Improving Clinical Care — Commentary

Revisiting oxygen therapy in patients with exacerbation of chronic obstructive pulmonary disease

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Controlling oxygen delivery to limit oxygen saturation should reduce the incidence of hyperoxic hypercapnia

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The report by Joosten et al in this issue of the Journal (page 235)[1] is a timely reminder of the importance of avoiding the induction of hyperoxic hypercapnia in patients with acute-on-chronic respiratory failure. The complication of acute hypercapnic respiratory failure precipitated by giving oxygen has long been recognised; most resident medical and nursing staff are aware of this problem. The natural intervention in patients presenting with acute-on-chronic respiratory failure is to relieve any hypoxia with supplemental oxygen, but this can be associated with carbon dioxide retention, narcosis, respiratory acidosis, and death. That the use of controlled oxygen flow rates could avoid this complication (and the need, in those days, for tracheostomy and invasive ventilation) was first recognised in the 1940s and 1950s.[2] Although hyperoxic hypercapnia can now be managed with non-invasive ventilation, the article by Joosten et al reminds us that it still has adverse consequences for morbidity, length of stay and the use of hospital resources.[1]

Studies over the past 20–30 years have identified the characteristics of the patients most likely to have this problem, and have gone some way to identifying the mechanisms responsible. Chronic respiratory failure is the usual predisposing condition, and the most common cause of chronic respiratory failure is chronic obstructive pulmonary disease (COPD). Interestingly, hyperoxic hypercapnia is a phenomenon of acute exacerbations of COPD — giving oxygen to patients with stable

hypercapnia rarely, if ever, causes clinically significant further hypercapnia.[3] This may, of course, be related to the lower flow rates used for stable hypercapnia. Importantly, the degree of hypoxaemia at presentation is a better predictor of hyperoxic hypercapnia progressing to narcosis than is the initial degree of hypercapnia.[4]

Usual clinical teaching is that high concentrations of inspired oxygen remove the hypoxic drive to ventilation in susceptible hypoxaemic patients; the narcotic effect of the rising hypercapnia amplifies this effect, promoting further hypoventilation. However, a number of studies have cast doubt on this as the most important mechanism, at least up to the point of narcosis.[5-7] The most comprehensive study of mechanisms, using the multiple inert gas elimination technique, suggests that relative hypoventilation is the defining event in those who retain carbon dioxide, but that worsening ventilation–perfusion mismatching and an accompanying increase in dead space ventilation contribute about 50% of the increase in carbon dioxide levels.[8] This finding is clinically important because it identifies non-invasive ventilatory support as the appropriate intervention before narcosis progresses.

The dictum “hypoxia kills quickly, hypercapnia slowly” engages the clinician when confronted with this situation. How can hyperoxic hypercapnia be avoided without exposing these patients to the more acute risk of inadequate oxygenation? Oxygen delivery controlled to an appropriate flow rate appears to be the answer, but there are no large-scale studies to indicate how the oxygen “dose” should be determined and monitored.[9,10] In the absence of clinical trial evidence, it is reasonable to control oxygen flow rate to achieve an arterial oxygen saturation of 90%, but not above 93%–95%. This corresponds with an arterial oxygen tension of 60–70 mmHg at the start of the “flat part” of the oxyhaemoglobin dissociation curve, and ensures adequate arterial oxygen content and delivery in most circumstances. This is also consistent with the data of Joosten and colleagues, who found an arterial oxygen tension of less than 74.5 mmHg to be protective.[1] The ready availability of continuously reading pulse oximeters makes the above recommendation a practical procedure, and its wide application in wards, emergency departments and, particularly, ambulances should substantially reduce the incidence of the hazardous and largely unnecessary complication of hyperoxic hypercapnia.

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The Role of Hypoventilation and Ventilation-Perfusion Redistribution in Oxygen-induced Hypercapnia during Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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The detailed mechanisms of oxygen-induced hypercapnia were examined in 22 patients during an acute exacerbation of chronic obstructive pulmonary disease. Ventilation, cardiac output, and the distribution of ventilation-perfusion ($\dot{V}_A/\dot{Q}$) ratios were measured using the multiple inert gas elimination technique breathing air and then 100% oxygen through a nose mask. Twelve patients were classified as retainers (R) when Pa_{CO_2} rose by more than 3 mm Hg (8.3 ± 5.6; mean ± SD) after breathing 100% oxygen for at least 20 min. The other 10 patients showed a change in Pa_{CO_2} of −1.3 ± 2.2 mm Hg breathing oxygen and were classified as nonretainers (NR). Ventilation fell significantly from 9.0 ± 1.5 to 7.2 ± 1.2 L/min in the R group breathing oxygen ($p = 0.007$), whereas there was no change in ventilation in the NR group (9.8 ± 1.8 to 9.9 ± 1.8 L/min). The dispersion of $\dot{V}_A/\dot{Q}$ ratios as measured by log SD of blood flow (log SD $\dot{Q}$) increased significantly in both R (0.96 ± 0.17 to 1.13 ± 0.17) and NR (0.77 ± 0.20 to 1.04 ± 0.23, $p < 0.05$) groups breathing oxygen, whereas log SD of ventilation (log SD $\dot{Q}$) increased only in the R group (0.97 ± 0.24 to 1.20 ± 0.46, $p < 0.05$). This study suggests that an overall reduction in ventilation characterizes oxygen-induced hypercapnia, as an increased dispersion of blood flow from release of hypoxic vasoconstriction occurred to a significant and similar degree in both groups. The significant increase in wasted ventilation (alveolar dead space) in the R group only may be secondary to the higher carbon dioxide tension, perhaps related to bronchodilatation.

