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Editorial

Hypercapnia during oxygen therapy in airways obstruction: a reappraisal

Hypercapnia and acidosis after oxygen therapy in patients with acute exacerbations of chronic airways obstruction is well recognised, and an understanding of its pathogenesis is essential if successful strategies to limit the rise in arterial carbon dioxide tension ($Paco_2$) are to be designed.

The acute rise in $Paco_2$ during oxygen therapy was first ascribed to reduced hypoxic drive (due to the rise in Pao_2), an acquired insensitivity to carbon dioxide, and consequent hypoventilation.[1] This led to the introduction by Campbell of controlled oxygen therapy to give hypoxic patients a small increase in arterial oxygen tension (Pao_2), sufficient to increase significantly the arterial oxygen saturation (Sao_2), but not to depress seriously the ventilatory drive.[2] Other mechanisms for this oxygen induced hypercapnia were considered (table 1) but were originally thought to be playing only a minor part. Recently new experimental data[3] in patients with acute respiratory failure have cast doubt on the classic explanation of hypoventilation. Instead, it was suggested that the rise in alveolar oxygen tension reduces the adaptatory pulmonary vasoconstriction that normally helps to maintain ventilation-perfusion ($\dot{V}A/\dot{Q}$) matching. Thus a deterioration in $\dot{V}A/\dot{Q}$ matching rather than hypoventilation became the favoured explanation for the hypercapnia. Interpretation of data in this field is extremely difficult and there are inadequate experimental data available to prove one or other of these hypotheses.

The purpose of this article is to discuss the possible mechanisms of carbon dioxide retention after oxygen therapy and to re-examine the relevent data, particularly those of Aubier *et al*.[3] The conclusions are at variance with those of some other authors—namely: (*a*) release of hypoxic vasoconstriction has a minimal effect; (*b*) the major factor causing extra carbon dioxide retention is decreased hypoxic drive due to the rise in Pao_2, as originally proposed; (*c*) the Haldane effect plays a smaller part in the steady state increase in $Paco_2$ than previously supposed.

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Table 1 *Suggested causes of raised arterial carbon dioxide tension after oxygen therapy in patients with chronic airways obstruction*

1	Hypoventilation from reduced hypoxic ventilatory drive due to the rise in arterial oxygen tension
2	Increased ventilation-perfusion mismatching: (*a*) loss of hypoxic vasoconstriction (*b*) development of collapsed alveoli
3	Haldane effect—displacement of carbon dioxide from oxygenated blood
4	Reduced slope of the carbon dioxide content curve for blood as carbon dioxide tension rises—reduction in effective partition coefficient

Effect of oxygen during acute exacerbations of chronic airways obstruction

Although clinically it was well recognised that high inspired oxygen concentrations led to severe hypercapnia in acute exacerbations of chronic airways obstruction, it was not until 1980 that Aubier *et al* made comprehensive measurements of gas exchange in this condition.[3]

METHODS

Aubier *et al* looked at 22 patients with chronic airways obstruction during an episode of acute on chronic respiratory failure. All were severely hypoxic and hypercapnic (table 2). Ventilation was measured with a mouthpiece, one way valve, and pneumotachograph (deadspace 75 ml). Ventilation, blood gases, mixed expired carbon dioxide, and cardiac output were measured before and at the end of 15 minutes of breathing 100% oxygen. The physiological deadspace $V_{D_{phys}}$ to tidal volume (V_T) ratio was calculated from the simplified equation:

$$\frac{V_{D_{phys}}}{V_T} = \frac{(Paco_2 - P_Eco_2)}{Paco_2},$$

where P_Eco_2 = mixed expired CO_2 tension.

