

Vascular and cardiac reactivity in pulmonary hypertension due to chronic obstructive lung disease: assessment with various oxygen concentrations

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ABSTRACT: The aim of the present work was to evaluate vasoreactivity in patients with pulmonary hypertension related to chronic obstructive lung disease. This was done by comparing haemodynamic data recorded while patients were breathing room air, and hypoxic and hyperoxic mixtures. We estimated the role of vasoconstriction in determining the level of pulmonary hypertension.

This study included 26 patients with moderate pulmonary hypertension mean pulmonary arterial pressure (MPAP) = 27.3 ± 1.2 mmHg secondary to chronic obstructive lung disease (COLD), forced expiratory volume in one second (FEV_1) = 0.95 ± 0.13 l; arterial oxygen tension (Pao_2) = 8.7 ± 0.25 kPa. After insertion of a thermodilution catheter in the pulmonary artery and a cannula in the femoral artery, mixtures containing 15, 21, 30 and 100% oxygen were randomly administered for 20 min each.

As fractional inspiratory oxygen (F_{iO_2}) increased, MPAP decreased relatively less than cardiac index. Cardiac output was at its highest during room air breathing and the hypoxic mixture did not lead to a further increase. Unlike normal subjects, in whom adjustment of cardiac output is achieved by heart rate alone, haemodynamic regulation in these patients also involved stroke volume. Variations in MPAP and cardiac index were strongly correlated with arterial oxygen saturation (Sao_2). The greatest variations were noted in the patients with the highest pulmonary hypertension. Under normoxic and hyperoxic condition the relationship between pulmonary artery driving pressure and cardiac index was linear and its slope steeper in patients having the highest pulmonary hypertension at steady-state. In these patients the relationship remained linear at 15% F_{iO_2} , i.e. pulmonary artery driving pressure is a linear function of cardiac output. Conversely, in less severe patients, during hypoxic conditions pulmonary pressure increased but cardiac index remained constant suggesting an enhancement of hypoxic vasoconstriction.

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Chronic hypoxic pulmonary vasoconstriction is considered to be the primary cause of pulmonary artery hypertension (PAH) and cor pulmonale in patients with chronic obstructive lung disease (COLD). Long-term alveolar hypoxia leads to structural changes in pulmonary arterioles, internal and medial hypertrophy, e.g. muscularization and sustained PAH [1-5].

The relationship between pulmonary vasomotricity and hypoxia has been extensively studied in healthy subjects, especially at high altitude, [6-10]. ABRAHAM *et al.* [11] demonstrated an inverse correlation between arterial oxygen saturation (Sao_2) level and pulmonary artery pressures (PAP) during hypoxic breathing. WEITZENBLUM *et al.* [12] pointed out the variations of individual responses to hypoxia. Oxygen therapy has been shown to be beneficial for COLD patients with

PAH [13-18]. More recently, interest in pulmonary vascular reactivity to fractional inspiratory oxygen (F_{iO_2}) has been revived in the study of sleep apnoea syndrome [19].

The aim of the present work was to evaluate acute pulmonary vasoreactivity in COLD patients with PAH by measuring haemodynamics at different F_{iO_2} levels.

Patients and methods

Patients

The study included 26 male patients (mean age 63 ± 2 yrs) with PAH secondary to COLD (mean pulmonary artery pressure (MPAP) 27.3 ± 1 mmHg). In all subjects,

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functional tests documented serious respiratory impairment (forced expiratory volume in one second (FEV₁) = 0.945 ± 0.13 l, FEV₁/forced vital capacity = 39 ± 10% of predicted, residual volume = 142 ± 5.5% of predicted). All subjects had dyspnoea and fatigue after minimal or moderate exertion but were clinically stable and had been free of bronchopulmonary infection, acute respiratory distress or right ventricular failure for at least 2 months prior to the study. None had taken vasodilators, long-acting theophylline, β₂-agonists, almitrine, diuretics or digitalis for at least one week prior to the study. Two patients were under long-term O₂ therapy, which was stopped 24 h before investigation. All were in sinus rhythm with no clinical, electrocardiographic, X-ray or echocardiographic evidence of left ventricular dysfunction. The investigative protocol was approved by our Institutional Ethics Committee. Informed consent was obtained from the patients.

