RELATIONSHIPS BETWEEN INSPIRED OXYGEN CONCENTRATION AND VENOUS ADMIXTURE DURING NITROUS OXIDE–OXYGEN–HALOTHANE ANAESTHESIA

J. H. KERR, P. FOEX AND D. A. PYBUS

The tendency for venous admixture (Qva/Qt) to increase at high fractional inspired oxygen concentrations (FI\textsubscript{O\textsubscript{2}}) has been demonstrated frequently within the past decade (McAslan et al., 1973; Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Douglas et al., 1976; Drummond, Wildsmith and Masson, 1978; Reines and Civetta, 1979; Douglas, Downs and Snook, 1980; Oliven, Abinader and Bursztein, 1980; Shaper et al., 1980) and this finding has been accompanied by the realization that changes must be occurring within the lungs as the F\textsubscript{I\textsubscript{O\textsubscript{2}}} is altered (Kerr, 1975).

Whether such changes are primarily the result of a redistribution of ventilation or of perfusion has yet to be established but, by measuring continuous ventilation:perfusion (Va/Q) ratio distributions within the lung, Wagner and colleagues were able to confirm that intrapulmonary shunting increased after pure oxygen breathing in subjects with normal (Wagner et al., 1974) and abnormal (Wagner et al., 1977) respiratory function. As a result of this work, Dantzker, Wagner and West (1975) hypothesized that the changes in venous admixture occur primarily as a result of a redistribution of ventilation. They described a parallel compartment, multiple unit, computer model of the lung in which the dispersion of the Va/Q ratios was log normal and in which the degree of dispersion (and many other variables) could be manipulated by the investigator. Using this model, the authors extended the concept of absorption atelectasis and introduced that of

---

**SUMMARY**

The inspired oxygen concentration (F\textsubscript{I\textsubscript{O\textsubscript{2}}}) was changed on 43 occasions at about 30-min intervals in 13 patients during artificial ventilation with mixtures of nitrous oxide (N\textsubscript{2}O), oxygen and halothane. Ventilator settings remained unchanged for each patient and at the end of each period, samples of arterial and central venous blood (and, in six patients, pulmonary arterial blood) and inspired and expired gases were collected. Oxygen tension was measured with a dedicated electrode shown to be unaffected by N\textsubscript{2}O. Venous admixture (Qva/Qt) was calculated at each F\textsubscript{I\textsubscript{O\textsubscript{2}}}. There was a highly significant correlation between the direction of change of F\textsubscript{I\textsubscript{O\textsubscript{2}}} and that of Qva/Qt, irrespective of whether F\textsubscript{I\textsubscript{O\textsubscript{2}}} increased or decreased. In 10 patients, there was a progressive increase in Qva/Qt as F\textsubscript{I\textsubscript{O\textsubscript{2}}} increased above 40%, and in all patients Qva/Qt on nearly 100% oxygen was greater than that measured at the next lowest concentration (60–80%). These results are at variance with the pattern of behaviour predicted from the "critical Va/Q" theory and support the concept of an oxygen-dependent redistribution of perfusion.

"critical Va/Q"—a ventilation:perfusion ratio at which expiration from the alveolar unit ceased because all the inspired gases had been absorbed by the blood flow. In units with Va/Q ratios below the critical value, the volume of gas entering during inspiration would be less than that carried away by the blood flow, so that such units would tend to collapse and thereafter contribute to the measured venous admixture. During inspiration of mixtures of nitrogen and oxygen, the critical Va/Q ratio will increase as F\textsubscript{I\textsubscript{O\textsubscript{2}}} is increased from 0.2 to 1.0 with a consequent increase in Qva/Qt.
HYPEROXIC SHUNTING DURING N\textsubscript{2}O ANAESTHESIA

1151

FIG. 1. Upper diagrams illustrate the relationship between "Critical Va/Q" and F\textsubscript{1O\textsubscript{2}} when the balancing gas is nitrogen (on left) and nitrous oxide (on right). With N\textsubscript{2}/O\textsubscript{2} mixtures, lung units with sub-critical Va/Q ratios (shown by hatched areas) will tend to collapse as F\textsubscript{1O\textsubscript{2}} increases and so produce an increase in Q\textsubscript{va}/Q\textsubscript{t} as indicated in the lower left diagram. With N\textsubscript{2}O/O\textsubscript{2} mixtures, the tendency to collapse does not alter significantly as F\textsubscript{1O\textsubscript{2}} increases, and one would not expect there to be a change in Q\textsubscript{va}/Q\textsubscript{t} from this cause as F\textsubscript{1O\textsubscript{2}} increases (lower right diagram).

which is particularly apparent in the F\textsubscript{1O\textsubscript{2}} range 0.5–1.0 and in inefficient lungs containing many poorly ventilated alveoli (fig. 1). This predicted increase in Q\textsubscript{va}/Q\textsubscript{t} does not require an active physiological response to oxygen, since it can be explained on the basis of the differing solubilities of the constituent alveolar gases. The authors went on to suggest that substitution of the relatively insoluble balancing gas (N\textsubscript{2}) with a more soluble gas (N\textsubscript{2}O) at the same fractional concentration would further increase the critical Va/Q. They calculated that the critical Va/Q would remain essentially unchanged as F\textsubscript{1O\textsubscript{2}} was increased from 0.4 to 1.0 (fig. 1). By implication, therefore, it can be predicted that the usual oxygen-dependent increase in Q\textsubscript{va}/Q\textsubscript{t} seen with N\textsubscript{2}/O\textsubscript{2} mixtures should be absent if N\textsubscript{2}O was the balancing gas.

The present study was devised to test this prediction and to provide further information about the mechanisms responsible for the increases in Q\textsubscript{va}/Q\textsubscript{t} often seen at high values of F\textsubscript{1O\textsubscript{2}}.

