Effect of pulmonary hypertension on gas exchange

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ABSTRACT: This paper reviews the effects of pulmonary artery hypertension on gas exchange by exploring three different issues, namely: 1) how does gas exchange behave in diseases characterized by increased vascular tone (primary pulmonary hypertension (PPH), chronic obstructive pulmonary disease (COPD) and interstitial pulmonary fibrosis (IPF)); or decreased vascular tone ('hepatopulmonary syndrome'); 2) how does exercise, as a non-pharmacological tool of increasing pulmonary blood flow, modify gas exchange in these diseases; and 3) how do several drugs that lower (vasodilators) or increase (almitrine) the active component of pulmonary hypertension interact with gas exchange.

Available data show that: 1) in PPH a high pulmonary vascular tone enhances gas exchange and when it is lowered, either by oxygen or vasodilators, ventilation-perfusion (VA/Q) distributions deteriorate; 2) in COPD a lowered (vasodilators) or augmented (almitrine) active vascular tone is almost invariably paralleled by a deterioration or enhancement of ventilation-perfusion matching, respectively; 3) in IPF an adequate active response of the pulmonary vasculature is essential to maintain gas exchange, both at rest and during exercise; and 4) in patients with liver cirrhosis a low pulmonary vascular tone induces an abnormal VA/Q distribution.

In summary, these data show that any situation and/or therapeutic intervention that lowers the active vascular tone deteriorates VA/Q relationships and vice versa. The final effect of pulmonary vascular tone on arterial oxygen tension (PaO₂) is less predictable. The reason for this uncertainty is that the actual PaO₂ value depends on the interplay of the intrapulmonary factors that control gas exchange in humans, and not only on the degree of VA/Q mismatching.


Pulmonary hypertension is a common and severe complication of lung disease. Its deleterious effects on right ventricular mechanics and performance have been well described. However, the effects of pulmonary hypertension on gas exchange are less well understood. The purpose of this paper is to show that gas exchange in pulmonary hypertension, as a result of high vascular tone, is much better than in lung diseases characterized by low pulmonary vascular tone.

It is important to differentiate structural and functional changes of the pulmonary vasculature which cause pulmonary hypertension. Functional change is characterized by the contractile response to hypoxia (hypoxic pulmonary vasoconstriction), where vascular tone is increased. Its main physiological characteristic is that of reversibility when normoxia is restored. Structural change is where there is a fixed component from anatomical derangement or loss of pulmonary capillary surface area. Such pulmonary hypertension is caused by the lung disease itself. By definition, this fixed form is not reversible by oxygen or drugs.

To demonstrate that a high pulmonary vascular tone enhances and preserves a more homogeneous ventilation-perfusion (VA/Q) matching, three different issues will be explored: 1) the contrasting effects on gas exchange in those diseases where vascular tone is increased, e.g. primary pulmonary hypertension, chronic obstructive pulmonary disease (COPD) and cryptogenic fibrosing alveolitis, compared with diseases where pulmonary vascular tone is decreased, e.g. hepatopulmonary syndrome [1, 2]; 2) the way in which exercise, as a non-pharmacological tool of increasing pulmonary blood flow, modifies gas exchange in these diseases; and 3) the effects of drugs lowering (vasodilators), or increasing (almitrine), pulmonary vasomotor tone on gas exchange.

The majority of studies used the multiple inert gases elimination technique (MIGET) [3–5] to estimate the distribution of VA/Q relationships, this being the most suitable technique to determine pulmonary gas exchange in patients and to study its relationship to pulmonary vascular resistance [6, 7]. The methods used in MIGET will not be described in detail; we refer the reader to recent reviews on this subject [6, 7].

Gas exchange in diseases associated with high vascular tone

Primary pulmonary hypertension (PPH)

PPH can be considered the model of diseases characterised by increased pulmonary vascular tone. DANZKIR and
Bower [8] were the first to use the MIGET in a group of patients with PPH. They showed that, at rest breathing room air, \( V_{A}/Q \) relationships were essentially well-preserved, with most of the ventilation and perfusion being distributed to alveolar units with normal \( V_{A}/Q \) ratios; most patients also showed a small second mode characterised by perfusion of units with a very low \( V_{A}/Q \) ratio (<0.1 excluding shunt), or even with a \( V_{A}/Q \) ratio of zero (<0.005, shunt) [8].