Methods

Right heart catheterization was performed via a femoral vein with a 7 F flow-directed balloon-tipped thermodilution catheter (Spectramed). Systemic arterial pressure measurements and arterial blood sampling were made through a 4 F cannula in the femoral artery. Intravascular pressures were measured relative to atmospheric pressure with a zero reference point at the mid-axillary line.

Pressures were measured during apnoea at the end of expiration. Cardiac output (CO; l·min⁻¹) was determined by the thermodilution technique (Spectramed device) and expressed as the mean of four consecutive readings varying less than 10%. Arterial oxygen tension (Pao₂), arterial carbon dioxide tension (Paco₂) and pH were determined with a Radiometer BMS 3 MK2 blood gas analyser and Sao₂ with a Radiometer OS M2 device. Haemoglobin levels (Hb) were measured with a Technicon M 6000. Haemodynamic variables were calculated as follows: cardiac index (CI) (l·min⁻¹·m⁻²) = CO/body surface area; stroke volume (SV) (ml/systole) = CO/heart rate (HR); pulmonary artery driving pressure (PADP) = mean pulmonary artery pressure (MPAP) - pulmonary artery wedge pressure (PWP); pulmonary vascular resistance (PVR mmHg·l⁻¹·s) = PADP × 60/CO; oxygen delivery (To₂; ml·min⁻¹·m⁻²) = CI × Cao₂/10, where Cao₂ is arterial oxygen content (ml·l⁻¹ of blood) = (13.4 × Sao₂ × Hb) + (0.031 × Pao₂) where Hb (haemoglobin level) is expressed in g·l⁻¹.

Study design

Patients were allowed to rest for 30 min after insertion of the catheters. Baseline determinations were performed when heart rate, vascular pressures and respiratory rate were stable. Oxygen was administered pure (100%) or mixed at 15% (hypoxic mixture), 21% (room air) and 30% (hyperoxic mixture) with nitrogen. Mixtures were administered in random order through a

high concentration mask. Blood gases and haemodynamic parameters were recorded after 20 min without interrupting inhalation.

Statistical analysis

All values are expressed as mean (±SEM). Comparisons were made by analysis of variance and paired student's t-tests. Correlation between parameters was assessed by linear regression.

Results

Haemodynamic and blood gas data recorded during room air, hypoxic and hyperoxic breathing are shown in table 1. HR progressively decreased to 25.5% as Fio₂ increased from 15 to 100%.

The increase in MPAP from 21 to 15% Fio₂ was higher proportionally (+10% for a -6% loss in Fio₂) than the decrease from 21% to 100% Fio₂ (-20% for a +79% gain in Fio₂). The absolute increase in systolic pressure was twice that of the increase in diastolic pressure when Fio₂ decreased from 30 to 15%.

Patients with the highest MPAP during room air breathing exhibited the greatest decreases in MPAP when Fio₂ was increased from 15 to 30% (r=0.711, p<0.0001) (fig. 1a). This observation was confirmed by the fact that the 12 patients exhibiting low MPAP variations when Fio₂ was decreased from 30 to 15%, (i.e. <5 mmHg) had significantly lower room air MPAP than the 14 patients with higher MPAP variations, (i.e. >5 mmHg) (23.9±0.9 vs 30.1±1.2 mmHg, p<0.0001). Changes in MPAP also correlated well with concomitant variations in Sao₂ from 15 to 30% Fio₂ (r=0.677, p<0.0001) (fig. 1b).

