Causes of hypercarbia with oxygen therapy in patients with chronic obstructive pulmonary disease

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Objectives: To compare data derived from a computer model of the pulmonary circulation with data from a case series of patients with chronic obstructive pulmonary disease (COPD). To evaluate the specific factors contributing to CO_2 retention due to oxygen therapy in patients with acute exacerbations of COPD.

Design: Data from a computer model of the pulmonary circulation were compared with a previous case series.

Patients: Patient data were derived from previous case series.

Interventions: Simulated application of oxygen therapy.

Measurements and Main Results: The computer model of the pulmonary circulation generates data comparable with those data from a series of patients with COPD treated with supplemental oxygen and permits identification of the causes for hypercarbia. Therapy with supplemental oxygen alters hypoxic pulmonary vasoconstriction and modulates the Haldane effect, resulting in changes in physiologic deadspace.

Conclusion: Changes in physiologic deadspace are sufficient to account for the hypercarbia developed by patients with acute exacerbations of COPD when treated with supplemental oxygen. (Crit Care Med 1996; 24:23–28)

KEY WORDS: chronic obstructive pulmonary disease; hypercapnia; vasoconstriction; pulmonary circulation; respiratory deadspace; ventilation/perfusion ratio; lung diseases; critical illness; pulmonary emergencies

Patients with chronic obstructive pulmonary disease (COPD) are often hypoxemic and hypercarbic, as typified by the so-called "blue-bloater." Acute exacerbations due to bronchitis or pneumonia can cause further deterioration in gas exchange with systemic hemoglobin desaturation. Injudicious application of oxygen therapy results in a dangerously increased $Paco_2$ in a subset of patients with COPD. This hypercarbia has generally been attributed to depression of hypoxic respiratory drive (1, 2) in patients with blunted or absent ventilatory response to hypercarbia, with a consequent decrease in minute ventilation. There are, however, little clinical data to support this explanation. Studies in the 1980s by Aubier and colleagues (3, 4) of patients with COPD and acute respiratory failure showed that "the changes in $Paco_2$ elicited by the inhalation of O_2-enriched air did not correlate with the changes in ventilation."

Other potential causes for the increase in CO_2 are increased ventilation-perfusion maldistribution in the lung (5, 6) and the Haldane effect, which refers to the decreased carriage of CO_2 by oxyhemoglobin when compared with reduced hemoglobin (Fig. 1A) (7, 8).

The present work evaluates the relative contributions of the Haldane effect and of changes in ventilation/perfusion ratios to CO_2 retention in chronic obstructive pulmonary disease.

MATERIALS AND METHODS

This work did not involve the collection of data from human or animal subjects and therefore, our Institutional Review Boards were not involved. A computer model has been developed that combines the multiple compartment ventilation-perfusion model of gas exchange developed by Wagner et al. (9) with a model of the pulmonary circulation (10). The model permits analysis of gas exchange and pulmonary hemodynamics in ~50 compartments and for any combination of mechanical, constrictive, obstructive, or physiologic factors.

The following parameters are used in the computer model (11, 12), which has been described elsewhere: shunt fraction; ventilation-perfusion distribution (lnSD[Q]) for an arbitrary number of compartments; cardiac output; pulmonary artery occlusion pressure; positive end-expiratory pressure; mixed venous oxygen saturation; hematocrit; temperature; degree of active vasoconstriction; vascular occlusion; and vascular obstruction. The model can be initiated with actual values (when they are known), assumed values, or any combination of the two.

A single pressure-flow curve for the entire lung is derived from the starting parameters based on the work of Fung (13) and Marshall (10), in which the effects of factors such as hypoxic pulmonary vasoconstriction, flow rate, hematocrit, vessel caliber, elasticity, and outflow pressure on pressure-flow relationships in pulmonary vessels were experimentally determined. The model assumes that each of these parameters, with the exception of hypoxic pulmonary vasoconstriction, are constant in every compartment. The degree of activity of hypoxic pulmonary vasoconstriction is calculated in each compartment and then used to modify the pressure-flow, and therefore ventilation-perfusion relationship in each compartment.

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This study was supported, in part, by grants GM29628 and GM07612 from the National Institutes of Health.

