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Role of hypoxic pulmonary vasoconstriction in pulmonary gas exchange and blood flow distribution

2. Pathophysiology

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Abstract. In this review, the second of a two part series, the analytic techniques introduced in the first part are applied to a broad range of pulmonary pathophysiologic conditions. The contributions of hypoxic pulmonary vasoconstriction to both homeostasis and pathophysiology are quantitated for atelectasis, pneumonia, sepsis, pulmonary embolism, chronic obstructive pulmonary disease and adult respiratory distress syndrome. For each disease state the influencce of principle variables, including inspired oxygen concentration, cardiac output and severity of pathology are explored and the actions of selected drugs including inhaled nitric oxide and infused vasodilators are illustrated. It is concluded that hypoxic pulmonary vasoconstriction is often a critical determinant of hypoxemia and/or pulmonary hypertension. Furthermore this analysis demonstrates the value of computer simulation to reveal which of the many variables are most responsible for pathophysiologic results.

Key words: Atelectasis – Chronic lung disease – Adult respiratory distress – Nitric oxide – Computer model

In part 1 [1] of this review an analytic method was introduced that permits information on the distribution of ventilation/perfusion ratios to be combined with a detailed biodynamic model of the pulmonary circulation. This approach, therefore, allows many of the variables to be included that are common to patients with pulmonary pathophysiology and that influence pulmonary gas exchange and steady state hemodynamics. In part 2 the influence of some of these principal variables is explored with respect to the role of hypoxic pulmonary vasoconstriction in atelectasis, pneumonia, sepsis, pulmonary embolism, chronic obstructive pulmonary disease and adult respiratory distress syndrome.

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Although the results obtained herein are supported by a wide range of observations and may be regarded with a reasonable degree of confidence, nevertheless some qualifications are warranted. Thus the multiple inert gas technique from which the distribution of ventilation/perfusion ratios is derived does not assign positional or anatomic sites for the compartments and therefore gravitational influences are not specifically included. The branching structure and responses of the pulmonary vessels on which the pressure-flow curves are based are generalized from observation in a variety of animal species the precision of which will undoubtedly be improved with further research. The focus of this work is the perfusion side of the ventilation/perfusion ratio and alteration of the distribution of ventilation as a result of changes in a variable are not included. Finally, the conditions considered are those of steady state blood flow and therefore only mean pulmonary vascular resistances and pulmonary artery pressures are considered. In the pulmonary circuit unlike the systemic, a considerable proportion of the cardiac work is extended in generating oscillatory flow and the present analysis cannot provide an accurate assessment of the cardiac energy cost of the conditions considered.

Within the bounds of these caveats, however, the methods discussed here include the steady state variables commonly recognized in clinical practice including airway pressure, pleural pressure, hematocrit, hemoglobin, P_{50}, pH, left atrial pressure, cardiac output, oxygen consumption, carbon dioxide excretion, minute ventilation, dead space, shunt, ventilation/perfusion distribution, inspired gas composition, size of the lung and variety of vascular states including embolism, constriction and pathologic narrowing (i.e. fibrous or thrombosis etc.).

HPV in disease states

Atelectasis with remaining lung homogenous

Atelectasis, at the microscopic or macroscopic level, refers to the collapse of lung regions as gases are resorbed from underventilated alveoli. Atelectasis may be due to

space occupying pathology, splinting, or regional airway obstruction by retained secretions or a foreign body and consequent hypoventilation of a specific lung region. Patients with airway obstruction, breathing room air, develop atelectasis slowly. The high concentration of nitrogen in air, and its relative insolubility in blood results in longer alveolar stability than in patients treated with resorbable gases (e.g. nitrous oxide or oxygen). Alveolar units with very low V_A/Q ratios can become unstable and collapse, because more gas is removed by the blood from the alveolus than is excreted into the alvelous.

Hypoxic pulmonary vasoconstriction limits perfusion to atelectatic portions of the lung [2]. In atelectasis, the stimulus for HPV is dependent only on the $P\bar{v}O_2$. If the $P\bar{v}O_2$ is raised to 13.3 kPa (100 mmHg), blood flow to atelectatic lung returns to normal [3] which indicates that there is no mechanical obstruction to blood flow [4] in collapsed lung. In clinical situations where mixed venous oxygen tension is low (anemia, diminished cardiac output, systemic hypoxemia), the stimulus for HPV is increased in atelectatic lung, and blood flow to ventilated portions of the lung is proportionately greater, unless HPV begins to be stimulated also in the remaining ventilated lung.

The influence of increasing atelectasis and/or increasing inspired oxygen concentration on the arterial oxygen tension and the observed pulmonary shunt is illustrated in Fig. 1 for both a homogenous lung (lnSD(Q) = 0) and for a lung corresponding to chronic lung disease (lnSD(Q) = 1.5). A homogenous lung is one in which all alveoli have ventilation/perfusion ratios that are identical to the mean VA/Q. There is no spread of the ratios around the mean and therefore the standard deviation (lnSD(Q)) around the mean is zero. This conditions is never obtained in real lungs but is a useful analytical device because in such lungs the efficiency of gas exchange is dependent only on the existence of shunt. If the shunt is zero the alveolar gas, alveolar end-capillary blood and systemic arterial blood would all have the same oxygen and carbon dioxide tensions.

For the homogenous lung (Fig. 1 a, b) arterial oxygen tension decreases as atelectasis increases and as F_{IO_2} is reduced. The shunt observed remains relatively constant and the degree to which the shunt percentage is less than the atelectasis percentage is one measure of the effectiveness of HPV. However a more relevant measure of the efficacy of HPV is obtained by comparing the calculation in the presence and absence of HPV as has been done in Fig. 2.

Figure 2 shows that the presence of HPV always results in an increase in arterial oxygen tension when atelectasis is present, but the changes vary both with the extent of atelectasis and change in F_{IO_2}. In contrast a much more consistent pattern emerges when the same data are expressed as arterial oxygen contents and the presence of HPV is shown to be increasingly important as atelectasis increases.

This view is confirmed by the more detailed analysis shown for a homogenous lung in the left panel of Fig. 3. The figure shows that for each increment of atelectasis the oxygen content change increases and that this change is essentially constant for all F_{IO_2} greater than about 0.25. The results is important because it emphasizes that

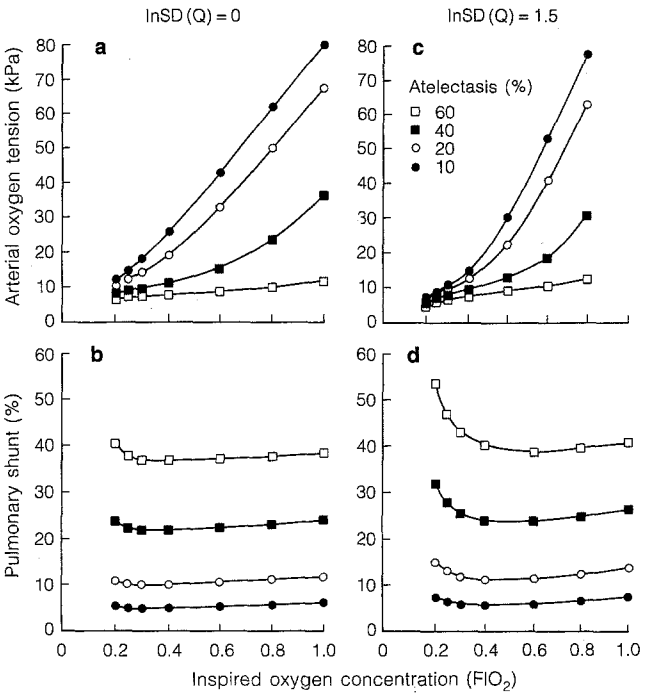

Fig. 1 a–d. The influence of increasing atelectasis, on arterial oxygen tension and pulmonary shunt as the inspired oxygen concentration is altered, is compared for lungs with no abnormality (**a, b**) of V_A/Q distribution (lnSD(Q) = 0) and for lungs with severe (**c, d**) maldistribution (lnSD(Q) = 1.5). The arterial oxygen tension is clearly reduced as atelectasis increases and more so in the presence of V_A/Q maldistribution. But notice that the commonly recognized insensitivity of Pa_{O_2} to increasing F_{IO_2} is not evident until the atelectasis is at least 40% of the lung volume. The effectiveness of HPV in reducing the shunt percentage below the atelectasis percentage is influenced by the extent to which HPV is stimulated in the rest of the lung; at lower F_{IO_2} and especially in the presence of V_A/Q maldistribution this flow diversion response to HPV is impaired

HPV improves the oxygen content of arterial blood to a greater extent with increasing abnormality. The basis for this outcome is not intuitively obvious, so it is worth some further analysis.