The course of chronic obstructive pulmonary disease (COPD) is characterized by acute exacerbations, commonly requiring hospital admission and often associated with the development of respiratory failure. The causes and precise pathophysiology of acute exacerbations are difficult to determine, so treatment is usually broadly based, encompassing imprecisely targeted bronchodilator, corticosteroid, and antibiotic therapy, supplemental oxygen, and physiotherapy. Some therapies may have unintended deleterious effects; in particular, the hypercapnia induced by oxygen therapy in some patients with COPD.

The problem of oxygen-induced hypercapnia in the setting of an acute exacerbation has been recognized and investigated for some 30 yr. The most important mechanisms are considered to be a reduction in ventilation associated with removal of a hypoxic stimulus and increasing ventilation-perfusion ($\dot{V}_A/\dot{Q}$) inequality caused by release of hypoxic vasoconstriction (1). However, studies of ventilatory responses to hypoxia and hypercapnia in patients with COPD have shown variable results. Some patients remain sensitive to hypoxia and hypercapnia, whereas others have absent responses, and responses differ between stable states and acute exacerbations (2–9).

The relative importance of a reduction in total ventilation and an increase in Bohr dead space (V_D/V_T) in causing hyperoxic hypercapnia remains controversial. The former is associated with control of ventilation or muscle function, whereas the latter is associated with the intrapulmonary control of ventilation-perfusion matching. Identification of one or the other as the defining abnormality would therefore have important management implications. The earliest work suggested a fall in minute ventilation; however, this mechanism was disputed by Aubier and colleagues (10) who identified an increase in V_D/V_T as the major factor. Since then, Sassoon and colleagues (8) have supported this finding, whereas Dunn and colleagues (6) have found more evidence for a reduction in respiratory drive to ventilation. The various studies have been performed under widely varying conditions, the latter in mechanically ventilated, relatively stable patients.

The most comprehensive study of carbon dioxide (CO_2) retention during acute exacerbations of COPD (10) documented a relatively stable minute ventilation ($\dot{V}_E$) in the presence of increasing Pa_{CO_2} with oxygen therapy, and inferred an increase in V_D/V_T and hence an increase in $\dot{V}_A/\dot{Q}$ inequality by applying the Bohr equation. This study, however, did not compare the responses of a group of non-CO_2 retainers with a group of CO_2 retainers. Moreover, detailed studies of gas exchange using the multiple inert gas elimination technique (MIGET) in stable patients with COPD have not demonstrated significant changes in $\dot{V}_A/\dot{Q}$ inequality with oxygen therapy (11), and large surveys of stable patients with COPD receiving continuous oxygen therapy have not shown significant further increases in Pa_{CO_2} (12). This suggests that clinically significant hypercapnia associated with hyperoxia is a phenomenon of acute exacerbations rather than a constant characteristic of individual patients.

Our study was designed to further examine the particular question of whether a reduction in ventilation or an increase in $\dot{V}_A/\dot{Q}$ inequality could be identified as the defining characteristic of patients developing hyperoxic hypercapnia compared with patients who did not become hypercapnic in this circumstance during acute exacerbations of COPD. We did not set out to measure changes in respiratory drive or pattern of breathing directly. We employed MIGET to gain detailed gas exchange data that would be independent of CO_2 production and elimination and be able to separate the effects of change in pattern of breathing on the V_D/V_T from true change in $\dot{V}_A/\dot{Q}$ inequality (6). In particular, we identified a group of patients whose Pa_{CO_2} changed by 3 mm Hg or less and compared their detailed physiologic changes with those of a group of patients whose Pa_{CO_2} rose by more than 3 mm Hg. Thus, the mechanism most accounting for the difference between eucapnia and hypercapnia in these conditions could be identified directly. No other study has directly addressed this issue in the

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TABLE 1

PATIENT CHARACTERISTICS (GROUP NR: NONRETAINERS OF CO_2)

Subject No.	Age (*yr*)	BMI (kg/m^2)	FEV_1, L (*% pred*)	FVC (*L*)	Pa_{O_2} on Air (*mm Hg*)	Pa_{CO_2} on Air (*mm Hg*)	ΔPa_{CO_2} on 100% O_2 (*mm Hg*)
1	58	18	0.76 (33)	1.8	52	63	−0.6
2	65	20	1.12 (42)	2.23	71	56	−0.6
3	63	27	0.84 (29)	1.61	51	61	1.9
4	55	27	0.6 (25)	2.02	53	43	−4.6
5	60	29	0.5 (17)	1.45	56	42	1.0
6	66	22	0.21 (8)	0.8	76	44	−2.0
7	75	22	0.75 (26)	1.92	70	43	−4.1
8	75	21	0.96 (32)	2.67	70	48	−1.2
9	60	22	0.85 (38)	1.7	73	42	−3.4
10	43	16	0.51 (17)	0.74	55	55	0.8
Mean	62.0	22.5	0.71 (27)	1.69	62.7*	49.7	−1.3
SD	9.4	4.7	0.26 (10)	0.59	10.0	8.3	2.2