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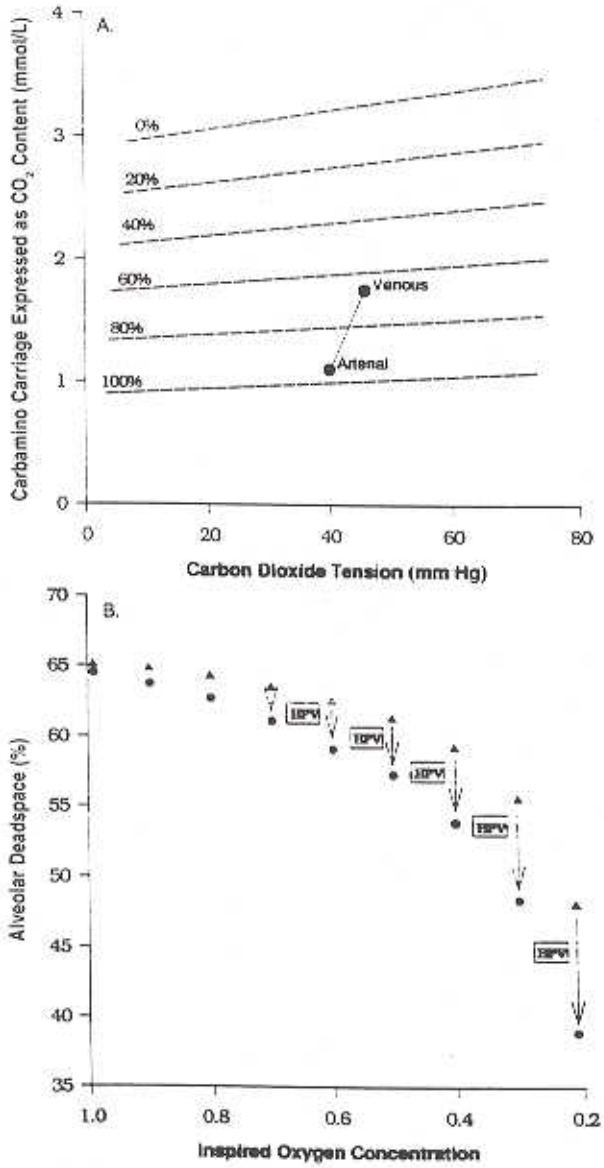

Figure 1. *A)* Carbamino carriage of CO_2 in arterial and venous blood. The *dotted lines* indicate different levels of hemoglobin saturation with oxygen, and demonstrate that at any given Pco_2, carbamino carriage is greater in desaturated blood. Reproduced with permission from Nunn JF (2). *B)* Hypoxic pulmonary vasoconstriction (*HPV*) acts to redistribute blood to poorly perfused units and thereby reduce deadspace. Its effects are more prominent at low inspired oxygen concentrations.

The shunt and ventilation-perfusion distribution are used to calculate pulmonary gas exchange, and therefore alveolar oxygen tension, in each compartment (14). The stimulus for hypoxic pulmonary vasoconstriction is calculated for each compartment from the mixed venous oxygen tension and the alveolar oxygen tension, using the following equation: stimulus oxygen tension = alveolar oxygen tension$^{3.6}$ + mixed venous oxygen tension$^{3.4}$ (15).

The stimulus oxygen tension determines the degree of hypoxic pulmonary vasoconstriction response in each compartment, from which a family of pressure-flow curves can be generated describing the *relative* flow to each compartment (which must add up to total flow). Since there is only one pulmonary arterial pressure that satisfies both the individual and the total flow requirements for the compartment and starting conditions respectively, the flow to each compartment can be determined. The flow in each compartment now differs from that described by the starting conditions and therefore, the compartmental alveolar oxygen tension has changed. The new alveolar oxygen tension is applied to the stimulus oxygen tension equation (in above paragraph), resulting in a new family of pressure-flow curves, and this sequence is reiterated until Pao_2 converges to a preselected precision.

The model assumes that the influence of hypoxic pulmonary vasoconstriction is homogeneous within the pulmonary vascular bed. It also assumes that the effects of gravity are small relative to the effects of disease in determining inhomogeneity in blood flow distribution. Finally, the effects of respiratory gases on airways are ignored. The degree of inhomogeneity in ventilation is explicit in the starting parameters (the log standard distribution of ventilation/perfusion ratios), and the model assumes that respiratory gases primarily affect the distribution of blood flow rather than ventilation. Current research indicates that both airway tone and collateral ventilation are modified homeostatically by respiratory gases, but that these effects are trivial compared with the effects of respiratory gases on the distribution of blood flow in the lung (16).