RESULTS

They found[3] that, initially, overall ventilation fell by 18% but then rose to 93% of the control level during the 15th minute of oxygen administration. Although the 7% fall in ventilation at the 15th minute was

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Table 2 *Data on gas exchange in patients studied by Aubier et al[3] with acute on chronic respiratory failure before and after they had breathed 100% oxygen*

	Air	*Oxygen*	*% change*
P_{aCO_2} mm Hg (kPa)	65 (8·7)	88 (11·7)	+35
$\dot{V}$ (l/min)	10·2	9·5	− 7
f (b/min)	32	31	− 3
V_T (ml)	341	323	− 6
$V_{D_{phys}}/V_T$ (%)	77	82	+ 6

P_{aCO_2}—arterial carbon dioxide tension; $\dot{V}$—minute ventilation; f—breathing frequency; V_T—tidal volume; $V_{D_{phys}}$—physiological deadspace.

significant, neither the frequency nor the V_T changes responsible for this fall reached statistical significance. P_{aCO_2} rose by 23 mm Hg (3·06 kPa) (35%), carbon dioxide production remained unchanged (270 versus 268 ml/min), and cardiac output rose slightly from 7·2 to 7·5 l/min. The calculated $V_{D_{phys}}/V_T$ ratio rose significantly from 77% to 82% ($p < 0.01$).

CONCLUSIONS

Aubier *et al* concluded that most of the rise in P_{aCO_2} was due to a deterioration in $\dot{V}_A/\dot{Q}$ matching, on the basis of the following statements. (1) $\dot{V}_E$ fell only 7% and thus could account for only 5 mm Hg (0·66 kPa) of the rise in P_{aCO_2}. (2) The Haldane effect calculated from Lenfant's nomogram[4] accounted for 7 mm Hg (0·93 kPa). (3) There was a significant rise in $V_{D_{phys}}/V_T$ and, since V_T did not change significantly, $V_{D_{phys}}$ must have changed. Thus $\dot{V}_A/\dot{Q}$ matching in the lungs must have worsened.

CRITIQUE

These statements are probably incorrect deductions from the data provided for the following reasons.

The conversion of changes in overall ventilation to expected changes in P_{aCO_2} is extremely difficult and depends on certain assumptions. The classic way is via the formula

$$P_{aCO_2} = \frac{k \cdot \dot{V}_{CO_2}}{f \times (V_T - V_{D_{phys}})} \text{ or } \frac{k \cdot \dot{V}_{CO_2}}{\dot{V}_E \times (1 - V_{D_{phys}}/V_T)},$$

where k = a constant, $\dot{V}_{CO_2}$ = carbon dioxide production, f = frequency. With this approach, and Aubier's data, the calculated $V_{D_{phys}}$ is 263 ml (341 × 0·77) for air and 265 ml (323 × 0·82) for oxygen. Hence $V_{D_{phys}}$ did *not* change at all. The $V_{D_{phys}}/V_T$ ratio rose only because V_T fell and the error made was to assume that a statistically insignificant change could not be physiologically important.

The problem with this approach is in trying to interpret changes in $V_{D_{phys}}/V_T$ (or just $V_{D_{phys}}$) to indicate changes in $\dot{V}/\dot{Q}$ matching in the face of changing V_T. In normal subjects $V_{D_{phys}}$ falls a little as V_T falls. In patients with stable chronic airways obstruction $V_{D_{phys}}$ falls more with a fall in V_T than in normal subjects, but this proportion is very variable.[5] The higher $\dot{V}/\dot{Q}$ units contribute most to the change in $V_{D_{phys}}$ with V_T.[5] Thus in Aubier's experiment a small fall in $V_{D_{phys}}$ might have been expected with the fall in V_T if $\dot{V}_A/\dot{Q}$ matching had remained unchanged. There are, however, no relevant control data for estimating this fall except from patients with stable chronic airways obstruction, whose tidal volumes tend to be higher. Read and Lee[5] show that, on average, $V_{D_{phys}}$ falls 0·4 ml with each 1 ml fall in V_T in patients with stable chronic airways obstruction. Presumably in the acutely ill patients studied by Aubier, whose tidal volumes were closer to their anatomical-plus-instrument deadspaces, the physiological deadspaces could not have fallen much further. Nevertheless, from the data of Read and Lee, which probably overestimate, the $V_{D_{phys}}$ in Aubier's experiment might have been expected to fall to 256 ml (263–0·4 × (341–323)) had there been no change in $\dot{V}_A/\dot{Q}$ matching. So 60% of the rise in P_{aCO_2} after administration of oxygen can be ascribed to a fall in ventilation and 40% to a deterioration in $\dot{V}_A/\dot{Q}$ matching because the actual $V_{D_{phys}}$ was 265 ml, compared with a predicted value of 256 ml. If the Haldane effect and slope change of the carbon dioxide content curve after oxygen therapy are considered they would also be expected to raise the $V_{D_{phys}}$ (by about 6 ml). This then virtually eliminates any need to invoke $\dot{V}_A/\dot{Q}$ changes to explain the observed rise in P_{aCO_2}.