On the other hand, we studied the relationship between PADP and CI according to the severity of PAH. The patients were divided into three groups according to the level of PADP at 21% Fio₂: Group 1 (10 patients) PADP <15 mmHg; Group 2 (8 patients) PADP 15–20 mmHg; Group 3 (8 patients) PADP >20 mmHg. The slope of the relationship between PADP and CI (at Fio₂ 15, 21, 30 and 100%) was linear only in the patients with the highest PAH (Group 3) (fig. 2). In the other two groups the relationship was linear only between Fio₂ 21% and 100%. During normoxic and hyperoxic breathing, the slope of the relationship increased with the severity of basal PAH (2.0 in Group 1, 5.3 in Group 2, 7.6 in Group 3). When Fio₂ was decreased to 15%, a clear change in the slope was observed in Groups 1 and 2, corresponding to an increase in PVR during hypoxia. In Group 3, PVR remained constant.

In our patient population taken as a whole, there was no difference in the CI or SV measurements recorded during hypoxic and room air breathing. Conversely, hyperoxic breathing (30 and 100%) led to a notable decrease in CI (-14% and -34% (p<0.0001), respectively) and SV (-6.5% (p<0.0001) and -16.5% (p<0.0001), respectively).

Table 1. - Haemodynamics and blood gases according to various F_{IO₂} levels

F _{IO₂} %	15	p	21	p	30	p	100
HR b·min ⁻¹	83.8±3.1	<0.0001	80.4±3	<0.0001	76.3±3.1	<0.0001	63.6±2.4
MRAP mmHg	11.4±0.6	NS	11±0.6	NS	10.7±0.6	NS	9.4±1.4
SPAP mmHg	38.5±1.3	<0.0001	35.2±1.1	<0.0001	32.3±1.1	<0.0001	28.6±1.1
DPAP mmHg	21.5±0.9	<0.0001	19.9±0.9	<0.0001	18.6±0.8	<0.05	16.2±0.6
MPAP mmHg	30.1±1.2	<0.0001	27.3±1.1	<0.0001	25.3±0.9	<0.0001	21.8±0.7
PWP mmHg	11.2±0.4	NS	10.8±0.5	NS	10.7±0.5	NS	10.4±0.4
MAP mmHg	98±5	NS	95±4	NS	94.5±4	NS	94±6
CI l·min ⁻¹ ·m ⁻²	3.56±0.17	NS	3.49±0.15	<0.0001	3.02±0.1	<0.0001	2.3±0.12
SV ml	81±4	NS	79±4	<0.0001	74±4	<0.0001	68±3
PVR mmHg·l ⁻¹ ·s	180±13	<0.001	158±11	NS	165±11	NS	159±10
Pao ₂ kPa	6.84±1.4	<0.0001	8.7±0.25	<0.0001	12.6±0.52	<0.0001	46.1±0.4
Pvo ₂ kPa	4.6±0.09	<0.0001	5.17±0.09	<0.0001	5.53±0.08	<0.0001	6.13±0.06
Paco ₂ kPa	4.93±0.14	<0.001	5.2±0.16	<0.05	5.46±0.22	<0.05	5.6±0.18
Sao ₂ %	82±2	<0.0001	91±1.1	<0.0001	96±1.7	<0.0001	98±0.8
To ₂ ml·min ⁻¹ ·m ⁻²	519±24	<0.0001	570±29	<0.001	523±29	<0.0001	404±20

p value from Student's t-test. F_{IO₂}: fractional inspiratory oxygen; HR: heart rate; MRAP: mean right atrial pressure; SPAP: systolic pulmonary artery pressure; DPAP: diastolic pulmonary artery pressure; MPAP: mean pulmonary artery pressure; PWP: pulmonary artery wedge pressure; MAP: mean arterial pressure; CI: cardiac index; SV: stroke volume; PVR: pulmonary vascular resistance; Pao₂: arterial oxygen tension; Pvo₂: mixed venous oxygen tension; Paco₂: arterial carbon dioxide tension; Sao₂: arterial oxygen saturation; To₂: oxygen delivery.