In order to investigate the contribution of the Haldane effect and alterations in ventilation-perfusion distribution to hypercarbia in COPD, the model was initiated with physiologic parameters derived from the patients in the study by Aubier et al (4). Ventilation, perfusion, and pressure were derived for a 20-compartment model based on the stimulus for hypoxic pulmonary vasoconstriction in each compartment. (Twenty compartments were used for ease of calculation: the model converges on the final solution more rapidly than with fifty compartments, although the same results are achieved.) The initial compartments were generated using a $\ln SD(Q) = 2.3$ and shunt of 30%, which are assumed values. These values are consistent with experimentally determined values in COPD patients and give room air blood gases similar to those room air blood gases in Aubier's patients. Polycythemia, which is typical in this patient population, was simulated using a hematocrit of 50%. A supranormal cardiac output of 8.0 L/min was used to be consistent with the clinical findings of Aubier et al. (4), as was an alveolar minute ventilation of

6.0 L/min. Oxygen consumption was fixed at 250 mL/min. F_{IO_2} was varied between 0.21 and 1.00.

RESULTS

When the starting parameters were modeled at an F_{IO_2} of 0.21, and when the effects of hypoxic pulmonary vasoconstriction were simulated, a Pa_{O_2} of 34 torr (4.5 kPa) and Pa_{CO_2} of 57 torr (7.6 kPa) were derived. The alveolar deadspace (Model calculations refer to alveolar deadspace rather than physiologic deadspace. Anatomical deadspace can be added for calculation purposes and minute ventilation adjusted independently) was 39% and mean pulmonary arterial pressure was 42 mm Hg. As F_{IO_2} was increased to 1.0 with constant minute ventilation, alveolar deadspace increased to 64%. The Pa_{CO_2} increased to 84 torr (11.2 kPa), and pulmonary arterial pressure decreased to 25 mm Hg.

Pa_{CO_2} also increased when the effect of hypoxic pulmonary vasoconstriction was absent (which would be analogous to the use of a direct-acting vasodilator, such as sodium nitroprusside, or the presence of sepsis). At an F_{IO_2} of 0.21, when the effects of hypoxic pulmonary vasoconstriction were absent, Pa_{O_2} was 20 torr (2.7 kPa), Pa_{CO_2} 73 torr (9.7 kPa), alveolar deadspace 48%, and pulmonary arterial pressure 25 mm Hg. At an F_{IO_2} of 1.0, Pa_{O_2} was 222 torr (29.6 kPa), Pa_{CO_2} 85 torr (11.2 kPa), alveolar deadspace 65%, and pulmonary arterial pressure 25 mm Hg. The increase in Pa_{CO_2} that occurs in the absence of a change in minute ventilation and when the hypoxic pulmonary vasoconstriction effect is not active is entirely attributable to the Haldane effect.

DISCUSSION

The conventional explanation for the hypercarbia that occurs in COPD patients when treated with supplemental oxygen is that with increased Pa_{O_2}, hypoxic ventilatory drive is diminished and Pa_{CO_2} increases. The studies by Aubier et al. (4) of COPD patients in acute respiratory failure, which are summarized in Table 1, showed that while there is minimal change in minute ventilation after 15 mins of F_{IO_2} 1.0, the expected increase in Pa_{CO_2} occurred. Aubier et al. (4) surmised that the increase in Pa_{CO_2} was due to "increased V_{CO_2} or, more likely V_D." Our data indicate that a comparable change in Pa_{CO_2} can be entirely accounted for by a combination of the Haldane effect on alveolar deadspace and the effects of hypoxic pulmonary vasoconstriction on venous admixture and alveolar deadspace.

The patient with severe COPD has a limited ability to increase minute ventilation due to diaphragmatic flattening, fixed chest expansion, and limitations to expiratory flow. This patient population cannot, therefore, dynamically compensate for increases in alveolar deadspace or CO_2 production, and Pa_{CO_2} increases.

Haldane Effect. The Haldane effect is of experimental interest but generally relegated to a footnote in standard clinical texts, despite the fact that it is responsible for about one half of the normal arterial-venous CO_2 content difference. As the distribution of ventilation/perfusion ratios increases with pathophysiology, the Haldane effect functions less efficiently and its relevance to CO_2 excretion becomes more prominent.