Definition of abbreviation: BMI = body mass index.
* $p < 0.05$, Group NR compared with Group R; Student's unpaired *t* test.

detail possible through the use of MIGET. There are very few studies with MIGET data in acute exacerbations of COPD (13), and no others examining the effects of oxygen administration in this particular circumstance.

METHODS

Subjects

Twenty-two patients (14 male) with a mean ± SD age of 64 ± 7 yr were studied. All patients had histories, physical findings, and lung function tests consistent with COPD, according to American Thoracic Society criteria (14) and all were admitted to hospital with an acute exacerbation of their disease, defined as increased cough, breathlessness, and sputum production requiring inpatient care. Patient characteristics are shown in Tables 1 and 2. Patients who were hemodynamically unstable or who required mechanical ventilation were excluded from the study. All patients received standard treatment with bronchodilators, corticosteroids, supplemental oxygen, and antibiotics at the discretion of the treating physician. The study protocol was approved by the Central Sydney Area Health Service Ethics Committee, and informed consent was obtained from each patient.

Procedures

Spirometry was obtained using a Vitalograph wedge spirometer (Vitalograph Ltd, Buckingham, UK). Arterial blood samples for inert gas measurements were collected from an indwelling catheter inserted into the radial artery. Arterial pH, Pa_{O_2} and Pa_{CO_2} were analyzed using a self-calibrating analyzer (Blood Gas Analyzer 178; Corning Glass Works, Medfield, MA). A peripheral venous cannula was inserted into a superficial vein in the opposite arm for the inert gas infusion. In 17 patients, a central venous catheter was used to inject indocyanine green dye for measurement of cardiac output by the dye dilution method (DC-410, CO-10; Waters Instruments Inc., Rochester, NY). In the remaining five patients, a pulmonary artery catheter (Grandjean microcatheter; Plastimed, St. Lev-La-Forey Cedex, France) was inserted and cardiac output was calculated from the mixed venous blood inert gas data (15). Patients breathed through a nasal mask (Resmed; Sullivan, Sydney, Australia) held by elasticized tapes around the head, according to standard nasal continuous positive airway pressure (CPAP) administration. The seal around the nose was frequently and carefully checked for leaks, and each patient's mouth was lightly sealed with adhesive tape. The patient could easily break this seal if necessary. We considered collection of expired gas from a nasal mask as possibly less likely to induce an artefactual increase in ventilation than collection from a standard mouthpiece (16). The nasal mask was attached to a one-way valve (Model 2700; Hans Rudolph Instruments, Kansas City, MO), with all expiratory flow directed through heated tubing to a 15-L heated mixing box, to allow collection of mixed expired gas. The inspiratory limb of the circuit was either open to air or attached to an oxygen supply via a demand valve (A8G; CIG, Sydney, Australia), to deliver an FI_{O_2} of 100%. A calibrated volumeter (Drager, Lübeck, Germany) was used in the breathing circuit to measure expired $\dot{V}E$.

TABLE 2

PATIENT CHARACTERISTICS (GROUP R: RETAINERS OF CO_2)

Subject No.	Age (*yr*)	BMI (kg/m^2)	FEV_1, L (*% pred*)	FVC (*L*)	Pa_{O_2} on Air (*mm Hg*)	Pa_{CO_2} on Air (*mm Hg*)	ΔPa_{CO_2} on 100% O_2 (*mm Hg*)
11	58	24	0.57 (17)	2.04	62	48	3.2
12	56	32	0.87 (36)	2.49	59	46	3.7
13	79	28	1.64 (73)	2.54	41	74	17.5
14	69	16	0.63 (30)	1.58	69	43	3.1
15	57	21	0.50 (15)	2.39	62	52	8.3
16	60	27	0.85 (32)	1.58	48	64	6.0
17	66	19	0.75 (37)	1.91	51	67	11.2
18	62	25	0.40 (14)	1.20	41	67	11.3
19	75	22	0.60 (18)	2.91	46	78	19.6
20	69	21	0.68 (28)	1.41	55	36	5.7
21	75	26	0.70 (35)	1.50	66	43	3.9
22	60	27	1.44 (45)	2.24	54	57	6.1
Mean	65.5	24.0	0.80 (32)	1.96	54.5*	56.3	8.3
SD	7.9	4.4	0.37 (16)	0.57	9.4	13.6	5.6

Definition of abbreviation: BMI = body mass index.
* $p < 0.05$, Group NR compared with Group R; Student's unpaired *t* test.