Recall that the total content of oxygen carried from the lungs per minute is made up of that carried in the shunted blood plus that passing through ventilated lung:

$$Ca_{O_2} \times \dot{Q}_T = C\acute{c}_{O_2} \times (\dot{Q}_T - \dot{Q}_S) + C_{\bar{v}O_2} \times \dot{Q}_S \quad (1)$$

The equation can be simplified by dividing through by $\dot{Q}_T$ and expressing the shunt as a fraction of the cardiac output. This equation succinctly divides the arterial oxygen content into the two weighted contributions:

$$Ca_{O_2} = C\acute{c}_{O_2} \times (1 - Fs) + C_{\bar{v}O_2} \times Fs \quad (2)$$

This equation states that the final arterial oxygen content (Ca_{O_2}) is the sum of the oxygen delivered from the ventilated alveoli ($C\acute{c}_{O_2} \times (1 - Fs)$) and that crossing the lung via unventilated or atelectatic alveoli ($C_{\bar{v}O_2} \times Fs$). Recall also that the arterio-venous oxygen content difference is dependent only on the oxygen consumption and the cardiac output:

$$Ca_{O_2} - C_{\bar{v}O_2} = \dot{V}_{O_2}/Q_T \quad (3)$$

The expression ($Ca_{O_2} - V_{O_2}/Q_T$) can be substituted for $C_{\bar{v}O_2}$ in Eq. 2 and after rearranging:

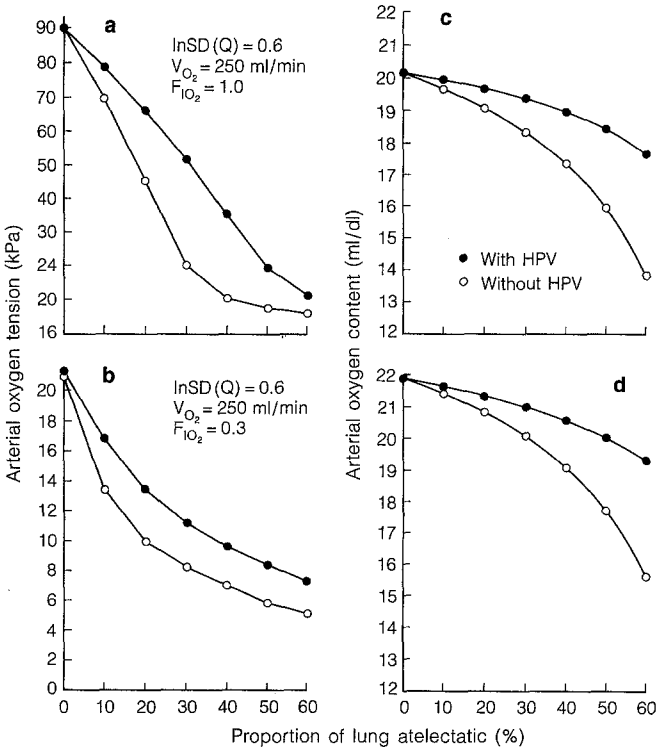

Fig. 2a–d. The influence of HPV on arterial oxygen tension and content are shown for lungs with increasing proportions of the lung atelectatic and with V_A/Q distribution at the upper limit of normal (lnSD(Q) = 0.6) with F_{IO_2} = 1.0 (*upper panels*) and F_{IO_2} = 0.3 (*lower panels*). The solid circles are calculated in the presence and the open circles in the absence of the ability of the pulmonary vessels to respond with HPV. The figures demonstrate that tension changes are complex and disproportional both with increasing atelectasis and increasing F_{IO_2} whereas the content changes reveal a consistent pattern that appears similar with increasing F_{IO_2}. For any particular atelectasis value the difference between the points plotted with and without HPV appears to be almost the same at F_{IO_2} = 1.0 or 0.3. (The *insets* define the initial lung conditions)

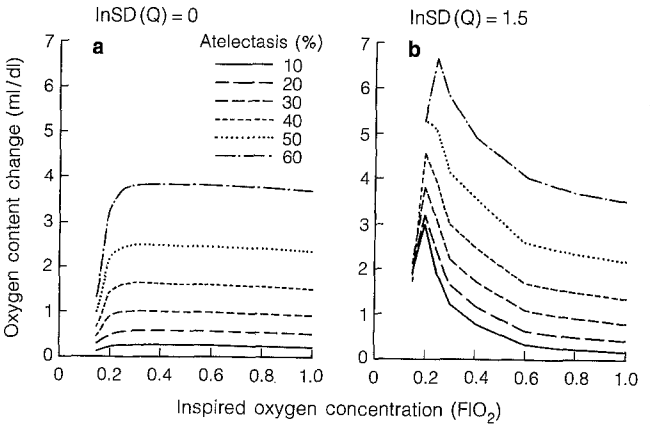

Fig. 3a, b. The difference between the arterial oxygen content with HPV present (Ca_1) and that with HPV absent (Ca_2) is plotted as the change in oxygen content for a wide range of atelectasis volumes and inspired oxygen concentrations. An homogenous lung with lnSD(Q) = 0 is shown on the left and a lung with initial lung conditions of severe maldistribution (lnSD(Q) = 1.5) is shown on the *right*. The curves are a direct measure of the effectiveness of HPV to preserve oxygenation. Note that with an homogenous lung HPV improves arterial oxygen content to a greater extent as atelectasis increases but that the change is almost independent of F_{IO_2} at inspired oxygen concentrations greater than about 0.25. In the presence of V_A/Q maldistribution the importance of HPV is greater at each volume of atelectasis but the changes are strongly and alinearly dependent on F_{IO_2}. See text for explanations

$$Cao_2 = C\acute{c}_{O_2} - (V_{O_2}/Q_T)Fs/(1-Fs) \quad (4)$$

For clarity let Ks replace Fs/(1−Fs), and omit the subscript O_2 for Ca and Cć. The oxygen content change between any two states can then be expressed as:

$$Ca_1 - Ca_2 = (C\acute{c}_1 - C\acute{c}_2) + (V_{O_2}/Q_T)(K_{S2} - K_{S1}) \quad (5)$$

where the subscripts 1 and 2 in the present context refer to the presence and absence of HPV respectively. The value of V_{O_2}/Q_T is that of the arterio-venous oxygen content difference. In the calculations that follow V_{O_2} = 250 ml/min and Q_T = 60 dl/min (note the adjustment of the units to be consistent with the expression of oxygen content as ml/dl). The value of 4.17 may, therefore be substituted for V_{O_2}/Q_T. The separate terms of Eq. 5 retain the same relationship as those described for Eq. 2. Thus, the change in arterial oxygen contents ($Ca_1 - Ca_2$) is the sum of that due to blood from ventilated alveoli ($C\acute{c}_1 - C\acute{c}_2$) and that from unventilated alveoli ($4.17(K_{S2} - K_{S1})$).