The Haldane effect is proportional to the difference between venous hemoglobin oxygen saturation and arterial hemoglobin oxygen saturation. Deoxygenated hemoglobin binds hydrogen ion more effectively than oxygenated hemoglobin. As a result, at any given Pa_{CO_2}, deoxygenated blood carries more CO_2 in the form of bicarbonate than oxygenated blood. CO_2 also binds directly to deoxygenated hemoglobin more effectively than oxygenated hemoglobin. As a red blood cell moves from the venous circulation through the pulmonary bed and hemoglobin is oxygenated, hydrogen ion and CO_2 are released and an increased proportion of the total CO_2 content enters the gas phase, equilibrates with ideal alveolar gas, and is exhaled.

The change in CO_2 content due to the Haldane effect ($\dot{C}[\bar{v}\text{-}a]CO_2$) across the pulmonary circulation is inversely proportional to the difference between mixed venous oxygen saturation and arterial oxygen saturation—the greater the gradient, the more CO_2 molecules are released. As $C(\bar{v}\text{-}a)CO_2$ decreases, the amount of CO_2 exhaled must decrease and calculated alveolar deadspace increases. The term "Haldane deadspace" can therefore be used to refer to the apparent increase in alveolar deadspace due to a diminished gradient between venous and arterial hemoglobin oxygen saturation.

It is axiomatic that as the ventilation-perfusion distribution widens in the diseased lung, a greater percentage of the cardiac output flows through poorly ventilated lung (where venous blood is poorly oxygenated). Since this portion of the blood flow has a less than normal increase in oxygenation, Haldane deadspace increases. A second cause for the greater influence of Haldane deadspace at high F_{IO_2} relates to the shape of the oxyhemoglobin dissociation curve. As F_{IO_2} is increased from 0.21 to 1.0, there is a larger increase in mixed venous oxygen saturation (on the steep portion of the curve) than in arterial saturation (on the flattened portion of the curve)

Table 1. Data from Aubier's study of 22 patients with "acute on chronic" respiratory failure

	F_{IO_2}		
	0.21	1.0[a]	*p* Value
Pa_{O_2} (torr)	38 ± 2	225 ± 23	< .001
(kPa)	5.1 ± 0.3	30 ± 3.1	
Pa_{CO_2} (torr)	65 ± 3	88 ± 5	< .001
(kPa)	8.7 ± 0.4	11.7 ± 0.7	
pH	7.34 ± 0.01	7.25 ± 0.02	< .001
$\dot{V}_E$ (L/min)	10.2 ± 0.5	9.5 ± 0.7	< .01
f	32 ± 2	31 ± 2	NS
V_T (mL/min)	341 ± 26	323 ± 21	NS
V_D/V_T	77 ± 2	82 ± 2	< .01

$\dot{V}_E$ minute ventilation; f, frequency; V_T, tidal volume; V_D/V_T, deadspace/tidal volume ratio.
[a]After 15 mins oxygen breathing.
Adapted from Aubier et al (4).

and therefore, Haldane deadspace increases.

Hypoxic Pulmonary Vasoconstriction. By reducing the width of the distribution of ventilation/perfusion ratios, hypoxic pulmonary vasoconstriction enhances the efficiency of pulmonary gas exchange (and compensates for Haldane deadspace) in two ways: a) reduction of venous admixture (or physiologic shunt) by redirection of blood flow from poorly ventilated to better ventilated compartments; and b) reduction of alveolar deadspace. As perfusion is redistributed, ventilation to individual anatomical units of the lung may remain unchanged, but the altered perfusion causes a change in the ventilation/perfusion *ratio* of that unit. The effects of hypoxic pulmonary vasoconstriction over the entire lung can be expressed by comparing ventilation to compartments at room air when hypoxic pulmonary vasoconstriction is active and at an F_{IO_2} of 1.0 (17). On room air, hypoxic pulmonary vasoconstriction acts to redistribute blood to units with high ventilation/perfusion ratios, lowering the ventilation/perfusion ratio in those compartments and thereby reducing deadspace.