Ventilation-perfusion distributions were estimated using the multiple inert gas elimination technique. Our application of this technique has been previously described (15). The detailed measurements chosen for analysis were the dispersions (second moments) of the distributions of ventilation and perfusion on a logarithmic scale, log SD V and log SD Q, respectively. Disp R-E* was used as an overall measure of $\dot{V}_A/\dot{Q}$ inequality (normal value ≤ 3.0). It is calculated directly from the measured retentions and excretions of the six gases and is the root mean squared difference between the retention and excretion, after correcting for acetone excretion (17). Disp R-E* includes the effect of any intrapulmonary shunt, if present. Intrapulmonary shunt was defined as the fraction of cardiac output perfusing lung units with a $\dot{V}_A/\dot{Q}$ ratio less than 0.005 and dead space was defined as the fraction of ventilation to lung units with a $\dot{V}_A/\dot{Q}$ ratio greater than 100. This MIGET dead space approximates anatomic dead space.

Experimental Protocol

All patients were studied within 72 h of admission in a semirecumbent position in bed. After a 40-min period of inert gas infusion to attain a steady state while the patient breathed room air, duplicate arterial blood samples and quadruplicate mixed expired gas samples were taken for MIGET analysis. Dye dilution cardiac output measurements were made, at least in triplicate or until satisfactory duplicate measurements were obtained. A steady state was ensured by documenting a stable $\dot{V}_E$ and heart rate (within ± 5%) in the preceding 10 min. After a rest period, during which the inert gas infusion continued, each patient breathed 100% oxygen for at least 20 min before the same samples were taken for MIGET analysis and repeat cardiac output measurements were made. No attempt was made to document the time course of any change in ventilation from the start of oxygen administration, although it was generally noted that ventilation was lower at 5 to 10 min than at 20 min after starting 100% oxygen, as found by Aubier and colleagues (10).

Statistical Analysis

Data are expressed throughout as mean ± standard deviation unless otherwise specified. Differences between the R and NR groups were tested using Student's two-sample *t* tests. Differences between intervention and baseline conditions within each group were analyzed using Student's paired *t*-tests. Least squares linear regression was used to determine all correlation coefficients in the relationships described. Probability values less than 0.05 were considered statistically significant.

RESULTS

Gas Exchange

All patients had markedly abnormal gas exchange while breathing room air, with a group mean Pa_{O_2} of 58.2 ± 8.9 mm Hg and a group mean Pa_{CO_2} of 53.2 ± 9.9 mm Hg, as shown in Tables 1 and 2. The mean value of each patient's duplicate measurements at each time point was used for further calculations.

Patients were classified as CO_2 retainers (R) if the Pa_{CO_2} increased by more than 3 mm Hg from baseline after breathing 100% oxygen for 20 min (12 patients). In this group, eight patients showed an increase in Pa_{CO_2} of more than 5 mm Hg, and four patients showed an increase in Pa_{CO_2} of 3 to 4 mm Hg. The other 10 patients were classified as nonretainers (NR), and seven patients in this group showed a fall in Pa_{CO_2} while breathing oxygen. The largest increase in Pa_{CO_2} while breathing oxygen in the NR group was 1.9 mm Hg. The choice of a greater than 3 mm Hg difference was made to definitely exceed three times the standard deviations of repeated measurements on the CO_2 electrode, which are 0.5, 0.6, and 1.1 mm Hg for values of 35, 50, and 70 mm Hg, respectively (*see Technical Specifications Manual* issued with Corning Blood Gas Analyzer model 178; Corning Glass Works).

The mean increase in Pa_{CO_2} while breathing oxygen in the R group was 8.8 ± 5.6 mm Hg. The mean increase in Pa_{CO_2} while breathing oxygen in the NR group was −1.4 ± 2.3 mm Hg. The mean Pa_{O_2} while breathing air in the R group (54.5 ± 7.5 mm Hg) was significantly lower than the mean Pa_{O_2} while breathing air in the NR group (62.6 ± 9.3 mm Hg) (p = 0.03). There were no significant differences between the two groups in any other baseline characteristics, including Pa_{CO_2} while breathing air.

Ventilation and Perfusion Distributions

The effects of 100% oxygen breathing on pulmonary gas exchange measurements are shown in Table 3.

Air breathing. Mean $\dot{V}_E$ was 8.95 ± 1.50 L/min for Group R and 9.82 ± 1.80 L/min for group NR. Mean cardiac output was 5.57 ± 1.30 L/min in Group R and 4.51 ± 0.93 L/min in Group NR. There were no significant differences between the two groups in $\dot{V}_E$ or in cardiac output. All patients showed significant $\dot{V}_A/\dot{Q}$ inequality while breathing room air. The dispersion of pulmonary blood flow (log SD Q) was 0.96 ± 0.17 for Group R and 0.77 ± 0.20 for Group NR, whereas the dispersion of alveolar ventilation (log SD V) was 0.97 ± 0.24 for Group R and 1.05 ± 0.39 for Group NR (normal ≤ 0.6 for both log SD Q and log SD V). There were no significant differences between the two groups in their indices of baseline $\dot{V}_A/\dot{Q}$ distributions.