Using the simpler approach favoured by West[6] in analysing this sort of problem, we come to the same conclusions. If we assume that the anatomical deadspaces in Aubier's patients were on average about 175 ml (mean age of patient 65 years) and add the instrument deadspace (75 ml) this leaves 91 ml (341–250) as the V_T reaching the alveoli. On the basis of the equation

$$\dot{V}_A = f[V_T - (V_{D_{anatomical}} \text{ and } V_{D_{instrumental}})]$$

the $\dot{V}_A$ with air becomes 2·91 l/min and with oxygen 2·26 l/min^{-1}, a fall of 22%. This would be expected to raise the P_{aCO_2} from 65 to 84 mm Hg (8·6 to 11·2 kPa), leaving only a further 4 mm Hg (0·53 kPa) to be explained by other mechanisms. The figure shows how as the initial P_{aCO_2} rises smaller and smaller falls in $\dot{V}_A$ are required to produce a given further rise in P_{aCO_2}. This is an obvious point but one often forgotten. In addition, because the tidal volumes of the acutely ill patients in Aubier's study were so small and thus close to the total deadspace, only very small falls in V_T were necessary to produce a physiologically significant fall in $\dot{V}_A$.

The data of Aubier *et al*[3] actually lend more support to the hypothesis that hypoventilation is the cause of the hypercapnia than to the hypothesis that increasing $\dot{V}_A/\dot{Q}$ mismatch is responsible.

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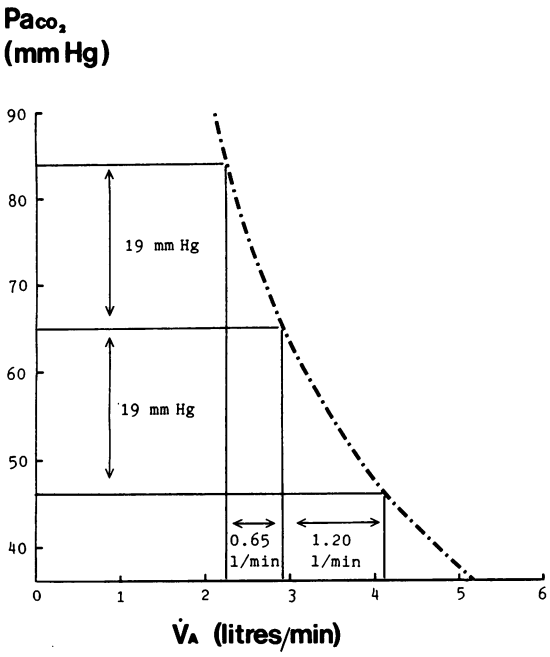

Relationship between alveolar ventilation ($\dot{V}_A$) and arterial carbon dioxide tension ($Paco_2$) based on the data of Aubier et al.[3] Carbon dioxide production = 270 ml. As the initial $Paco_2$ rises, smaller decreases in $\dot{V}_A$ are required to produce the same rise in $Paco_2$.
Conversion: traditional to SI units—$Paco_2$: 1 mm Hg = 0·133 kPa.

Are data from patients with stable chronic airways obstruction relevant in acute exacerbations?