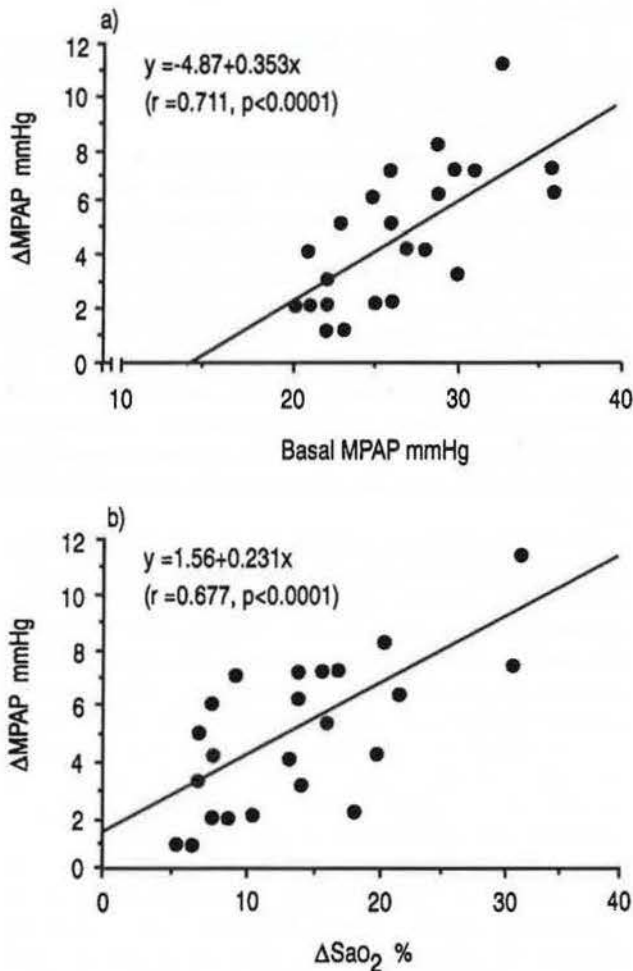


Fig. 1. - Decreases in mean pulmonary artery pressure (Δ MPAP) when F_{IO₂} was increased from 15 to 30% plotted against: a) basal MPAP (MPAP, F_{IO₂} = 21%); b) concomitant Sao₂ variations (Δ Sao₂).

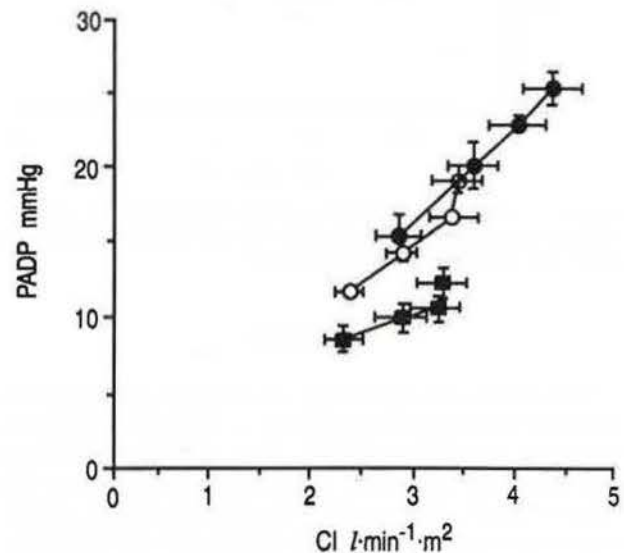


Fig. 2. - Relationship between pulmonary artery driving pressure (PADP) and cardiac index (CI) at F_{IO₂} 15, 21, 30 and 100%, in the following three groups of patients: Group 1 PADP < 15 mmHg: —■—; Group 2 PADP 15-20 mmHg: —○—; Group 3 PADP > 20 mmHg: —●—. F_{IO₂}: fractional inspiratory oxygen.