100% oxygen breathing. The effects of breathing 100% oxygen on $\dot{V}_E$ and $\dot{V}_A/\dot{Q}$ inequality in the two groups are shown in Figure 1. In Group R, mean $\dot{V}_E$ fell by 1.54 L/min to 7.24 ± 1.20 L/min (p = 0.007). There was no significant change in $\dot{V}_E$ in Group NR or in cardiac output for either group. Comparison of the change in ventilation (air to 100% oxygen) between Group R and Group NR approached significance (p = 0.06). $\dot{V}_A/\dot{Q}$ inequality increased significantly in both groups, with a rise in the overall index of $\dot{V}_A/\dot{Q}$ heterogeneity (Disp R-E*) of 4.52 in Group R (p = 0.004) and 3.08 (p = 0.005) in Group NR. The effects of breathing 100% oxygen on log SD Q and log SD V in the two groups are shown in Figure 2. Log SD Q increased significantly in both groups, to 1.13 ± 0.17 in Group R (p = 0.003) and to 1.04 ± 0.23 in Group NR (p = 0.002). Log SD V increased to 1.20 ± 0.46 in Group R (p = 0.04) but did not change significantly in Group NR (p = 0.65).

The Bohr dead space ($\dot{V}_D/\dot{V}_T$), calculated by the MIGET program using the recovered distribution, increased significantly, although to a smaller degree than the log SD V, in the R group breathing oxygen because the $\dot{V}_D/\dot{V}_T$ is "diluted" by the stable MIGET (approximating anatomic) dead space component (Table 3). This stability of the percent MIGET dead space between air and oxygen breathing is consistent with the change in $\dot{V}_E$ being a change in frequency rather than tidal volume, although we did not measure breathing pattern. On the other hand, there could have been changes in ventilation to $\dot{V}_A/\dot{Q}$ units with a ratio > 100 to compensate for the pattern change. There was no significant change in the Bohr $\dot{V}_D/\dot{V}_T$ or the MIGET dead space in the NR group (Table 3). There were no significant differences between the R and NR groups in the changes in $\dot{V}_A/\dot{Q}$ distribution indices (i.e., log SD Q, log SD V and Disp R-E*) from air to 100% oxygen, presumably because subject numbers were not sufficient. The distributions for a typical patient from the NR group (A) and from the R group (B) breathing air and 100% oxygen are shown in Figure 3. Both patients developed an increase in blood flow to lung units with low $\dot{V}_A/\dot{Q}$ ratios, but only the R patient showed an increase in ventilation to lung units with substantially higher $\dot{V}_A/\dot{Q}$ ratios and a fall in overall ventilation.

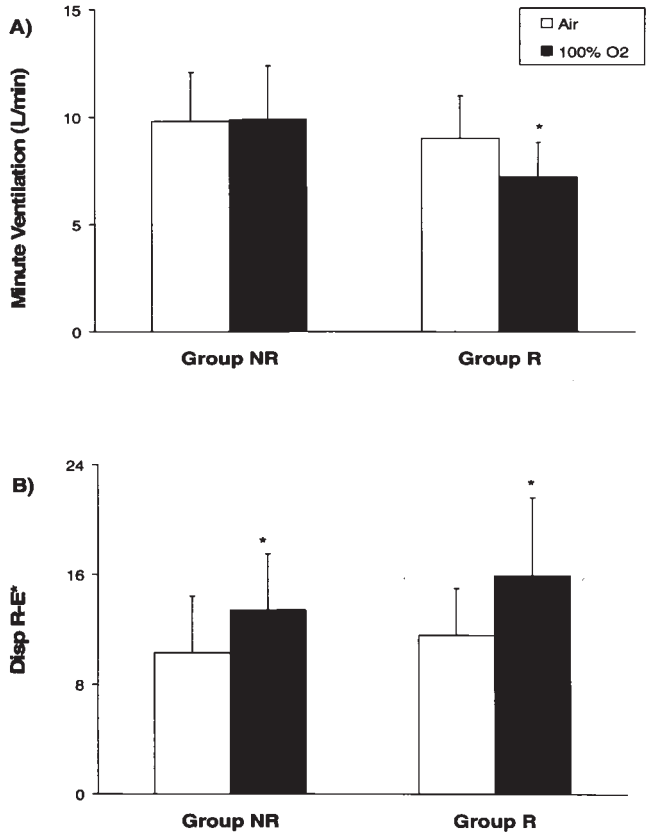

Figure 1. Changes in: (*A*) minute ventilation ($\dot{V}_E$); and (*B*) ventilation/perfusion ($\dot{V}_A/\dot{Q}$) inequality (expressed as Disp R-E* calculated from the inert gas data) for both groups from breathing air (*open bars*) to breathing 100% oxygen (*closed bars*). Group mean data are shown, with standard deviation. *p < 0.05, comparison within groups; Student's paired *t* test.