It has been stated that patients with chronic airways obstruction respond differently to oxygen therapy depending on whether they are stable or in acute respiratory failure.[7] This is based largely on the observation that $PaCO_2$ tends to rise more during oxygen therapy in acute respiratory failure than it does in chronic respiratory failure. For several reasons it seems unnecessary to invoke any essential differences.

The $\dot{V}_A/\dot{Q}$ mismatch of chronic airways obstruction (plus the lack of an adequate ventilatory response to the retained carbon dioxide) can reduce PaO_2 to levels that will stimulate ventilation. Breathing is thus mainly sustained in these patients by a mixture of normal or depressed oxygen and carbon dioxide drives. If PaO_2 is then raised by oxygen therapy, part of the drive to breathe may be lost, ventilation may fall, and the carbon dioxide level will then slowly rise. The lower the initial PaO_2 (as in an exacerbation) then the greater will be the loss of hypoxic drive when the inspired oxygen concentration is increased. As already discussed, the increase in $PaCO_2$ will depend on the fall in alveolar ventilation and the initial $PaCO_2$ rather than the overall ventilation. If the breathing pattern is rapid and shallow (as in an exacerbation) then a small fall in V_T represents a large fall in alveolar ventilation, and if the $PaCO_2$ is already raised then a given fall in $\dot{V}_A$ will produce a larger absolute rise in $PaCO_2$ than if it had been initially lower (figure).

The degree to which this rise in $PaCO_2$ is limited by the stimulation of ventilation depends on carbon dioxide sensitivity in the brainstem, the initial $PaCO_2$, and the capacity of the respiratory muscles to respond to increased drive, versus the impairment of the mechanics of the respiratory system. Since the centres in the brainstem responsible for carbon dioxide drive probably respond to changes in hydrogen ion concentration $[H^+]$,[8] bigger changes in $PaCO_2$ are required to produce changes in ventilation when the $PaCO_2$ is already high and compensated for:

$$\dot{V} \propto [H^+] \propto PCO_2/[HCO_3^-]$$

On the basis of these considerations alone, without the need to invoke different $[H^+]$ sensitivities, patients with high breathing frequencies, low tidal volumes, low PaO_2, and already high $PaCO_2$ (all features of an acute exacerbation of chronic airways obstruction) would be expected to have the biggest changes in $PaCO_2$ after any reduction in hypoxic drive from oxygen therapy. Two groups have found the rises in $PaCO_2$ after oxygen therapy in stable chronic obstructive lung disease to correlate well with the initial degree of hypoxia and hypercapnia.[9 10]

These considerations suggest that the data on hypercapnia after oxygen therapy derived from patients with stable chronic obstructive lung disease might be relevant to acute exacerbations since there is no reason to believe that the underlying mechanisms are any different.

EFFECT OF OXYGEN ON PATIENTS WITH STABLE CHRONIC OBSTRUCTIVE LUNG DISEASE

Measuring minute ventilation ($\dot{V}_E$) and $\dot{V}_A/\dot{Q}$ during oxygen therapy presents its own problems. Furthermore, mouthpieces alter ventilation[11 12] and may mask oxygen induced hypoventilation, as occurs in patients with acute asthma.[13] The use of surface measurements to estimate ventilation is unfortunately considerably less accurate.[14]

Lee and Read[15] have performed extensive studies on 58 patients with stable chronic airways obstruction, using changes in $V_{D_{phys}}/V_T$ ratios to estimate changes in $\dot{V}_A/\dot{Q}$ distribution after 100% oxygen therapy. They found variable rises in $V_{D_{phys}}/V_T$ ratios accompanied by falls in V_T. Using their control data[5] of $V_{D_{phys}}$ changes with V_T (0·4 (SD 0·2) ml per ml V_T) they concluded that the rise in $V_{D_{phys}}/V_T$ on oxygen was a little more than could be accounted for by the

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fall in V_T. Unfortunately no allowance was made for the rise in $V_{D_{phys}}$ due to the Haldane effect or the rise in P_{aCO_2} itself (see below).