CI response to hypoxic and hyperoxic breathing was greatest in patients exhibiting highest PAH ($r=0.786$; $p<0.0001$). A correlation was also noted between variations in CI and Sao₂ ($r=0.756$, $p<0.0001$).

Although MPAP always increased with CI when F_{IO₂} was lowered, there were individual haemodynamic variations (fig. 3).

No significant variation in mean right atrial, pulmonary wedge or systemic arterial pressures was noted. PVR increased significantly during hypoxic breathing ($p<0.001$) but did not change during hyperoxic (30 and 100%) breathing. Pao₂ increased almost linearly up to

100% Fio_2 , whereas mixed venous oxygen tension (Pvo_2) increased more gradually and virtually levelled off at 30%. Sao_2 and venous oxygen saturation (Svo_2) displayed the same evolution as Pvo_2 with increasing Fio_2 . Oxygen delivery was most efficient when the patients inhaled room air. It decreased during both hypoxic and hyperoxic breathing. During hypoxia CI was the same as during room air breathing but arterial oxygen content was lower. During hyperoxia the decrease in CI was proportionately greater than the increase in arterial oxygen content.

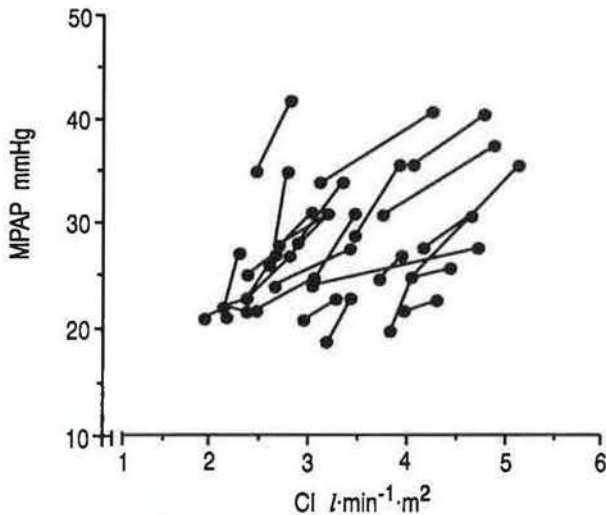


Fig. 3. — Individual variations in mean pulmonary artery pressure (MPAP) and cardiac index (CI) when Fio_2 was increased from 15 to 30%. Fio_2 : fractional inspiratory oxygen.

Discussion

This study was undertaken to evaluate vasoreactivity in stable patients with PAH due to COLD. Hyperoxic breathing resulted essentially in a greater decrease in CO than MPAP. This explains why PVR, *i.e.* the ratio between MPAP and CO, did not change during hyperoxic breathing. Several studies have demonstrated that acute hyperoxia does not modify MPAP [9, 20, 21]. Decreases in MPAP are generally concomitant with a decrease in CO and consequently PVR do not change [22]. This was observed in our study. In our patient population taken as a whole, hypoxic breathing further increased MPAP but did not affect CO. The rise in MPAP, which as in normal subjects was due to an augmentation of systolic pressure [2, 6, 8–10], led to an increase in PVR.

In the patients with the most severe PAH, both PADP and CI increased in the same proportion under hypoxic conditions and PVR remained constant. However, in less severe patients, PADP increased whilst CI remained constant, thus enhancing vasoconstriction.

There is a discrepancy in the literature about the effects of hypoxia on CO. Several studies have shown that CO in normal subjects increases at altitude or after hypoxic breathing at sea level [6, 7, 9, 23, 24]. In their

study performed on healthy young adults, NAEJE *et al.* [24] concluded that hypoxia resulting from Fio_2 at 12.5% was offset by an increase in CO since no change in O_2 transport occurred.

More recently, isocapnic hypoxia was shown to induce a significant dose-dependent increase in CO in normal young adults [25]. In contrast, MOTLEY *et al.* [10] reported a decrease in CO after inhalation of 10% oxygen for 10 min.