The way in which hypoxic pulmonary vasoconstriction acts to redistribute blood flow to compartments with "excessive" ventilation, therefore improving the ventilation/perfusion ratio of those compartments, is not intuitively obvious, and only is operative in patients with clinically important lung disease. Patients such as those in the study by Aubier et al. (4) are hypoxic on low inspired oxygen concentrations, and therefore have increased overall pulmonary vascular tone. The pulmonary arterial pressure on room air in the modeled data was 16 mm Hg higher than that pressure on an F_{IO_2} of 1.0. At low F_{IO_2} values, with hypoxic pulmonary vasoconstriction operative, the higher perfusion pressure is sufficient to recruit blood flow to compartments with high ventilation/perfusion ratios, therefore lowering ventilation/perfusion ratios in those units and reducing deadspace (Fig. 1*B*). CO_2 excretion is consequently more efficient for a given minute ventilation and P_{aCO_2} decreases.

Comparison of data derived from the computer model and Aubier's (4) "average" patient show remarkably similar results (Table 2).

In the patients studied by Aubier et al. (4), minute ventilation decreased by 0.7 L/min when F_{IO_2} was increased from 0.21 to 1.00, accounting for 5 torr (0.7 kPa) of the average 23 torr (3.1 kPa) increase in P_{aCO_2} (from 65 torr [8.7 kPa] to 88 torr [11.7 kPa]). An additional 7 torr (0.9 kPa) could be accounted for by the Haldane effect, while the remainder (11 torr [1.5 kPa]) was attributed to changes in deadspace (Table 3).

In the computer model, when ventilation was fixed, and F_{IO_2} varied between 0.21 and 1.00, the P_{aCO_2} increased by 27 torr (3.6 kPa), from 57 torr (7.6 kPa) to 84 torr (11.2 kPa). The Haldane effect accounted for 12 torr (1.6 kPa), while the remaining 15 torr (2 kPa) was due to worsened ventilation-perfusion matching as hypoxic pulmonary vasoconstriction decreased at higher F_{IO_2} (Table 3).

The overall influence of the Haldane effect and hypoxic pulmonary vasoconstriction on CO_2 excretion are illustrated in Figures 2*A* and *B*. Figure 2*A* shows the four elements that contribute to P_{aCO_2} in the absence of hypoxic pulmonary vasoconstriction. Basal CO_2 excretion is fixed despite changes in F_{IO_2}, as is the deadspace due to ventilation-perfusion

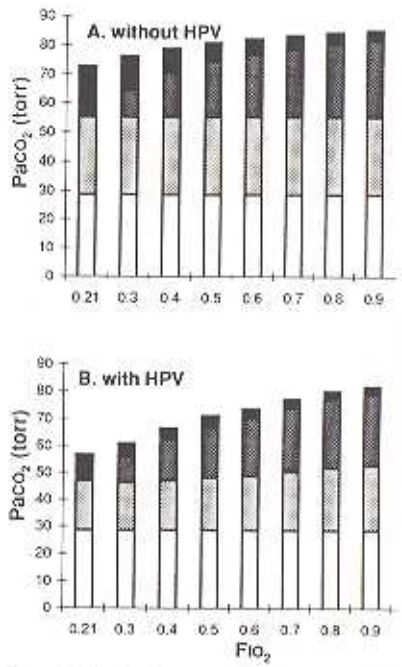

Figure 2. The four factors contributing to arterial pressure of CO_2 are shown in graph *A* (in which hy pulmonary vasoconstriction is not active) and in *B* (in which hypoxic pulmonary vasoconstriction is tive). The contribution from basic CO_2 excretion determined by metabolic rate and respiratory quo is shown in white (*bottom bars*). The contribution deadspace due to ventilation-perfusion mismatc shown in light gray (*second bars*). The contribu from deadspace due to the Haldane effect is show dark gray (*third bars*). The contribution from deadsp due to venous admixture in black (*top bars*). Gra shows the way in which hypoxic pulmonary vaso striction acts to reduce the contribution of both ver admixture and alveolar deadspace to P_{aCO_2} (com with graph *A*) by reducing ventilation-perfusion match. Note that the efficacy of hypoxic pulmo vasoconstriction is lost at higher F_{IO_2}.