Horsfield *et al*[16] found a 10% rise in P_{aCO_2} and an accompanying 8% fall in ventilation in 17 patients with chronic airways obstruction after 80% oxygen breathing. There was also pulmonary vasodilation (cardiac output unchanged) but this was presumably not specifically in low $\dot{V}/\dot{Q}$ areas since the efficiency of carbon dioxide excretion was not affected. Using a gamma camera and nitrogen-13, Eiser *et al*[17] demonstrated a small but significant redistribution of blood flow in six of 16 patients with chronic airways obstruction given 30% oxygen. The effect of this on gas exchange, however, was calculated to be inadequate to produce a rise in P_{aCO_2}. Using a similar technique but longer equilibration times, Guenard *et al*[18] found no redistribution of blood flow in 17 patients with chronic airways obstruction breathing 30% oxygen, but noted a tendency for the overall reduction in ventilation observed (9·4%, $p < 0·05$) to be mainly in the low $\dot{V}_A/\dot{Q}$ areas. Thirty minutes after a period of breathing about 60% oxygen Rudolf *et al*[19] found a 3 mm Hg increase in alveolar-arterial gradient for oxygen (P_{aCO_2} was unchanged) in 18 patients with airways obstruction. This small change, which was taken as evidence for persisting deterioration in $\dot{V}_A/\dot{Q}$ matching, could also have been due to a change in respiratory quotient of as little as 0·04 (which was not measured). Using an inert gases technique for measuring $\dot{V}_A/\dot{Q}$ matching in 23 patients with chronic airways obstruction, Wagner *et al*[20] were unable to document any consistent effect of 100% oxygen on either $\dot{V}_A/\dot{Q}$ distribution or conversion of low $\dot{V}_A/\dot{Q}$ units to shunt as predicted and found in normal subjects.[21] Using the same inert gases technique, Castaing *et al*[22] studied the effect of 26% oxygen on $\dot{V}_A/\dot{Q}$ matching in 14 patients with stable chronic airways obstruction. They found a small but consistent shift of blood flow to low $\dot{V}_A/\dot{Q}$ units, suggesting release of hypoxic vasoconstriction. The rise in P_{aCO_2} (1·7%) was not significant, neither were the small falls in overall ventilation and cardiac output.

In another study 12 patients with stable chronic airways obstruction were observed by means of surface measurements of ventilation and a 7% fall in ventilation was found after they had breathed 50% oxygen.[23] This fall was theoretically sufficient to explain the associated 7% rise in P_{aCO_2}. Without a mouthpiece, however, carbon dioxide production could not be measured, and this limits the extent to which the data can be interpreted.

In summary, studies on patients with stable disease have failed to show an effect of raising inspired oxygen concentration on $\dot{V}_A/\dot{Q}$ matching that is large enough to raise P_{aCO_2} significantly.

Other mechanisms raising P_{aCO_2} after oxygen therapy

THE HALDANE EFFECT

The carbon dioxide content curve for blood depends on the degree of oxygenation of haemoglobin. The more oxygenated the haemoglobin the less carbon dioxide can be carried at a given P_{CO_2}; this produces a parallel shift of the relationship between P_{CO_2} and the carbon dioxide content of blood (that is, the slope is unchanged) over the normal range of P_{CO_2} and above. Thus if a hypoxaemic patient is given oxygen, the rise in arterial and venous oxygen saturation will cause carbon dioxide to be evolved and the P_{CO_2} will rise (for example, by 6 mm Hg (0·8 kPa) when P_{aCO_2} is 65 mm Hg (8·7 kPa)) and oxygen saturation will go from 70% to 100%.[13] Christiansen *et al* first described this effect[24] and Lenfant[4] drew up a nomogram based on in vitro, closed system data,[25] using only the change in saturation and the starting P_{aCO_2} to predict the rise in P_{aCO_2}. It has been suggested that the Haldane effect, through this mechanism, accounts for a calculable increase in the steady state P_{aCO_2} that follows the administration of oxygen. Although the Haldane effect does increase the P_{aCO_2} by this mechanism, it does so only transiently. In a closed system the P_{CO_2} will rise, because the evolved carbon dioxide cannot escape; in vivo the majority of the extra carbon dioxide is blown off via the lungs. This transient rise in carbon dioxide evolution, early on during oxygen therapy, will produce an initial instability of the P_{aCO_2}.