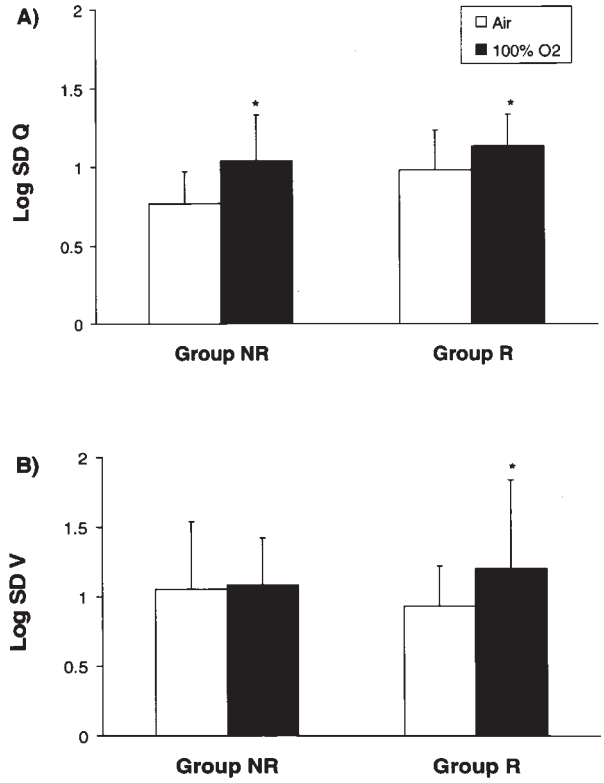

Figure 2. Changes in: (*A*) log SD $\dot{Q}$; and (*B*) log SD $\dot{V}$ for both groups from breathing air (*open bars*) to breathing 100% oxygen (*closed bars*). Group mean data are shown, with standard deviation. *p < 0.05, comparison within groups; Student's paired *t* test.

DISCUSSION

Although the literature addressing hyperoxic hypercapnia in COPD extends back 30 yr, this study is the first to report a detailed analysis of gas exchange during hyperoxia in acute exacerbations of COPD and to compare the responses of patients who became hypercapnic with those who remained eucapnic. In view of remaining controversies surrounding the relative contributions of hypoventilation and an increase in wasted ventilation caused by worsened $\dot{V}_A/\dot{Q}$ maldistribution, our study was particularly designed to examine this further using the MIGET technique to estimate detailed distributions of $\dot{V}_A/\dot{Q}$ ratios and to obtain a measure of $\dot{V}_A/\dot{Q}$ inequality independent of changes in Pa_{CO_2}. The distinction between hypoventilation and deteriorating $\dot{V}_A/\dot{Q}$ inequality has important clinical ramifications because our finding that a significant fall in ventilation occurred only in the retaining group would indicate that change in ventilatory control is the major discriminating factor. It is important to emphasize that there was a significant fall in ventilation maintained for more than 20 min of hyperoxia in the retaining group, not just a failure of ventilatory response to the increase in Pa_{CO_2}. This shifts the focus of any further investigation of this phenomenon, and its management, from control of intrapulmonary $\dot{V}_A/\dot{Q}$ distribution to control of overall ventilation, as has been attempted by Dick and colleagues (5).

Ventilation in the R group was 20% lower than baseline after at least 20 minutes of hyperoxia. This fall in ventilation is greater than reported by other groups and may be related to our use of a nasal mask rather than a mouthpiece to measure ventilation. In a group of patients studied during an acute exacerbation of COPD, Aubier and colleagues (10) found that

TABLE 3

PULMONARY GAS EXCHANGE DATA DURING INHALATION OF ROOM AIR AND 100% OXYGEN*

	Retainers (Group R)		Nonretainers (Group NR)	
	Room Air	100% Oxygen	Room Air	100% Oxygen
Pa_{O_2}, mm Hg	54.5 ± 7.5	371.5 ± 67.1†	62.7 ± 10.0	442.7 ± 57.9†
Pa_{CO_2}, mm Hg	56.3 ± 13.6	64.6 ± 15.3†‡	49.7 ± 8.3	48.5 ± 9.9
$\dot{V}_E$,L/min	9.0 ± 2.0	7.2 ± 1.6†	9.8 ± 2.3	9.9 ± 2.5
Dead space, % (MIGET = $\dot{V}_A/\dot{Q}$ > 100)	57 ± 7	55 ± 6	55 ± 4	54 ± 7
V_D/V_T (Bohr), %	59.9 ± 6.0	63.1 ± 6.5†	60.6 ± 7.1	60.7 ± 7.5
CO, L/min	5.6 ± 1.3	4.7 ± 1.5	4.4 ± 1.2	4.5 ± 2.4
Shunt, %	2.3 ± 2.7	2.4 ± 3.0	1.4 ± 1.8	1.6 ± 2.2
Log SD $\dot{Q}$	0.96 ± 0.25	1.13 ± 0.20†	0.77 ± 0.19	1.04 ± 0.29†
Log SD $\dot{V}$	0.93 ± 0.29	1.20 ± 0.64†	1.05 ± 0.49	1.08 ± 0.34

Definition of abbreviations: $\dot{V}_E$ = minute ventilation; dead space = inert gas dead space = % of ventilation to units with $\dot{V}_A/\dot{Q}$ ratios > 100; V_D/V_T (Bohr) = physiologic dead space calculated by the Bohr equation; CO = cardiac output; shunt = % of cardiac output perfusing alveolar units with ratios $\dot{V}_A/\dot{Q}$ < 0.005; log SD $\dot{Q}$ = dispersion of pulmonary blood flow distribution; log SD $\dot{V}$ = dispersion of alveolar ventilation distribution excluding ventilation to $\dot{V}_A/\dot{Q}$ ratios > 100.