Table 2. Comparison of the blood gas values derived from Aubier's patients, and those derived by the computer model

	F_{IO_2} (Aubier's Study)		F_{IO_2} (Computer Study)*	
	0.21	1.00	0.21	1.00
pH	7.34 ± 0.01	7.25 ± 0.02	7.33	7.20
P_{aO_2} (torr)	38 ± 2	225 ± 23	34.0	269.0
(kPa)	5.1 ± 0.3	30 ± 3.1	4.5	35.8
P_{aCO_2} (torr)	65 ± 3	88 ± 5	57.0	84.0
(kPa)	8.7 ± 0.4	11.7 ± 0.7	7.6	11.2

*With hypoxic pulmonary vasoconstriction applied and base excess equal to 0.0.

Table 3. The individual contribution change in minute ventilation ($\dot{V}_E$), Haldane effect, and change in alveo deadspace ($V_{D_{Alv}}$) to the increase in Pa when F_{IO_2} is increased from 0.21 to 1.0. N that the total change in P_{aCO_2} is the sun the individual components in each colu which equals the difference in P_{aCO_2} (at two F_{IO_2} values) from Table 2

	Aubier's Study	Comput Study
$\Delta \dot{V}_E$		
(torr)	5.0	Fixed
(kPa)	0.7	Fixed
Haldane		
(torr)	7.0	12.0
(kPa)	0.9	1.6
$V_{D_{Alv}}$		
(torr)	11.0	15.0
(kPa)	1.5	2.0
Total ΔP_{aCO_2}		
(torr)	23.0	27.0
(kPa)	3.0	3.6

distribution. As F_{IO_2} increases in the setting of an abnormal ventilation-perfusion distribution, Haldane deadspace increases and P_{aCO_2} rises.

Hypoxic pulmonary vasoconstriction increases the efficiency of CO_2 excretion through its effects on venous admixture and alveolar deadspace (Fig. 2*B*), both resulting from changes in the distribution of ventilation/perfusion ratios in the lung. By redirecting blood flow from poorly ventilated portions of the lung, hypoxic pulmonary vasoconstriction diminishes venous admixture, thereby limiting the amount of blood that passes through the lung without the opportunity to excrete CO_2. Hypoxic pulmonary vasoconstriction also lessens deadspace ventilation by increasing perfusion to compartments with high ventilation/perfusion ratios, as described above, and improving the overall relationship between ventilation and perfusion (Fig. 3), which suggests that therapies that act to generally constrict the pulmonary circulation may be efficacious in this patient population.

Figure 4 summarizes the extent to which the degree of preexistent lung pathology affects the P_{aCO_2} when F_{IO_2} is varied. As lung pathology worsens, so does the distribution of ventilation/perfusion ratios and alveolar deadspace. Contrast the normal lung (room air alveolar deadspace of <10%), where increasing F_{IO_2} has little effect on alveolar deadspace and P_{aCO_2}, to the increasingly abnormal lung (room air alveolar deadspace of >30%), where alveolar deadspace and P_{aCO_2} rise substantially as F_{IO_2} increases.

The study by Aubier et al. (4) suggests that the hypercarbia is due primarily to changes in ventilation-perfusion relationships with oxygen therapy rather than to changes in minute ventilation. Our computer model, which simulates the Haldane effect and the influence of hypoxic pulmonary vasoconstriction on ventilation and perfusion, continues and expands the observations from the work of Aubier et al. (3, 4), and quantitatively establishes the theoretical basis for these results.

While the Haldane effect significantly enhances CO_2 excretion in health, its effectiveness requires a normal ventilation-perfusion distribution. The patients described in the studies by Aubier et al. (3, 4) are disadvantaged by several factors: compensatory increases in minute ventilation are constrained by diaphragmatic flattening and muscle fatigue, and ventilation-perfusion distribution is markedly abnormal. In this