Referring again to the left panel of Fig. 3; at any particular F_{IO_2} when lnSD(Q) is zero, the alveolar and hence the end capillary oxygen tensions and content are constant and independent of the degree of atelectasis or the presence or absence of HPV, and therefore the first term on the right side of Eq. 5 ($C\acute{c}_1 - C\acute{c}_2$) becomes zero and the oxygen content change is dependent only on the second term ($4.17(K_{S2} - K_{S1})$). Figure 4 shows the relationship between Fs and Ks. Since the greater the volume of atelectasis the greater the Ks value and the greater the flow of blood diverted by HPV it follows that the change in oxygen content of the arterial blood is also greater. Even though as F_{IO_2} changes the absolute value of the alveolar and end capillary oxygen tensions and therefore contents change, still the first term on the right side of Eq. 5 remains zero. Fig. 3a demonstrated that the second term, relating to shunt flow, remains essentially constant for all F_{IO_2} greater than 0.25 because the stimulus for HPV ($P\bar{v}_{O_2}$) and hence the final shunt remains almost constant despite the fact that the arterial oxygen tension changes markedly.

At F_{IO_2} values of less than 0.25, the entire lung demonstrates some HPV and pulmonary artery pressure increases, this has the effect of opposing the HPV in the atelectatic region and the change of arterial oxygen content is reduced.

Atelectasis with remaining lung not homogeneous

The altered pattern of changes of oxygen content observed with atelectasis when the rest of the lung is not homogeneous is illustrated in the right hand panels of Figs. 1 and 3. To understand the basis for these changes and the role of HPV it is necessary first to consider how increasingly abnormal distribution of the V_A/Q ratio (or lnSD(Q)) influences gas exchange and pulmonary artery pressure in the absence of atelectasis. In Fig. 5 it is appar-

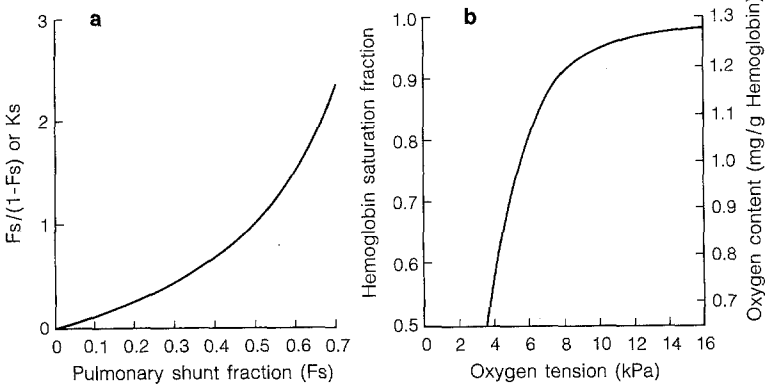

Fig. 4a, b. The relationship between the shunt function (Fs) and the expression (Fs/(1−Fs)) used in Eq. 5 is shown in **a**. **b** provides a portion of the hemoglobin dissociation curves so that oxygen saturations, contents and tensions can be related when considering the text discussion. A value of 1.306 ml/g is used for the oxygen carrying capacity of hemoglobin

ent that when breathing air $F_{IO_2} = 0.21$) the greater the lnSD(Q) the lower the Pa_{O_2} and the greater the pulmonary artery presure (and pulmonary vascular resistance). As F_{IO_2} increases, the influence of lnSD(Q) on oxygen tension lessens and is abolished at $F_{IO_2} = 1.0$. Note that lnSD(Q) itself is not abolished but only its effect on oxygen exchange. As discussed below carbon dioxide exchange is still affected by the lnSD(Q) when $F_{IO_2} = 1.0$.

The role of HPV is demonstrated in two ways in Fig. 5. First, the lower right panel demonstrates how the lnSD(Q) entered as the initial data is altered in the presence of HPV. At $F_{IO_2} = 1.0$ the final calculated distribution of the V_A/Q is equal to that entered, but as F_{IO_2} is reduced HPV effectively improves V_A/Q matching and lnSD(Q) is reduced. However, the extent of the improvement varies alinearly with both the lnSD(Q) and the F_{IO_2}. A more impressive demonstration of the influence of HPV is shown in the lower left panel of Fig. 5 where the arterial oxygen content change is plotted for each lnSD(Q) when HPV is present compared to when it is absent. Again there is no effect when $F_{IO_2} = 1.0$, but the effect of HPV is increasingly evident as lnSD(Q) increases and/or F_{IO_2} is decreased. Referring back to Eq. 5 in the previous section note that because atelectasis and therefore shunt are zero the second term on the right of this expession is zero and the results of Fig. 5C are summarized by

$$Ca_1 - Ca_2 = C\acute{c}_1 - C\acute{c}_2 \ .$$

This equality is consistent because in a lung without shunt the arterial oxygen content is the same as the end capillary oxygen content. Note however that the greater the lnSD(Q) the greater will be the difference between the alveolar gas oxygen tension and the end capillary blood oxygen tension. In other words the end capillary oxygen content decreases with increasing lnSD(Q) at all F_{IO_2} less than 1.0. From the data of Fig. 3A for the oxygen content change with atelectasis when lnSD(Q) = 0 and that of Fig. 5C for oxygen content change when lnSD(Q) is varied while atelectasis is zero it might be supposed that the two could be simply added to conclude how HPV influences diseases states when both atelectasis and abnormal V_A/Q distributions are combined. Perusal of Fig. 3B makes it clear that the results do not follow a simple summation.

To visualized how the role of HPV changes when both abnormalities are combined a more detailed analysis is shown in Fig. 6A for a condition with 40% atelectasis and lnSD(Q) = 1.5. The figure shows how by the use of Eq. 5 the shunt and the lnSD(Q) components to the oxygen content change can be identified at each F_{IO_2}. With this separation the conceptual basis for the changes is clarified. When $F_{IO_2} = 1$ the lnSD(Q) has no influence on arterial oxygen content and the change in oxygen content is entirely due to the effectiveness of HPV in reducing the shunt. As F_{IO_2} decreases the influence of HPV is reflected both in decreased shunt and improved oxygen content for the lnSD(Q) compartment. However, as HPV

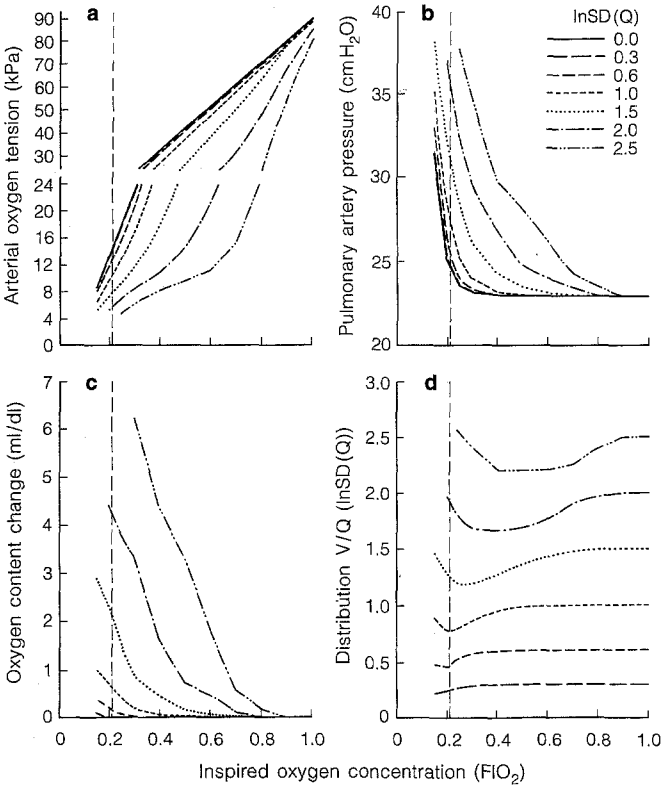

Fig. 5a–d. The influence of increasingly abnormal V_A/Q distribution (lnSD(Q)), in the absence of atelectasis, on gas exchange and hemodynamic function with increasing F_{IO_2}. The inset provide the key to the curves, but note that lnSD(Q) of zero is an homogenous lung with one compartment; 0.3 is a normal lung; 0.6 is the upper limit of normal; 1.0 and 1.5 represent moderate and severe abnormality respectively encountered in chronic lung disease while 2.0 and 2.5 result in the life-threatening impairment of gas exchange found in patients with ARDS. The *dotted vertical line* corresponds to F_{IO_2} of air. For discussion see text