The Haldane effect does, however, influence carbon dioxide excretion from a non-homogeneous lung over the longer term in a subtle but smaller way.[26] In gas exchange units with low $\dot{V}/\dot{Q}$, increasing inspired oxygen concentration will lead to bigger changes in oxygen saturation in capillary blood than in high $\dot{V}/\dot{Q}$ units, where the blood is already well saturated. Thus more carbon dioxide will be evolved into these low $\dot{V}/\dot{Q}$ alveoli because of the larger Haldane effect. Since ventilation to these alveoli is not increased, capillary P_{CO_2}, and hence P_{aCO_2}, must rise. This reduction in the matching of carbon dioxide evolution to alveolar ventilation, with a consequent wider spread of P_{CO_2} levels in the lung, will increase the alveolar-arterial gradient and physiological deadspace for carbon dioxide. As the magnitude of this effect depends on a complicated interaction between degree of $\dot{V}/\dot{Q}$ mismatch, haemoglobin concentrations, change in oxygenation, and starting P_{aCO_2}, it cannot be predicted from a simple nomogram. The West multicompartment steady state model of gas exchange in the lung[27] (set up with severe $\dot{V}/\dot{Q}$ mismatch, a starting P_{aCO_2} of 65 mm Hg (8·1 kPa), and a 30% change in S_{aO_2}) demonstrates this effect, but it amounts to no more than a 3 mm Hg (0·5 kPa) rise in P_{aCO_2}, about

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half of that predicted from Lenfant's nomogram.[4] Less severe degrees of $\dot{V}/\dot{Q}$ mismatching would produce less than a 3 mm Hg rise and be even less relevant clinically.

REDUCED SLOPE OF P_{CO_2}-CARBON DIOXIDE CONTENT CURVE AS P_{CO_2} RISES

Excretion of an inert gas from the lung depends on its effective partition coefficient.[28] The less soluble a gas the fewer molecules will be excreted for a given mixed venous-alveolar pressure gradient. In a non-homogeneous lung this effectively increases the physiological deadspace for that gas. Thus, because the relationship between P_{CO_2} and carbon dioxide content of the blood flattens as P_{CO_2} (or more correctly $[H^+]$) rises, the physiological deadspace will also rise,[28] as will the ratio of deadspace to tidal volume ($V_{D_{phys}}/V_T$) if V_T is kept constant. This mechanism will therefore slightly amplify a P_{aCO_2} rise caused by some other event. For example, a P_{CO_2} rise from 65 to 88 mm Hg (8·1 to 11·1 kPa) reduces the effective partition coefficient from 0·5 to 0·4 ml/100 ml blood/mm Hg. This would change the $V_{D_{phys}}/V_T$ ratio from 61·5% to 62·2% (a rise in $V_{D_{phys}}$ of about 2–3 ml).[28] Bigger effects would be seen at normal or subnormal values of P_{aCO_2}, since the slope change with P_{aCO_2} change is greater.

Conclusions

To understand the causes of hypercapnia that follows oxygen therapy in chronic airways obstruction is of clinical importance. Because the physiological arguments are complicated incorrect conclusions have been drawn. If the rise in P_{aCO_2} after oxygen therapy was due predominantly to increasing $\dot{V}_A/\dot{Q}$ mismatch and not hypoventilation, then the use of ventilatory stimulants in these circumstances would seem far less appropriate and perhaps likely to precipitate muscle fatigue. This would leave artificial ventilation as the only appropriate treatment for hypercapnia induced acidosis that was judged to be life threatening. If, however, the rise in P_{aCO_2} after oxygen therapy is indeed due to a fall in global ventilation (and Campbell was right after all), then judicious use of ventilatory stimulants to reverse some of this fall becomes theoretically appropriate, particularly if this produces an increase in V_T in preference to frequency.

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