To study the relationship of \( V_{A}/Q \) distribution to pulmonary hemodynamics in these patients, hypoxic pulmonary vasoconstriction was reversed with high fractional inspired oxygen levels. The cardiac output increased and pulmonary vascular resistance decreased. It can be concluded that restoration of normoxia reduced pulmonary vasoconstriction, so diminishing resistance to flow and enabling an increase in cardiac output. Normoxia appears, therefore, to have a beneficial effect on pulmonary haemodynamics. However, at the same time, the physiological shunt increased (from 2 to 7% of cardiac output) and the second mode in the perfusion distribution described above, that is the amount of blood flow perfusing poorly-ventilated areas, also increased significantly. Thus, despite the improved pulmonary haemodynamics with oxygen, \( V_{A}/Q \) relationships clearly deteriorated [8]. The investigators interpreted these findings as evidence of the deleterious effects of releasing hypoxic pulmonary vasoconstriction (active tone) on gas exchange in patients with PPH. Therefore, the increased pulmonary vascular tone of these patients under baseline conditions (breathing room air) was, in fact, contributing to preserve gas exchange [8].

Dantzer and Bower [8] also tested the effects of several vasodilator drugs on \( V_{A}/Q \) relationships in these patients. They observed that after infusing either isoproterenol or nitroprusside, \( V_{A}/Q \) relationships again deteriorated markedly, with a significant increase in both shunt and perfusion to poorly-ventilated alveolar units with low \( V_{A}/Q \) ratios (<0.1) [8]. Two years later, Melot et al. [9] reported similar results on \( V_{A}/Q \) relationships in patients with PPH after nifedipine, a calcium channel blocker.

In summary, studies in patients with PPH have shown that a high pulmonary vascular tone enhances gas exchange, and that when it is lowered, either by oxygen or with vasodilators, \( V_{A}/Q \) distributions deteriorate.

**Chronic obstructive pulmonary disease (COPD)**

Abnormal pulmonary gas exchange with hypoxaemia and hypercapnia is characteristic of COPD. These patients often develop pulmonary hypertension. Both structural and functional factors contribute to the development of pulmonary hypertension in COPD. The structural changes are associated with a loss of capillary surface area, particularly in patients with pulmonary emphysema. There is also increased pulmonary vascular tone, because of the presence of poorly-ventilated lung units, due to hypoxic pulmonary vasoconstriction. It is not clear how these two components of pulmonary hypertension interact with gas exchange, and more specifically \( V_{A}/Q \) relationships.

In 1990, Agusti et al. [10] investigated the effects of exercise and the vasodilator nifedipine on \( V_{A}/Q \) relationships in a group of patients with advanced, but otherwise clinically stable, COPD with mild to moderate pulmonary hypertension. The rationale behind their study was that exercise is a non-pharmacological method of increasing pulmonary blood flow, whilst nifedipine increases pulmonary blood flow by relaxing vascular smooth muscle. At the same time, nifedipine "reverses" the hypoxic pulmonary vasoconstriction component of pulmonary hypertension [10]. The authors choose to include patients with only moderate pulmonary hypertension on the assumption that these patients would probably have both increased active tone and anatomical derangement of the pulmonary vasculature, whilst patients with more advanced COPD and severe pulmonary hypertension may have a greater anatomical destruction of the capillary bed, and hence by less responsive to manipulations of the vascular tone [10]. This assumption has recently been stressed by other authors on the basis of physiological determinations [11], morphometric studies [12, 13] and, very recently, in vitro investigations of the functionality of the pulmonary endothelial cells of patients with COPD submitted to lung transplant [14, 15].

Figure 1 shows the haemodynamic profile (at rest and during exercise, with and without nifedipine) of the patients studied by Agusti et al. [10]. Without nifedipine (continuous line), submaximal exercise (at 60% maximal \( O_2 \) consumption) induced a marked increase both in cardiac output and mean pulmonary artery pressure. After nifedipine, at rest, mean pulmonary artery pressure did not change, but cardiac output increased. When these patients exercised after nifedipine (dashed line), cardiac output also increased (with respect to resting conditions with nifedipine). In absolute terms, cardiac output was higher than that measured during exercise without the drug. However, despite this higher cardiac output, pulmonary hypertension during exercise was lower with than without nifedipine. Overall, these data were interpreted as evidence of the vasodilator effect of nifedipine upon the pulmonary circulation.