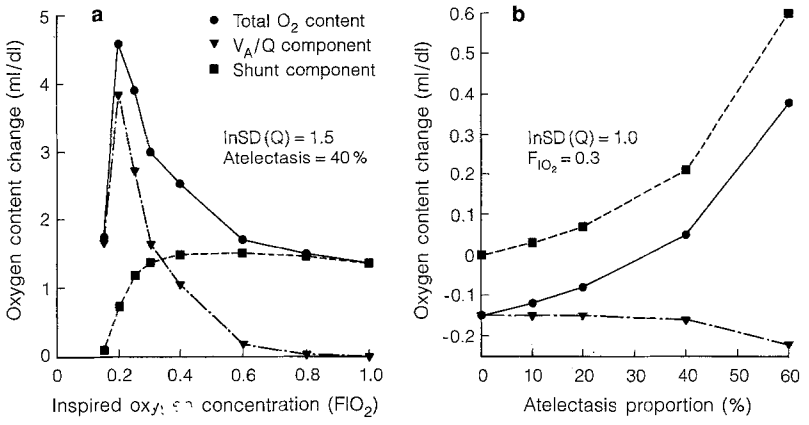

Fig. 6a, b. Analysis of the arterial oxygen content change due to HPV to reveal the changing contribution of the shunt and the V_A/Q distribution compartments as F_{IO_2} is altered. The results were obtained by solving Eq. 5 where the total oxygen content change is $(Ca_1 - Ca_2$. Panel **a** is for a lung with severe chronic lung disease and with initial conditions of lnSD(Q) = 1.5 and atelectasis = 40%. Ca_1 and Ca_2 are calculated for the presence and absence of HPV as F_{IO_2} is increased. Panel **b** is for a lung with moderate lung disease where the initial conditions where lnSD(Q) = 1.0 and $F_{IO_2} = 0.21$. The calculation is performed in the presence of HPV (Ca_1) and during the inhalation of 80 ppm of nitric oxide (Ca_2) as the proportion of atelectasis in increased. Note that the scale of the oxygen content change is expanded tenfold in Panel **b**. See text for discussion

increases throughout the lung with decreasing F_{IO_2} pulmonary vascular pressure rises; and while at first the effect of increasing pressure is offset by increased stimulation of HPV as $P\bar{v}O_2$ decreases, eventually at F_{IO_2} less than 0.4, HPV becomes less effective in the atelectatic regions, and the contribution of the shunt compartment to the improvement of oxygen content is reduced. When F_{IO_2} is 0.21 the combination is maximal with the effect of HPV being attributable as 84% to improvement of lnSD(Q) and 16% to reduction of shunt. When F_{IO_2} is reduced further the entire pulmonary vasculature is stimulated to constrict and useful redistribution is impaired. All of the curves illustrated in Fig. 3 B can be accounted for in this fashion so it is important to recognize that the effectiveness of HPV is not a simple function although the outcome in terms of oxygen tension or content changes may be represented as a more or less smooth continuous curve.

Pneumonia and sepsis

Lobar or regional pneumonia can be due to viruses, bacteria, fungi, obstruction or aspiration. Distinction between atelectasis and pneumonia is often difficult; the radiographic findings of each are similar and both may cause elevations in temperature and derangements in gas exchange. In the clinical setting, it is the presence or absence of purulent sputum or elevated white cell count which determines the diagnosis.

Alveolar filling, rather than alveolar collapse, causes gas exchange abnormalities in pneumonia, and as with atelectasis, HPV can effectively divert pulmonary blood flow from poorly ventilated alveoli, resulting in improved V_A/Q matching by the same method. It may be speculated also that loss of surface tension at the epithelial surfaces with reduction of the outward distending force on pulmonary vessels may promote diversion of blood flow with HPV.

There is evidence that HPV is impaired in acute and chronic infections [5, 6] and often abolished in sepsis [7], which accounts for the disproportionally increased shunting and acute hypoxemia frequently found in these states. There are also a variety of vasoactive mediators which may alter pulmonary vascular tone associated with infection and aspiration, including prostaglandins [8], leukotrienes [9], cytokines, metabolites [10] and platelet activating factors [11]. In the absence of chronic lung disease HPV acts on pneumonia both qualitatively in a manner similar to that described for atelectasis but quantitatively the ability of the vascular smooth muscles to contract is often impaired [5–7]. In the presence of chronic lung disease, the development of acute pneumonia combining additional lung injury with impairment of HPV often precipitates respiratory failure.

Loss of vascular bed

Concomitant with most forms of severe lung disordes, whether acute or chronic, is loss of the pulmonary vascular bed. Obstruction by various emboli, thrombosis, hyperplasia, fibrosis or space occupying lesions may each result in obliteration of some portion of the pulmonary vascular bed [12].

The incidence of pulmonary embolism is high and carries an acute mortality rate of about 10%, but unless the onset is precipitated by a massive pulmonary embolus this is usually a process that progresses in so subtle a manner as to go undetected. The vascular bed has a large reserve that must be reduced by 40% or more before the physical signs at rest show much change. A convincing way to demonstrate the functional effect is to measure the increase in pulmonary artery pressure during excercise but this requires invasive testing and is not often performed [13]. In the intensive care setting there is often so much pathophysiology present that subtle changes in pressure-flow relations are overlooked, except as a general pattern emerges when successive showers of microemboli reach the lung.

It is clear from a variety of data that the pulmonary vascular effects of emboli are not due solely to the mechanical obstruction of blood flow through the lungs. Intraoperative or diagnostic occlusion of a main pulmonary artery does not typically cause any significant elevation of pulmonary artery pressure, while occlusion of a similar amount of the pulmonary vasculature with clot causes a significant increase in pressure. There is a consis-

tent increase in lung water after embolism, which is probably multifactorial.

Arterial hypoxemia is virtually always present with a clinically significant embolism, and usually unrelieved by breathing 100% oxygen. Alveolar units near occluded pulmonary arteries may become atelectatic and edematous, in part due to loss of surfactant. Blood flowing through these areas is unoxygenated, simulating shunted blood. The combination of low cardiac output and poor arterial oxygen saturation results in diminished oxygen delivery to the tissues and low mixed venous oxygen saturation. Elevated pulmonary artery resistance places a strain on right heart function, which can ultimately lead to further decreases in cardiac output. A self-reinforcing cycle ensues, which, if uninterrupted, leads to right heart failure, secondary left heart failure, and death.

The coexistence of systemic hypoxemia and low mixed venous P_{O_2} represents a profound stimulus for generalized hypoxic pulmonary vasoconstriction, which accounts, at least in part, for the increase in pulmonary vascular resistance after pulmonary embolism. HPV in this circumstance is diffuse and maladaptive as compared to atelectasis and pneumonia where it is regional and beneficial. This represents a pathological state wherein HPV is detrimental to gas exchange and to cardiac performance. In a similar circumstance, neonates with tetralogy of Fallot can develop a deadly cycle wherein they become hypoxemic (from coughing, or hypoventilation), HPV ensues causing increased pulmonary arterial pressure. Increased pulmonary resistance worsens shunting across the ventricular septal defect and causes systemic hypoxemia and low mixed venous oxygen tension which increase the stimulus for HPV; a downward spiral ensues.

In Fig. 7 the effects of increasing loss of vascular bed are illustrated for three conditions. In the first condition the remaining vessels are normal, in the second the small arteries and veins have undergone a modest active constriction to 90% of their resting diameters and in the third condition the small arteries and veins have been moderately narrowed, as by pathology, to 90% of their resting diameter. The difference between constriction and narrowing is that constriction is fully reversible but the narrowing is not [14]. Most obvious in each panel of this figure is the quite abrupt increase in the degree of abnormality as the loss of vascular bed increases above 40%. All three conditions reveal the same trends, but it is noteworthy that whereas the pulmonary artery pressure increases progressively with conditions 1 and 2 and 3, for all other measures of gas exchange, as illustrated in Fig. 7, the constricted vasculature improves the performance while with the narrowed vasculature it deteriorates compared to the normal vessels. The reason for this behavior anticipates the discussion of ARDS below but basically is due to improvement of shunting and lnSD(Q) in the presence of constriction and the worsening with narrowing.