In COLD patients, SELINGER *et al.* [26] showed that when oxygen therapy was discontinued PVR increased 31% during rest and 29% during exercise, due to an increase in PAP with no change in PWP or CO. Discontinuing oxygen reduced SV, but increased HR, therapy maintaining CO. TUXEN *et al.* [21] reported similar findings. In our patient population taken as a whole, hypoxic breathing caused no further increase in CO. This is consistent with data previously reported by ABRAHAM *et al.* [11] in patients with frank congestive right ventricular failure secondary to severe PAH. In response to hypoxia normal subjects maintain O_2 delivery by increasing CO [2, 26]. COLD patients retain this ability in certain circumstances, *e.g.* during exercise [20, 27], but not necessarily in response to hypoxia [18, 26].

In our experience, the patients with the most severe PAH responded to enhanced hypoxia by increasing CO without modifying PVR. Less severe patients increased vasoconstriction and PVR.

Pulmonary vasoconstriction induced by alveolar hypoxia eventually leads to internal and medial hypertrophy of the pulmonary arterioles [3–5]. The resulting narrowing of the vessels is certainly a determinant factor for PAP. The same reduction of the radius will cause a greater pressure increase in a small vessel than in a large one. Thus, patients with higher pulmonary pressures may have smaller arteries. In our study, larger variations in CO and MPAP were measured in patients with higher PAH. In spite of this, PVR in these patients was constant, suggesting that PAH was not due to dynamic vasoconstriction [28].

In normal subjects, adjustment of CO in response to hypoxia is achieved only by an acceleration of HR [25]. Our results indicate that in COLD patients with PAH, adjustment also involves SV. Indeed, we observed a decrease in SV during hyperoxia and practically no change during hypoxia. TUXEN *et al.* [21] reported similar findings and, as mentioned earlier, SELINGER *et al.* [26] observed a decrease in SV after discontinuation of oxygen therapy. The inability of COLD patients to increase SV during hypoxia is due to reduced cardiac function [26], which may be the consequence of a direct effect of hypoxia on the myocardium [27], or of the increase in PAP and right ventricular stroke work caused by hypoxic vasoconstriction [26]. During hypoxic breathing we only observed a rise in right ventricular afterload, *i.e.* increase of PAP and PVR. The augmentation of SV from hyperoxic to room air conditions may be related to a positive inotropic effect of sympathetic stimulation. We observed no significant

variation in right atrial pressure, suggesting that right ventricular preload remained constant. In their radionuclide study, TUXEN *et al.* [21] found that right ventricular end-diastolic volume was unchanged during hypoxia, whereas it fell during hyperoxia. Systemic circulation load did not seem to play a role, since no significant modification in arterial systemic pressure or PWP was noted.

Interindividual variations in response to F_{IO₂} changes should be emphasized. Nocturnal polysomnographic studies showed that the increase in PAP caused by the same degree of desaturation varied greatly from one patient to another [2, 12, 19, 24]. Likewise, variable individual responses to hyperoxic breathing have been noted during long-term oxygen therapy [17, 18]. It has been reported that this variability has great prognostic value. Life expectancy can be indexed on the response to acute administration of oxygen, independently of the initial level of PAP [29]. Our patients were characterized by normal CO and resting PAH. This haemodynamic profile corresponds to the "hypoxaemic pattern" described by BURROWS *et al.* [30]. In this pattern, PAH results from a well-maintained CO in the presence of reversible and irreversible changes due to the degree of hypoxia and anatomical damage of the vascular bed [30].

Numerous studies indicate that PAH remains responsive to oxygen therapy for a long time [13–18]. The fact that patients with less severe basal PAH displayed the greatest variations in PVR during enhanced hypoxia, suggests that the relative role of reversible changes is greater in these patients. Thus, in terms of PAH, they probably benefit more from early long-term oxygen therapy.

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