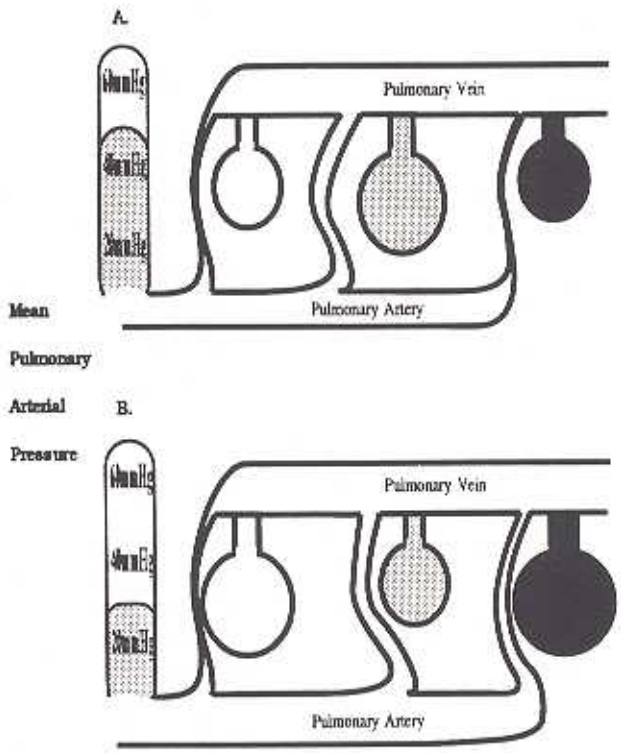

Figure 3. The ways in which F_{IO_2} acts on the pulmonary circulation in the patient with lung disease. When F_{IO_2} is low and hypoxic pulmonary vasoconstriction is active (*A*), vessels perfusing poorly ventilated lung constrict (*black*). This hypoxic pulmonary vasoconstriction increases overall pulmonary arterial pressure, which augments flow to poorly perfused lung (*white*), and narrows the distribution of ventilation/perfusion ratios. This process, in turn, reduces alveolar deadspace due to high ventilation/perfusion ratio, and increases the volume of lung in which gas exchange occurs at ideal ventilation/perfusion ratio (*gray*). When F_{IO_2} is increased and hypoxic pulmonary vasoconstriction is "released" (*B*), pulmonary arterial pressure decreases, there are significant perfusion of poorly ventilated lung, significant ventilation of poorly perfused lung, and a reduced volume of lung in which gas exchange is normal.

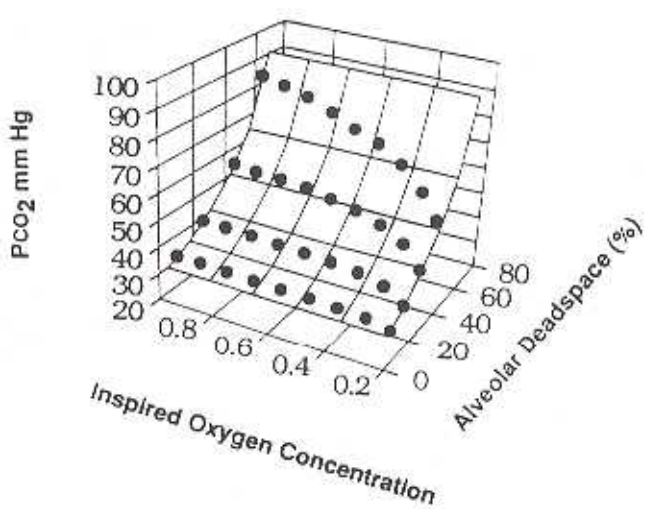

Figure 4. The interactions among F_{IO_2}, P_{aCO_2}, and alveolar deadspace. The four series of dots represent four increasingly diseased "patients," and their predicted changes in P_{aCO_2} as F_{IO_2} is varied. The patient in the foreground is normal (room air alveolar deadspace of <10%), and has essentially no change in P_{aCO_2} over the range of possible F_{IO_2} values. The patient in the far field has clinically important lung disease, such as the patients in the study by Aubier et al. (room air alveolar deadspace of >30%), and both P_{aCO_2} and alveolar deadspace increase significantly as F_{IO_2} is increased.

setting, Haldane deadspace interferes with CO_2 exchange as F_{IO_2} increases.

Hypoxic pulmonary vasoconstriction is the primary intrinsic pulmonary feedback regulator serving to optimize the distribution of ventilation/perfusion ratios, and therefore to improve pulmonary gas exchange at low F_{IO_2}. Previous work has emphasized the role of hypoxic pulmonary vasoconstriction in the improvement of oxygen exchange, but the present data indicate that hypoxic pulmonary vasoconstriction is also effective in minimizing physiologic deadspace, and therefore improving the efficiency of CO_2 exchange.

The development of Haldane deadspace and loss of the mitigating effects of hypoxic pulmonary vasoconstriction are sufficient to account predominately for the changes in P_{aCO_2} seen in patients with severe COPD when treated with oxygen.

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