Figure 2 shows the \( V_{A}/Q \) ratio distributions obtained in a representative patient of the series [10]. At rest, before nifedipine, there is a clearly abnormal \( V_{A}/Q \) distribution, with
perfusion distributed to low V\(\text{A}/Q\) units (<0.1 excluding shunt), and also ventilation to units with high V\(\text{A}/Q\) ratios (10 excluding dead space). This type of V\(\text{A}/Q\) distribution is characteristic of COPD [6, 7]. Exercise (before nifedipine) induced a marked improvement in gas exchange, as shown by the narrowing of both the ventilation and blood flow distributions. This improvement paralleled the marked increase in the pulmonary artery pressure (fig. 1). By contrast, at rest nifedipine induced both pulmonary vasodilation (fig. 1) and a significant deterioration of V\(\text{A}/Q\) relationships (fig. 2). It should be noted that after nifedipine (at rest) there is more blood flow distributed to alveolar units with a low V\(\text{A}/Q\) ratio. Therefore, the effects of nifedipine at rest upon pulmonary gas exchange in patients with COPD were very similar to those previously described for patients with PPH. That is, by lowering the active component of pulmonary hypertension, the mechanisms that tend to preserve V\(\text{A}/Q\) relationships became less effective. However, the study by Aucott et al. [10] extended previous observations to exercise conditions. The lower right panel of figure 2 shows that despite this deleterious effect of nifedipine on V\(\text{A}/Q\) distributions, exercise had an intense influence on gas exchange, and was still capable of improving V\(\text{A}/Q\) matching in these patients. Observe that with respect to resting conditions after nifedipine, V\(\text{A}/Q\) distributions obtained during exercise with nifedipine were narrower and less heterogeneous (fig. 2). Nevertheless, the effects of nifedipine (i.e. the effects of interfering with the active component of pulmonary hypertension) were still apparent during exercise, as shown by the broader V\(\text{A}/Q\) distributions shown during exercise with than without nifedipine.

Figure 3 summarizes all this information by presenting a plot of oxygen uptake (\(\text{VO}_2\), ml·min\(^{-1}\)), i.e., intensity of exercise, versus: a) Log\(_{10}\) perfusion (a variable that informs of the dispersion (\(sd\)) on a log scale (log) of the blood flow distribution [3, 7]; and b) the dead space to tidal volume ratio (\(VD/VT\)). The shaded areas represent the expected normal values at rest. ---: before nifedipine; ----: after nifedipine. COPD: chronic obstructive pulmonary disease. For further explanation, see text. * represents significance (From [10], reproduced with permission of Chest).
and without nifedipine, reveals that there is more $\dot{V}A/\dot{Q}$ mismatch following administration of the drug (fig. 3). This exemplifies the net effect of a lower pulmonary vascular tone on gas exchange during exercise in COPD patients. Taken together, these data in patients with COPD show again (as in the case of patients with PPH) that a high pulmonary vascular tone enhances and preserves gas exchange, both at rest and during exercise.

There are also data available exploring what happens to gas exchange if pulmonary vascular tone is pharmacologically augmented e.g., by giving almitrine bismesylate, a drug originally designed as a ventilatory stimulant, which has been shown to enhance hypoxic pulmonary vasoconstriction [16–18]. It has been clearly documented that, by increasing the active pulmonary vascular tone, almitrine improves ventilation-perfusion matching and, thereby, arterial oxygenation. However, this is at the expense of a slight, but significant, increase in pulmonary artery pressure, and some clinically significant neurological side-effects [16]. Therefore, at the present time, its clinical indication in patients with COPD is questioned. Nevertheless, for the purpose of this review, almitrine constitutes an excellent pharmacological example of how any increase in pulmonary vascular tone improves gas exchange.

In summary, it is clear that in patients with COPD, as well as PPH, a lowered (vasodilators) or augmented (almitrine) active pulmonary vascular tone is almost invariably paralleled by a deterioration or enhancement of $\dot{V}A/\dot{Q}$ matching, respectively. Whether or not this statement will be altered by the use of new drugs, such as urapidil or nitric oxide [15, 19, 20], which may have a highly selective effect on the pulmonary vasculature, is still a matter of current research.

**Idiopathic pulmonary fibrosis (IPF)**

Patients with IPF characteristically have restrictive ventilatory impairment, decreased diffusing capacity of the lungs for carbon monoxide (DLCO), and mild arterial hypoxaemia, that generally, but not always, worsens during exercise [21]. The histopathological picture reveals a structural loss of alveolar-capillary units. It is not surprising, therefore, that in advanced stages of the disease, patients with IPF develop pulmonary hypertension [22]. It has been attributed largely to the physical loss of capillary surface area. However, hypoxic pulmonary vasoconstriction may also play a role in the development of pulmonary hypertension in these patients [22]. Again, the relationship between the active component of pulmonary vascular disease and gas exchange in IPF is not clear.