These calculations assume that HPV is active and that cardiac output remains constant, but the effect of changes in one or both of these variables is illustrated in Fig. 8. A decreased cardiac output and/or decreased HPV results in reductions of both arterial oxygen tension and pulmonary artery pressure.

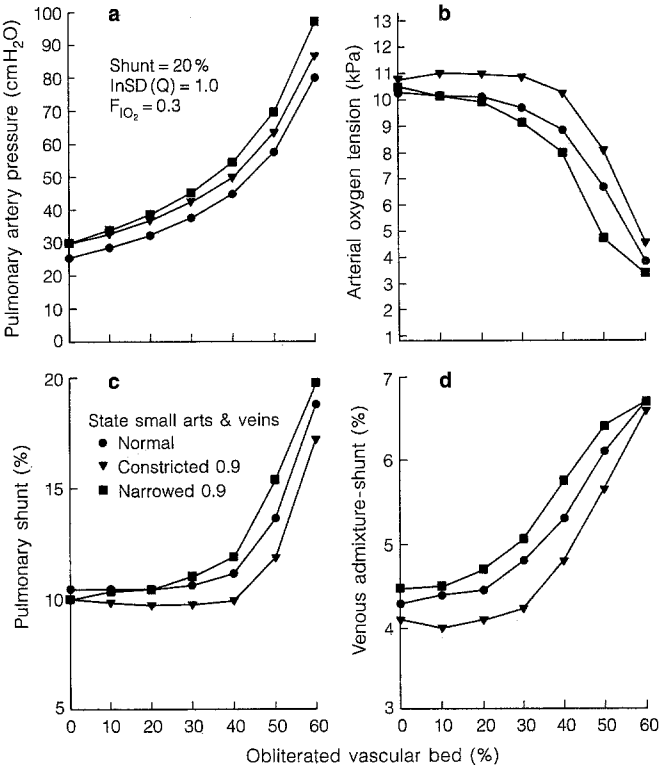

Fig. 7a–d. The influence of increasing obliteration of the vascular bed on gas exchange and hemodynamic function for a lung with moderate lung disease. The *three lines* correspond to normal vessels, to lungs in which the small vessels have been actively constricted slightly (to 0.9 of their diameter at rest) or narrowed slightly (to 0.9 of their diameter at rest). The abrupt increase in abnormal function is evident when more than 40% of the vascular bed is lost. See text for discussion. (*Inset* defines initial lung conditions)

Chronic lung disease

The common pulmonary parenchymal diseases of chronic bronchitis and emphysema are associated with all of the pathophysiologic entities discussed above. Atelectasis, increased distribution of V_A/Q ratios, loss of vasculature and intermittent acute infections are characteristic of these patients [13]. The pulmonary hypertension cor pulmonale and hypoxemia that characterize the "blue bloater" represent loss of vascular bed and ineffective HPV while for the "pink puffer" the principal disorder is destruction of total lung tissue. These represent extremes of a continum of presentations, and in both cases something, usually infection, surgery or some other stress, precipitates additional hypoxemia and acute respiratory failure.

In a study of fifty patients with COPD, Kawakami and colleagues [15] performed right sided cardiac catheterization and compared survival 4 years later. The 27 non-survivors were compared to 23 survivors. At the time of initial evaluation, the nonsurvivors differed from the survivors only in regards their lower Pa_{O_2} and $P_{\bar{v}O_2}$ and higher Pa_{CO_2} and $P_{\bar{v}O_2}$. Other parameters, such as mean pulmonary artery pressure, right ventricular work, oxygen transport and coefficient of oxygen delivery were not different. This suggests that effectiveness of HPV may

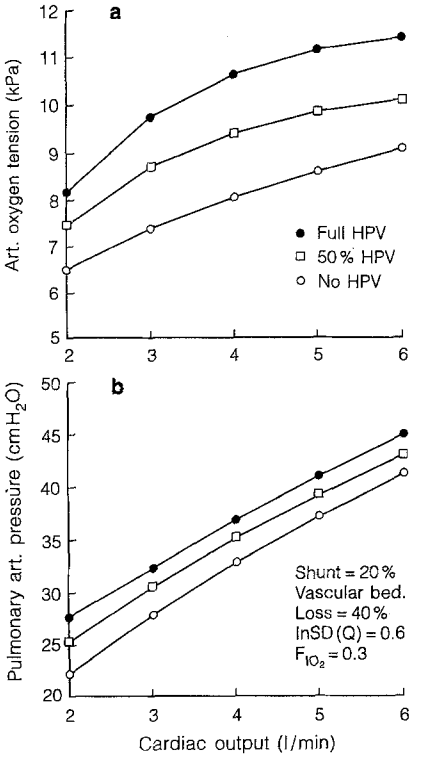

Fig. 8. The influence of cardiac output and of altered HPV activity on arterial oxygen tension and pulmonary artery pressure in a patient with chronic lung disease. Note that reducing the cardiac output has a greater proportionate effect on pulmonary artery pressure than on arterial oxygen tension whereas reducing HPV, the proportionate changes are reversed. (*Inset* defines initial lung conditions)

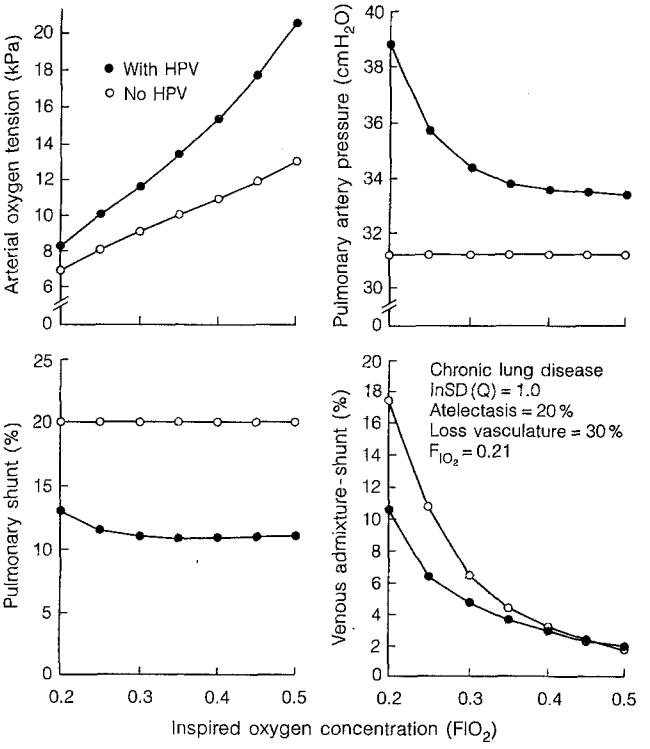

Fig. 9. The presence and absence of HPV in chronic lung disease is illustrated as F_{IO_2} is changed. The profound effects of HPV on arterial oxygen tension and pulmonary artery pressure are evident. Analysis of the inefficiency of oxygen exchange in terms of the pulmonary shunt and of pulmonary venous admixture minus the shunt is another way of expressing the changing influence of the V_A/Q distribution component. The inrease of the venous admixture at lower F_{IO_2} is evident. (*Inset* defines initial lung conditions)

correlate with survival in COPD, although increased severity of disease in the non-survivors is also probable.

Figure 9 illustrates chronic lung disease that has moderately affected function. When breathing air the pulmonary artery pressure is markedly increased and arterial hypoxemia is evident. The basis for the hypoxemia is both shunt from atelectasis and the extra venous admixture component from increased lnSD(Q). As F_{IO_2} increases the pulmonary artery pressure decreases indicating that HPV is active; but even at $F_{IO_2} = 0.5$, when lnSD(Q) is no longer causing constriction, the pulmonary artery pressure is well above normal reflecting both constriction through the shunt and the loss of vascular bed.

