed numerous microthrombi in pulmonary capillary bed, without any major embolisms (27). These patients probably also have remodelling of pulmonary vascular wall, partly due to hypoxaemia (28) occurring intermittently but repetitively with exercise. The safe parts of pulmonary vascular bed probably adapt to the high pressure occurring in vascular zones affected by fibrosis or in which microthrombi form. This phenomenon is similar to PH developing after destruction of the vascular bed following the obstruction of the major vascular trunks, with possible remodelling of pulmonary vascular wall (29) and in agreement with the fact that, SPAP is physiologically higher in older subjects due to reduction of pulmonary vascular bed (30).

Increased PAP with exercise is not correlated with the severity of respiratory function impairment. In our study, neither SPAP at rest (which was nor-

mal) nor SPAP at peak correlated with pulmonary function at rest. However, increased PAP on exercise was associated, in all our patients, with hypoxaemia on exercise, reflecting alveolar-capillary blockage in patients with IPF. One study demonstrated inverse correlations between SPAP and DLCO or between SPAP and resting PaO<sub>2</sub> or saturation, for resting SPAP above 50 mmHg. In this same study, no correlation was observed between SPAP at rest (normal or high) and the degree of restriction (25). No data have been published concerning possible correlations between SPAP (whether estimated by echocardiography coupled to Doppler or measured by right heart catheterisation), and markers of pulmonary function at rest suggesting that the existence of increased PAP with exercise could not be demonstrated by simple respiratory function test. Conversely, the presence of dead-space abnormalities during functional exercise test, as shown by an increase in VD/Vt, is predictive of increased PAP with exercise (31).

In conclusion, patients with IPF presenting moderate restriction and hypoxemia with exercise develop increased PAP with exercise, with high SPAP values recorded at low workloads. Oxygen does not improve increased PAP with exercise, but significantly increases tolerance to exercise. The mechanisms underlying this improvement remain unknown.

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