To clarify this question $\dot{V}A/\dot{Q}$ distributions were obtained in a group of patients with IPF studied at rest breathing room air (baseline conditions), at rest breathing 100% $O_2$ (to release hypoxic pulmonary vasoconstriction), and during exercise whilst breathing room air (again as a nonpharmacological tool to increase pulmonary blood flow) [23]. Figure 4 presents the $\dot{V}A/\dot{Q}$ ratio distributions obtained in

![Ventilation-perfusion distribution](image-url)

**Fig. 4.** Ventilation-perfusion distribution obtained in two representative patients (JSS and MRG) with idiopathic pulmonary fibrosis: a) at rest breathing room air; b) at rest breathing 100% $O_2$; and c) during exercise (breathing room air). — $\bigcirc$ : ventilation; • : perfusion. For further explanation, see text. (From [23], reproduced with permission of Am Rev Respir Dis).
two of these patients. Note that, at rest breathing room air, both patients showed relatively well-preserved V/Q distributions, with a very small amount of shunt and/or blood flow perfusing units with low V/Q ratios. Instead, these patients had most of their perfusion and ventilation going to alveolar units with essential normal V/Q ratios. Despite this similarity at baseline, the two patients displayed different patterns of response, both to the administration of oxygen and to exercise. The V/Q ratio distributions of the patient depicted in the upper panels of figure 4 (JSS) showed no noticeable change with high fractional inspiratory O₂ (PVo₂) or during exercise. By contrast, both oxygen and exercise had pronounced effects upon V/Q distributions in the patient depicted in the lower panels (MRG). It can be observed that, compared to baseline, the inhalation of O₂ by this patient induced a marked increase in the amount of blood flow perfusing poorly ventilated areas (shown in the figure as a second mode in the perfusion distribution) and shunt. However, when this patient exercised, V/Q mismatching was significantly improved with respect to baseline. These data indicate that some patients with IPF may have a pulmonary vasculature that is responsive to O₂ (MRG), whilst others are insensitive to it (JSS), thereby suggesting a more fixed (anatomical) vascular derangement. Interestingly, the former group improved V/Q relationships during exercise, while the latter showed no such response.

To test the hypothesis that the preservation of an active pulmonary vascular tone was desirable in terms of gas exchange (particularly during exercise), the authors tried to quantify the degree of pulmonary vascular responsiveness to O₂. As an "index" of pulmonary vascular reactivity, they calculated the increase in perfusion of poorly-ventilated lung units whilst breathing pure O₂, which probably represents release of hypoxic pulmonary vasoconstriction [7, 10, 23]. This variable, i.e. percentage change from baseline in the dispersion of the perfusion distribution whilst breathing 100% oxygen (Δlog Q), seems to be more sensitive to small changes in the pulmonary vascular tone than the standard haemodynamic measurements (pressure and flow) [7, 10, 23]. Figure 5 shows this index of pulmonary vascular reactivity plotted against the values (all of them during exercise) of: a) mean pulmonary artery pressure; b) an index of the overall degree of V/Q homogeneity, (DISP R-E⁹); and c) PaO₂. Figure 5a shows a significant relationship between "vascular reactivity" and pulmonary hypertension during exercise. Those patients having no or minimal vascular response to O₂ (at rest) suffered severe degrees of pulmonary hypertension during exercise, whilst those exhibiting evidence of release of hypoxic vasoconstriction at rest did not develop pulmonary hypertension during exercise. These latter patients probably had a more distensible and/or recrutable pulmonary circulation than the former ones. Figure 5b shows an excellent relationship between vascular reactivity and overall degree of V/Q mismatch during exercise. Those patients with more active tone at rest (i.e. those having more release of hypoxic vasoconstriction) had less V/Q mismatch during exercise. Finally, figure 5c shows that those patients with a high pulmonary vascular active tone at rest were those who did not present arterial desaturation during exercise, whilst those having no or minimal pulmonary vascular response to O₂ (at rest) presented significant arterial hypoxaemia during exercise [23].
lower \(P_aO_2\) during exercise (fig 5). Taken together, these data indicate that, an adequate active response of the pulmonary vasculature is also essential in patients with IPF to preserve gas exchange, both at rest and during exercise.