When HPV is lost the shunt and lnSD(Q) are no longer regulated and arterial oxygen tension and pulmonary artery pressure decrease. Pa_{O_2} breathing air is only about 7.0 kPa and even with 50% oxygen increases only to about 11 kPa. It is easy to understand how acute infections with sudden loss of gas exchange surface and perhaps more generalized interference with HPC precipitates rapid deterioration. Furthermore if cardiac output decreases or if oxygen consumption should increase, and especially if HPV is simultaneously reduced, as illustrated in Fig. 10, the threat to life is immediate. A recurring theme in these disease states is that of HPV either present but so generalized as to precipitate right heart failure, or so impaired as to reveal severe hypoxemia.

Adult respiratory distress syndrome (ARDS)

Patients may develop ARDS as an acute exacerbation of chronic lung disease or as a result of severe acute damage to a previously healthy lung. Characteristically, ARDS develops secondary to shock, trauma or sepsis and there are therefore many etiologies for this state but in all patients the severity of the pulmonary pathophysiology is such that sufficient gas exchange cannot be maintained breathing air spontaneously. Much of the enormous creative effort in respiratory intensive care has been directed at managing patients with acute lung injury or ARDS. Despite the significant advances that have benefitted all patients requiring periods of mechanical ventilation, the short term prognosis for patients with ARDS remains poor. One reason is that ARDS is often just one manifestation of multiple organ failure and the complexity is presently overwhelming. A second reason is that most of the treatments have been directed solely at maintaining sufficient oxygen and carbon dioxide exchange to permit time for antibacterials and natural healing processes to succeed. Improvements in outcome are likely to follow when treatments are specifically directed at regulating the pathophysiologic processes themselves so as to reduce or prevent the establishment of irreversible changes in pulmonary structure. Chief among these are

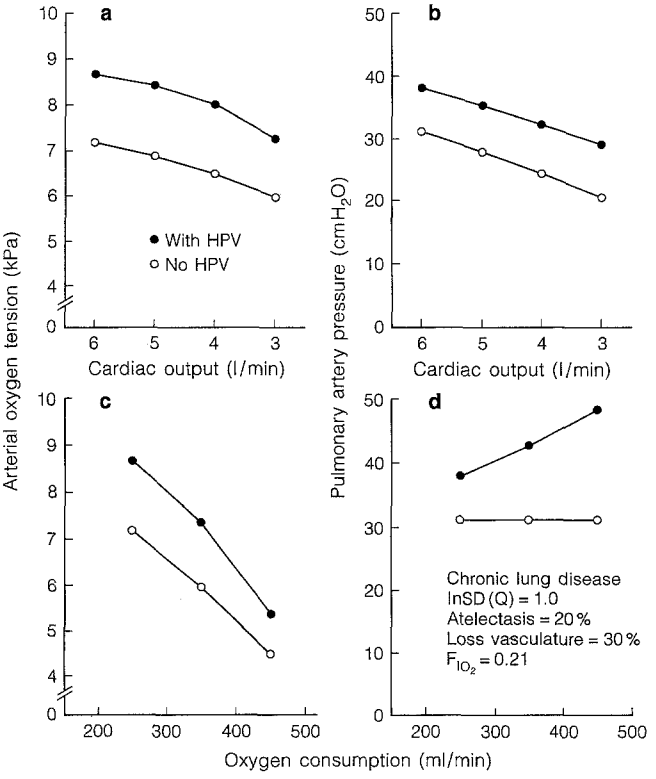

Fig. 10a–d. In chronic lung disease changes in cardiac output or oxygen consumption are illustrated in the presence and absence of HPV. Panels **a** and **b** show that oxygen tension and pulmonary artery pressure both declin as cardiac output decreases. In constrst, Panels c and d show that increasing oxygen consumption causes a profound reduction of arterial oxygen tension but increases pulmonary artery pressure. In the absence of HPV the deterioration of actual oxygen tension is enhanced in both examples and the pulmonary artery pressure changes demonstrate that the increased pressure with increasing oxygen consumption is entirely due to increased stimulation of HPV but with decreasing cardiac output the passive reduction in pressure is partially offset by increasing HPV attributable to increased stimulation as $P_{\bar{V}O_2}$ declines. (*Inset* defines initial lung conditions)

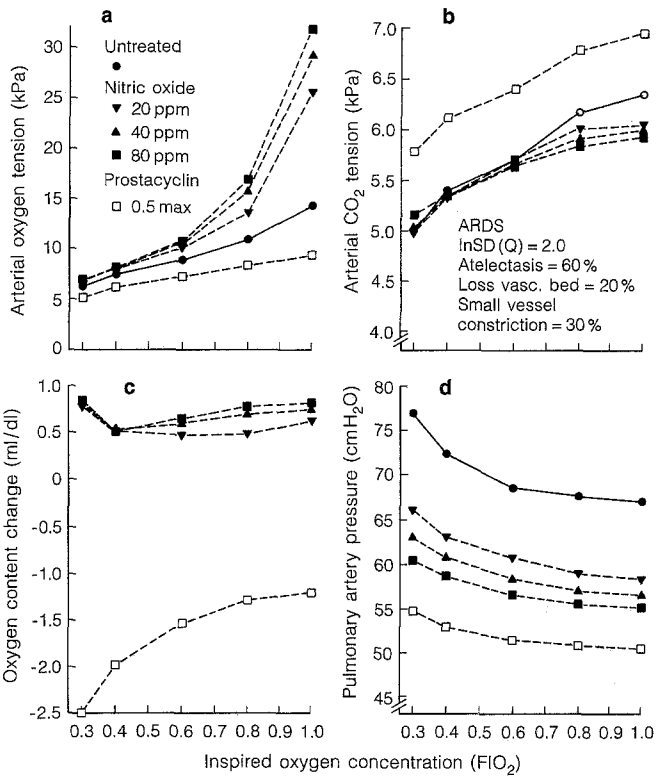

Fig. 11a–d. Adult respiratory distress syndrome. The values for arterial oxygen tension, arterial carbon dioxide tension and pulmonary artery pessure are shown for untreated patients and for patients treated with infusion of prostacyclin or nitric oxide. The dose of prostacyclin is such that it reduces constriction by 50% and the dose response relationship for nitric oxide was determined from published data. Note that, in addition to the conditions listed in the inset, the patients were assumed to be mechanically ventilated with positive end-expiratory pressure so that the alveolar and left atrial pressures were 15 cmH_2O and the pleural pressure was 5 cmH_2O while alveolar ventilation had to be increased to 10 l/min to adequately remove carbon dioxide. The oxygen content change in Panel **c** is calculated as $Ca_1 - Ca_2$, where Ca_1 is the untreated and Ca_2 the treated state. With both treatments pulmonary artery pressure was decreased but with prostacyclin oxygenation worsened while with nitric oxide it was improved; see text for discussion. (*Inset* defines initial lung conditions)

destruction of the pulmonary circulation with loss of vascular bed [16], narrowing of remaining vessels and fibrosis of the vascular wall with loss of HPV and hence the ability to regulate V_A/Q ratios and flow to atelectatic areas [17].

These pathophysiologic processes have not yet been sufficiently elucidated, but inappropriate pulmonary vascular constriction, whether resulting from HPV or from endogenous and/or exogenous vasoactive materials, is becoming recognized as one of the precipitating factors for ARDS and if too long sustained, constriction is the precursor for irreversible vascular changes [16].

That is why the current interest in the use of vasodilators, whether by inhalation (Nitric Oxide) or by infusion (i.e. Prostacyclin analogs, sodium nitroprusside, nitroglycerine or amrinone, et cetera), is so intense. This discussion will therefore focus on the functional pathophysiology of ARDS, the role of HPV and the rationale for the effective use of vasodilators. Note however that many drugs used for other purposes in these patients may also interfere with HPV. Such drugs include calcium channel blockers beta agonists, nitroglycerine and sodium nitroprusside.