* All values are expressed as mean ± standard deviation.

† $p < 0.05$ compared with room air within groups, Student's paired *t* test.

‡ $p < 0.05$, change in Group R compared with change in Group NR; Student's unpaired *t* test.

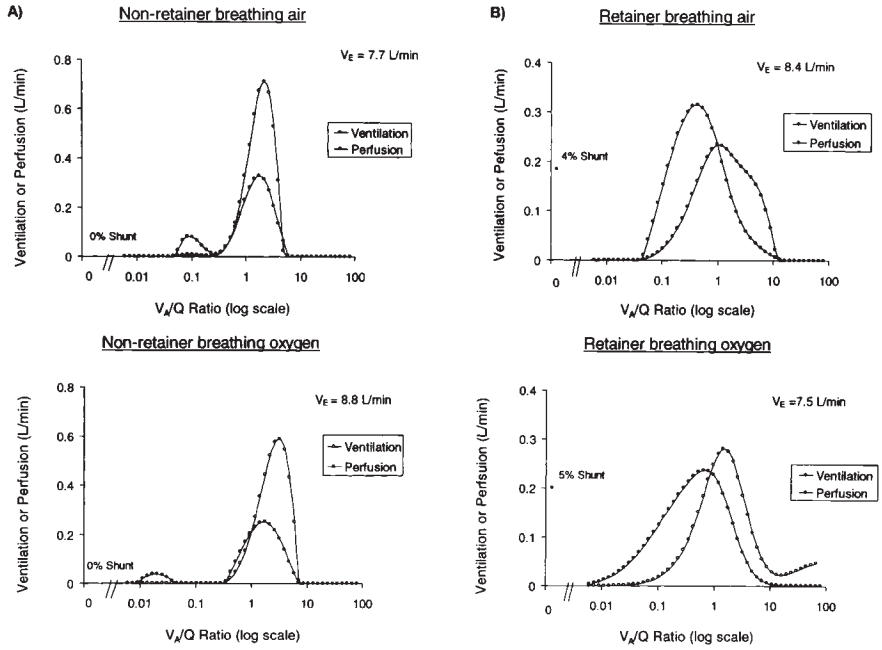

Figure 3. Typical $\dot{V}_A/\dot{Q}$ distributions in a patient from Group NR (*A*) and Group R (*B*) breathing air and 100% oxygen. Both patients show an increase in blood flow to low $\dot{V}_A/\dot{Q}$ units with oxygen, but the R patient shows an increase in alveolar dead space and a fall in overall ventilation.

hyperoxia initially induced a fall in ventilation of around 18%. However, this fall was transient and ventilation had returned to 93% of the control value after 20 min of hyperoxia. Increases in Pa_{CO_2} were attributed primarily to increased V_D/V_T. Sassoon and colleagues (8) studied clinically stable patients with COPD and found that although there was a small decrease in ventilation after 15 min of hyperoxia, changes in Pa_{CO_2} were predominantly due to changes in V_D/V_T. Indices of respiratory drive did not predict oxygen-induced changes in Pa_{CO_2}.

More recently, Dick and colleagues (5) also demonstrated minimal changes in ventilation after 15 min of hyperoxia in clinically stable patients. This group found that changes in ventilation could be predicted from modeling of hypoxic and hypercapnic responses and the interaction between them. They too concluded that hyperoxic-induced hypercapnia was due to increases in V_D/V_T. The studies of both Sassoon and Dick and their colleagues showed significant intrasubject and intersubject variability in responses to oxygen and in measures of respiratory drive, and neither distinguished between retainers and nonretainers. In our study, the R group showed a large fall in ventilation that was persistent for at least 20 min of hyperoxia, whereas the NR group showed no significant change in V_E. This suggests some failure of ventilatory response in the R group during an acute exacerbation that distinguishes it from the NR group.

The only difference between the two groups at baseline was a significantly lower Pa_{O_2} in the R group than in the NR group (54.5 ± 7.5 mm Hg versus 62.7 ± 10.0 mm Hg). This is consistent with previous studies showing that a low initial Pa_{O_2} is a better predictor of oxygen-induced CO_2 narcosis than the initial Pa_{CO_2} (18, 19).