**Gas exchange in diseases associated with low vascular tone**

**The hepatopulmonary syndrome**

The term "hepatopulmonary syndrome" was coined to describe the abnormalities of pulmonary gas exchange and lung circulation that may occur in patients with cirrhosis of the liver, in the absence of any intrinsic lung or heart disease [24]. The possibility that some patients with cirrhosis may associate cyanosis, clubbing and dyspnoea has been known since 1884 [25]. However, we have only recently begun to understand the pathophysiological basis for this clinical observation [1, 2, 26–29]. The hepatopulmonary syndrome is now thought to be a condition characterized by pulmonary vasodilation and abnormal gas exchange [1, 2, 26–29], with blunted or decreased pulmonary vascular response to hypoxia [30, 31]. It therefore seems appropriate for the purposes of this review to analyse in detail how this low active vascular tone affects pulmonary gas exchange.

The first study to use the MIGET in cirrhosis was published in 1987, by Rodriguez-Roisin et al [32]. All of the patients studied were in stable clinical condition (without ascites or fluid retention), had normal spirometry, and no evidence of cardiac disease [32]. At rest breathing room air, these patients showed the characteristic hyperdynamic cardiovascular state of cirrhosis, characterised by high cardiac output and low pulmonary vascular resistance [32]. When they were given 12% \(O_2\) to breathe (to investigate hypoxic pulmonary vasoreactivity), pulmonary vascular resistance increased only marginally, particularly in those patients with cutaneous spider naevi [32]. Subsequent studies during exercise confirmed this observation (blunted and/or absent hypoxic vasodilatation) and demonstrated that patients with cirrhosis usually have an abnormally dilated pulmonary circulation [33].

Despite the absence of airflow limitation and/or fluid retention, and the presence of normal cardiac function, patients with cirrhosis showed substantial \(V_a/Q\) mismatch [32, 33]. This was characterized by the presence of perfusion to low \(V_a/Q\) units and, in some patients, a moderate degree of shunt [32, 33]. These abnormalities of gas exchange were more pronounced in patients with cutaneous spider naevi (those who also depicted the more severe haemodynamic abnormalities) [32]. Studies by other groups extended these observations to patients with more severe degrees of arterial hypoxaemia, in whom pure shunt seems to acquire more physiological relevance [34–37], as well as some level of diffusion disequilibrium to oxygen transfer [35–36]. Both abnormalities of the pulmonary circulation and of gas exchange seem to be more pronounced in those patients with a severe degree of liver failure [1, 2, 31]. Also of interest is the fact that most of these gas exchange and haemodynamic abnormalities appear to resolve following normal-ization of liver function after transplant [2, 24]. Therefore, it is now generally accepted that the "hepatopulmonary syndrome" is characterized by an abnormally low pulmonary vascular tone, as evidenced by a blunted or absent hypoxic vasodilatation, that interferes with an appropriate matching of alveolar ventilation and capillary perfusion and that usually runs in parallel to liver function. Very recently, several diagnostic criteria for this syndrome have been proposed [2].

In summary, for the purpose of this review, the studies alluded to in patients with liver cirrhosis, stressed again the important interrelationships between the pulmonary vascular tone and gas exchange, by demonstrating that, in this case, a low pulmonary vascular tone interferes with the homogeneous distribution of \(V_a/Q\) ratios.

**Summary and conclusions**

We have reviewed the interaction of pulmonary vascular tone and gas exchange in primary pulmonary hypertension, COPD, IPF and liver cirrhosis. We have shown that any situation and/or therapeutic intervention that lowers the active vascular tone deteriorates \(V_a/Q\) relationships, and vice versa. Therefore, this paper has presented evidence to support the fact that, in terms of gas exchange, a high pulmonary vascular tone enhances \(V_a/Q\) matching in lung disease and is, therefore, desirable. However, the final effect of pulmonary vascular tone on arterial \(P_aO_2\) is less predictable. The reason for this uncertainty is that the actual \(P_aO_2\), value depends on the interplay of the intrapulmonary factors (\(V_a/Q\) relationships, intrapulmonary shunt and diffusion limitation to oxygen) and extrapulmonary factors (cardiac output, overall ventilation and oxygen consumption) that control gas exchange in humans, and not only on the degree of \(V_a/Q\) mismatching [7]. A deep analysis of these interactions is beyond the scope of this paper. The interested reader is referred to other papers that discuss this point in more depth [6, 7, 33, 38, 39]. Finally, we have not discussed the well-known deleterious effects of pulmonary hypertension on right ventricular mechanics and performance. Nonetheless, these latter effects should always be borne in mind when facing any given clinical decision.

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**References**