Pathophysiology of ARDS

The general changes and the basis for them are illustrated in Fig. 11 and 12 for a set of conditions that would be characterized as ARDS. There is no particular combination that should be designated typical. The characteristics are the functional outcome and in the example illustrated by the solid line and filled circles in Fig. 11 and 12 mechanical ventilation and supplemental oxygen are essential for maintenance of life. The arterial oxygen tension is less that 6 kPA even with $F_{IO_2} = 0.3$ and the alveolar ventilation has to be increased to twice normal to maintain carbon dioxide clearance. The combination of increased V_A/Q abnormality, atelectasis, loss of vascular bed and small vessel constriction from endogenous mediators in addition to HPV results in severe pulmonary hy-

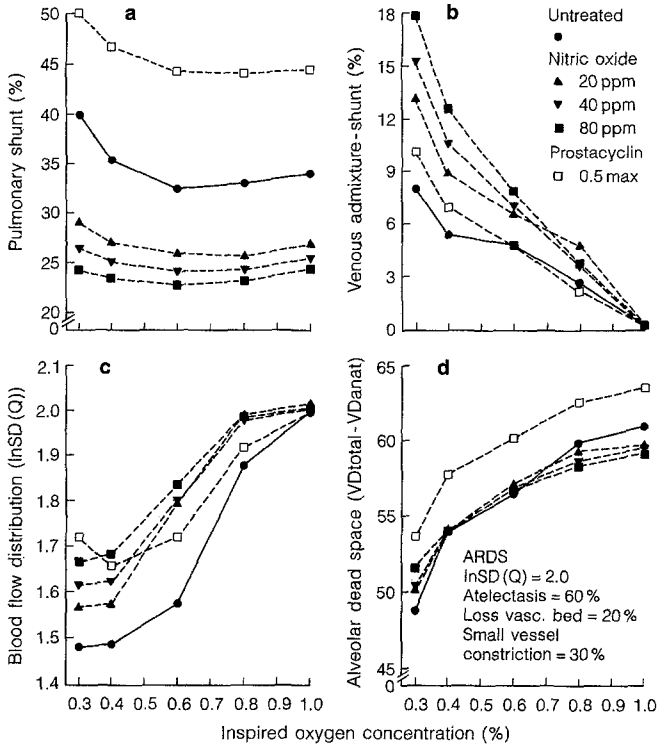

Fig. 12a–d. Adult respiratory distress syndrome: the pathophysiologic basis for the changes illustrated (in Fig. 11) are analyzed in terms of changes in pulmonary shunt, pulmonary venous admixture-shunt, V_A/Q distribution or lnSD(Q) and alveolar dead space. See text for discussion. (*Inset* defines initial lung conditions)

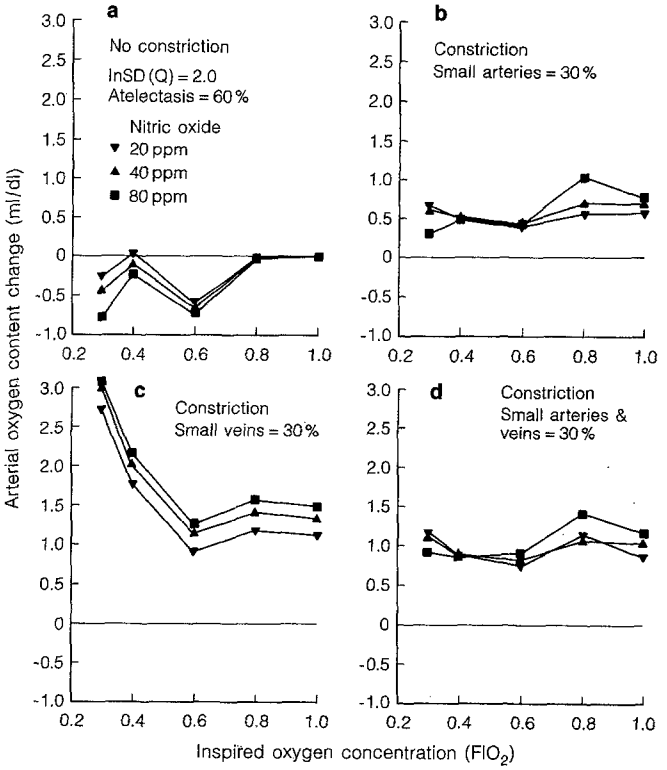

Fig. 13a–d. The adult respiratory distress syndrome conditions of (Fig. 11c) are modified to reveal the extent to which small vessel constriction determines the response to inhalation of nitric oxide. Arterial oxygen content change is calculated as $Ca_1 - Ca_2$ where Ca_1 is the oxygen content with treatment and Ca_2 is the untreated state. A positive change indicates that treatment improved oxygen exchange, a negative value indicates a worsening. Note that positive values were only obtained for the lung conditions where small vessel constriction was present in addition to HPV. See text for discussion

pertension. The functional outcome, summarized in Fig. 11, is therefore a patient at the limit of cardiac and respiratory reserves. The influence of increasing F_{IO_2} and the more detailed analysis provided in Fig. 12 reveal the basis for the functional impairment. Thus the modest increase in Pa_{O_2} when $F_{IO_2} = 1.0$ indicates a large shunt as the predominant cause of hypoxemia. The decreased pulmonary artery pressure with increasing F_{IO_2} is primarily due to the reduction of hypoxic constriction in the rest of the lung as the effects of lnSD(Q) become less pronounced. In Fig. 12d, for example, the lnSD(Q) is uncompensated when $F_{IO_2} = 1.0$; this is because all ventilated alveoli will be filled with oxygen and P_{SO_2} will be greater than 16 kPa, even if $P_{\bar{v}O_2}$ is reduced to 2.7 kPa, so that HPV is not stimulated (see [1] Fig. 4).

Even at $F_{IO_2} = 1.0$ pulmonary hypertension persists although whether due to constriction, narrowing or loss of vascular bed cannot be distinguished on the basis of this information alone. The worsening of lnSD(Q) as F_{IO_2} is increased is demonstrated by the increasing alveolar dead space which causes the arterial carbon dioxide tension to increase. It is this effect of increasing F_{IO_2} that appears to be responsible for hypercarbia in a spontaneously breathing patient with chronic obstructive pulmonary disease (COPD) and a severe lnSD(Q) rather than a reduction of an abnormal hypoxic ventilatory drive.

Vasodilator therapy

The critical distinction between nitric oxide (NO) [18] and all the other vasodilators (i.e. prostacyclin analogs (PG)) [19] is that NO is administered by inhalation and is delivered only to ventilated alveoli while PG is infused intravenously or into the pulmonary artery and is delivered to all regions of the lung. These drugs will reduce or abolish HPV and any other active vasoconstrictors only at the sites to which they are delivered and therefore the simplest expectation would be that both routes of administration will reduce the pulmonary vascular resistance and hence the pulmonary artery pressure but NO will not affect the HPV in atelectatic areas and therefore oxygenation might be better preserved.

This indeed was the outcome reported in a series of papers [20–22] and demonstrated in the dashed lines of Figs. 11 and 12. These figures show, as expected, that pulmonary artery pressure is reduced most with PG and also substantially with increasing inspired concentrations of NO. Furthermore both NO and PG are associated with increasing lnSD(Q) because HPV is reduced in the ventilated lung regions. But these are the only similarities and it is the differences that are more interesting.

The arterial oxygen tension decreases with PG because the generalized reduction of HPV results in a worsening of both lnSD(Q) and the pulmonary shunt. The substantial shunt increase also compounds the impaired excretion of carbon dioxide with a further effective in-

crease in alveolar dead space and Pa_{CO_2}. In contrast NO only reduces HPV in the ventilated lung so that lnSD(Q) is worsened but the reduction in constriction in this region of the lung allows more effective diversion of blood flow from the atelectatic region and shunt is reduced substantially even at he lowest concentrations. The improvement in oxygen exchange that results from the reduction of shunt more than makes up for the loss due to worsening lnSD(Q) and it follows that the greater the F_{IO_2} the greater the change will be.