Both patient groups developed further maldistribution of $\dot{V}_A/\dot{Q}$ ratios breathing 100% oxygen, with increased perfusion to lung units with low $\dot{V}_A/\dot{Q}$ ratios as shown by an increase in log SD $\dot{Q}$. This result is compatible with a number of other studies examining the effects of both low flow oxygen therapy (20) and 100% oxygen therapy (21–23) in patients with stable COPD, and in patients recovering from an exacerbation (24, 25). The increase in log SD $\dot{Q}$ is thought to be due to release of hypoxic vasoconstriction rather than to atelectasis, as minimal changes in intrapulmonary shunting have been demonstrated. However, our work is the first to show that indices of both low $\dot{V}_A/\dot{Q}$ inequality (log SD $\dot{Q}$) and overall $\dot{V}_A/\dot{Q}$ inequality (Disp R-E*) increase in both groups to the same degree, so these changes do not discriminate retainers from nonretainers.

In addition, a measure of ventilation to lung units with a higher than ideal (but less than 100) $\dot{V}_A/\dot{Q}$ ratios (log SD $\dot{V}$) was significantly greater in the R group than the NR group breathing 100% oxygen. An increase in log SD $\dot{V}$ represents an increase in true alveolar dead space. This is an intriguing finding and is consistent with the data of Aubier and colleagues (10) who found an increase in physiologic (Bohr) dead space (V_D/V_T) but were unable to separate that component of V_D/V_T because of a change in ventilation pattern, and hence the contribution from anatomic dead space, from that caused by increases in alveolar dead space. This substantial increase in alveolar dead space clearly leads to more wasted ventilation and will exacerbate the carbon dioxide retention in this group. The mechanism of the increased log SD $\dot{V}$ is unclear, as a reduction in overall ventilation will tend to reduce alveolar dead space in the presence of a stable log distribution of $\dot{V}_A/\dot{Q}$ ratios and stable cardiac output (26). Our finding implies some active redistribution of ventilation or perfusion to specifically increase alveolar dead space as ventilation falls, but only in those who develop hypercapnia.

The redistribution of blood flow to lung units with low $\dot{V}_A/\dot{Q}$ ratios secondary to release of hypoxic vasoconstriction in both the R and NR groups will necessarily create more units with high $\dot{V}_A/\dot{Q}$ ratios. The increase in V_D/V_T seen in patients with COPD given oxygen therapy, who become hypercapnic, has been attributed to this change (8, 10). However, this effect will be minimal, will occur equally in all patients, and will have little influence on carbon dioxide retention if the increase in high $\dot{V}_A/\dot{Q}$ is mainly a small shift in the mean $\dot{V}_A/\dot{Q}$ ratio of the ventilation distribution. This can be illustrated by the small effect on Pa_{CO_2} of increasing shunt fraction while holding total ventilation and cardiac output constant in computer models of a lung with an otherwise normal $\dot{V}_A/\dot{Q}$ distribution. This is because the contribution of blood flow from low $\dot{V}_A/\dot{Q}$ ratio units to hypercapnia in the presence of a relatively stable mixed venous carbon dioxide tension is small. This fact can be

readily appreciated by examining the classic oxygen/carbon dioxide diagram of Rahn and Fenn (27). Ventilation wasted in lung units with significantly higher $\dot{V}_A/\dot{Q}$ ratios causes hypercapnia by failing to efficiently eliminate carbon dioxide from the body as a whole, thus causing the mixed venous tension of this gas to rise, which in turn reflects in a raised Pa_{CO_2}.

The significant increase in log SD $\dot{V}$ in the R group, but not in the NR group, suggests an additional mechanism. A plausible hypothesis is that the hypercapnia that develops as overall ventilation falls in the R group causes some bronchodilatation, increasing ventilation to some parts of the lung and hence increasing alveolar dead space and further contributing to hypercapnia. Alternatively, some other mechanism may induce high $\dot{V}_A/\dot{Q}$ units in the R group, which is unrelated to the hypercapnia but is operating only in this group.

When the Bohr equation is applied (assuming a stable carbon dioxide output) to the mean data for Group R, shown in Table 3, the predicted Pa_{CO_2} is slightly higher than the observed Pa_{CO_2}. This suggests that carbon dioxide output at the lung fell in this group, possibly related to decreased CO_2 production from respiratory muscles as ventilation fell. In addition, carbon dioxide will still be entering body stores as the CO_2 tension rises: a new steady state for carbon dioxide will not have been reached within 20 min. These trends will reduce the impact of hypoventilation and increasing $\dot{V}_A/\dot{Q}$ inequality on the increase in Pa_{CO_2} (8).

In summary, ventilation fell by an average of 20% and log SD $\dot{V}$ (a MIGET measure of alveolar dead space) increased by 24% in patients who retained carbon dioxide with oxygen therapy. The only other significant finding with hyperoxia was an increase in low $\dot{V}_A/\dot{Q}$ units in both groups. None of the differences in oxygen response between the R and NR groups was significant, presumably because the numbers of subjects were not large enough. The change in ventilation approached significance at $p = 0.06$. Our results suggest that the major mechanism differentiating retainers from nonretainers is depression of ventilation rather than the redistribution of blood flow caused by release of hypoxic vasoconstriction. However, an increase in alveolar dead space is also a distinguishing feature of carbon dioxide retainers and this may be secondary to the hypercapnia.

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