This contrast is nicely illustrated by considering the change in arterial oxygen content. Fig. 11 c illustrates differences in the treated and the untreated state showing that the arterial oxygen content is increased by NO and decreased by PG.

This desirable outcome is not however obtained consistently. Most clinical investigators have observed quite variable effects during inhalation of NO. In some patients Pa_{O_2} remains unchanged or declines and in some the pulmonary vascular resistance does not respond. It is therefore useful to identify what factors determine the desirable responses to NO.

One approach is to analyze which of the pathophysiologic components of the ARDS illustrated in Fig. 11 and 12 are necessary for the effect of NO. This analysis is presented in Fig. 13 where the effectiveness of the NO treatments is evaluated as the change of arterial oxygen content from the untreated state. The data show that a positive oxygen content change is only seen with treatment when some constriction in addition to HPV is present in small arteries of veins or both. By far the greatest effect is seen with constriction of small veins, and treatment with NO in that circumstance will reduce pulmonary capillary pressure and the tendency to pulmonary edema simultaneously.

Before concluding that inhalation of NO will only be effective when some additional source of constriction is present it is useful to examine Eq. 5 again. For this equation subscript 1 now refers to the presence of NO while subscript 2 is the untreated state. Treatment will only result in a decrease of $C\acute{c}_1$ so the arterial oxygen content change will only be positive if the second term representing the effect of reducing the shunt is greater than the effect of worsening the lnSD(Q). The major requirement is that NO should reduce the vascular resistance in the ventilated lung regions so that shunt flow declines but at the same time not so reduce the end capillary oxygen as to offset the benefit to gas exchange.

Such conditions will exist when a large volume of atelectasis coexist with a moderate lnSD(Q) abnormality in the presence of an F_{IO_2} low enough to permit constriction in the ventilated lung. This condition is illustrated in Fig. 6B and demonstrates that NO may indeed improve oxygenation in patients without additional sources of vasoconstriction but the changes will be small and the requirement that F_{IO_2} not be too increased necessitates and undesirable degree of hypoxemia.

This conclusion suggests that the ability of NO to improve oxygenation should be enhanced when it is combined with an infused vasoconstrictor. This result is demonstrated in Fig. 14 where it is shown that a judicious selection of infused vasoconstrictor can almost double the improvement in Pa_{O_2} while still providing substantial reduction of pulmonary artery pressure. A clinical trial of such a combination is clearly warranted which in fact may already have inadvertently been the basis for some reported successes with NO.

Several additional factors may interfere with the efficacy of NO in patients with ARDS and two of these are illustrated in Fig. 15. The first of these (Fig. 15 a, b) is any circumstance that results in the reduction or loss of the HPV response. Pulmonary infection, septicemia and toxemia, direct lung trauma, lung hyperinflation, alcohol and systemic administration of vasodilator drugs are examples of common factors associated with reduction of the HPV response. The second example (Fig. 15 c, d) is the replacement of actively constricted small pulmonary vessels by fibrotic and irreversibly narrowed pulmonary vessels a sequence that becomes evident in most patients after a week or two of ARDS [16]. In both cases the response are substantially reduced or abolished compared to those previously illustrated in Fig. 11.

Conclusion

The survival of patients undergoing pulmonary intensive care is primarily dependent on the successful manage-

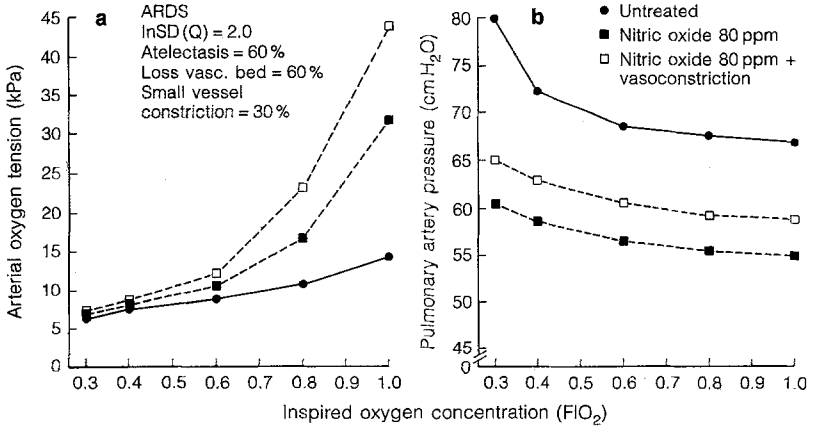

Fig. 14 a, b. In the condition of adult respiratory distress syndrome the combination of an infused vasoconstrictor with inhaled nitric oxide is shown to markedly enhance arterial oxygen tension compared to treatment with nitric oxide alone. At the same time substantial reduction of pulmonary artery pressure is observed. See text for discussion. (The inset defines the initial conditions)

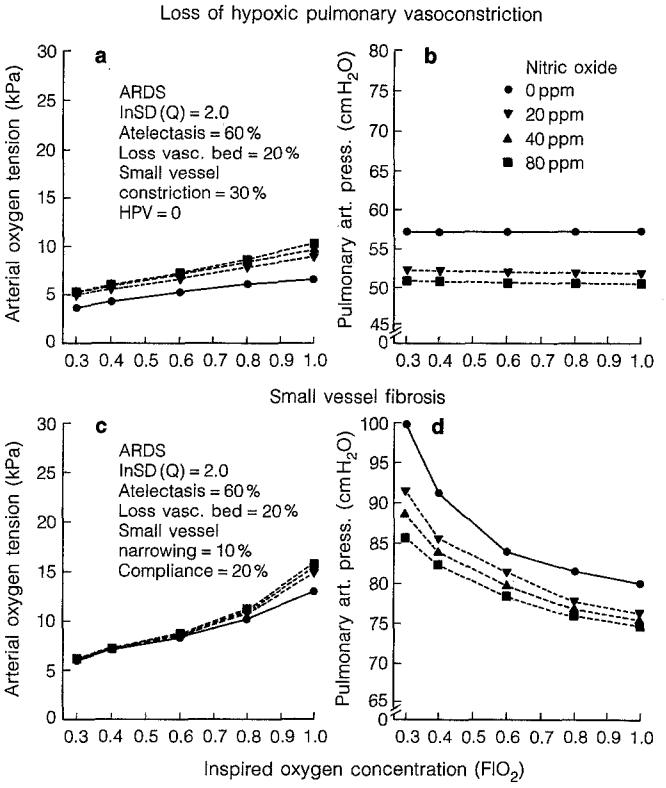

Fig. 15a–d. Additional factors that reduce the effectiveness of nitric oxide treatment in adult respiratory distress syndrome are: Panels **a** and **b**, loss of HPV, and Panels **c** and **d**, small vessel fibrosis so that active constriction is replaced by irreversible narrowing. See text for discussion

ment of pulmonary gas exchange and hemodynamics. This brief review has used some new analytical tools to evaluate the interactions between gas exchange and pulmonary blood flow and has revealed the central role of hypoxic pulmonary vasoconstriction. HPV is fundamental to efficient gas exchange both due to its homeostatic regulation of V_A/Q ratios and redirection of blood flow from atelectatic regions which would otherwise contribute to shunt. Its loss, due to pharmacologic interference or endogenous vasoactive mediators, can cause hypoxemia. The benefical effects of HPV are lost when constriction is so generalized that redistribution is no longer possible, and, in this circumstance, pulmonary artery pressures may rise to the point that right heart strain or failure results.

As more information about the specific cell biology of these disease states becomes available for therapeutic applications the effective use of pharmacologic agents will require a more detailed understanding of the state of the pulmonary circulation. It is anticipated that analytic approaches such as that introduced here may be able to contribute to that process.

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