PATIENTS AND METHODS

Patient selection and anaesthetic technique

Thirteen patients were studied during elective, non-thoracic vascular surgery. All patients had given informed consent for the investigation and the study had the approval of the Hospital’s Research Ethics Committee. Twelve of the patients were smokers and had smoked at least 10 cigarettes per day for 5 years before surgery. The 13th patient was a non-smoker, but had a history of dust exposure and had the clinical signs of Chronic Obstructive Airways Disease. At the time of surgery, none of the patients had significant sputum production, or was limited in activity by respiratory symptoms. Details of the patients are contained in table I.

Approximately 1 h before arrival in the anaesthetic room, the patients were premedicated with papaveretum and hyoscine. Anaesthesia was induced with thiopentone and tracheal intubation was facilitated with pancuronium. Ventilation of the lungs was commenced with a gas mixture of nitrous oxide, oxygen and halothane using a volume pre-set ventilator (Penlon “Oxford”) in a non-rebreathing mode at a frequency of 10 b.p.m.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Cigarettes /day</th>
<th>Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>55</td>
<td>74</td>
<td>20</td>
<td>Aorto-iliac endarterectomy</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>61</td>
<td>62</td>
<td>20</td>
<td>Femoro-popliteal bypass</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>52</td>
<td>68</td>
<td>15</td>
<td>Aorto-iliac endarterectomy</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>52</td>
<td>80</td>
<td>10</td>
<td>Femoro-popliteal bypass</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>56</td>
<td>72</td>
<td>20</td>
<td>Femoro-popliteal bypass</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>58</td>
<td>51</td>
<td>10</td>
<td>Femoro-popliteal bypass</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>60</td>
<td>67</td>
<td>20</td>
<td>Aorto-iliac endarterectomy</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>59</td>
<td>77</td>
<td>10</td>
<td>Aortic aneurysm repair</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>43</td>
<td>75</td>
<td>40</td>
<td>Aorto-iliac endarterectomy</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>51</td>
<td>72</td>
<td>40</td>
<td>Aorto-iliac endarterectomy</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>62</td>
<td>60</td>
<td>35</td>
<td>Femoro-popliteal bypass</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>69</td>
<td>74</td>
<td>Nil</td>
<td>Aortic aneurysm repair</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>54</td>
<td>89</td>
<td>20</td>
<td>Aortic aneurysm repair</td>
</tr>
</tbody>
</table>
Tidal volume was set in the range 8–12 ml/kg body weight and measured with a Wright's respirometer. These ventilator settings were not altered during the course of the study. A cannula was inserted to the radial artery to permit the continuous monitoring of arterial pressure, and for the sampling of arterial blood. In six patients, a flow-directed catheter was passed into a pulmonary artery, correct placement being confirmed by recognition of the typical waveform. In the remaining seven patients a central venous catheter was placed so that its tip was estimated to lie in the superior vena cava. Nasopharyngeal temperature was monitored continuously. Anaesthesia was maintained by the continuous administration of 0.5–1.0% halothane while the inspired oxygen and nitrous oxide concentrations were varied in accordance with the design of the investigation. As far as was possible a constant $F_iO_2$ was maintained throughout the period of study, although it was occasionally necessary to alter the concentration if unacceptable hyper- or hypo-tension occurred. Muscle relaxation was maintained with incremental doses of pancuronium and a few patients were given bolus doses of fentanyl 50–100 μg. Fluid requirements were met in most patients by the infusion of Hartmann's solution, although blood was replaced when indicated clinically. Body temperature was stabilized by the use of warming blankets and the warming of all i.v. fluids.

**Design of investigation**

During the course of the procedure the lungs of each patient were ventilated with at least four different gas mixtures in sequence (oxygen at an approximate concentration of 30, 50, 75 or 99%, halothane in the range 0.5–1.0% and nitrous oxide as the balance). The order of administration of the mixtures was varied from patient to patient and is shown in table II. After an equilibration period of 30 min, 5-ml specimens of arterial, central venous and, where available, pulmonary artery blood were taken anaerobically into plastic syringes and placed immediately in iced water before analysis. A specimen of inspired gas was taken and a 2-min sample of expired gas was collected in a Douglas bag which had been evacuated previously to a sub-atmospheric pressure of 20 mm Hg. Subsequently, three determinations of cardiac output ($Qt$) were made using a dye dilution technique. Once all the measurements had been obtained, a new $F_iO_2$ was selected and the cycle of observations was repeated.

**Analytical techniques**

Measurements of oxygen tension were made at 37°C using a platinum cathode (Clarke type) polarographic electrode filled with modified electrolyte (Schuler, 1966). Polarography with this electrode had shown that its readings were unaffected by gas mixtures containing nitrous oxide or halothane and that, if polarized at −800 mV, it gave a steady reading within 1 min of a change of sample. This dedicated electrode was operated by an experienced technician and was calibrated with an oxygen-free mixture ("white spot" nitrogen) and with an oxygen-in-nitrogen mixture (50%), the composition of which had been measured using a carefully calibrated paramagnetic oxygen analyser (Nunn et al., 1964). The calibration of the electrode was verified before and after each blood sample using the 50% mixture and the reading corrected to take into account any difference in the calibration measurements ("drift correction"). Potential errors from differences in the measurement in the blood and gas phases were minimized by the application of "blood-gas" factors which had been estimated over the entire range of $P_O_2$ using tonometered whole blood. $P_O_2$ values of less than 15 kPa were multiplied by 1.03, those between 15 and 38 kPa by 1.05 and those greater than 38 kPa by 1.09. Finally, a "time correction" factor, which related to both the elapsed time and the measured $P_O_2$, was applied (Kelman and Nunn, 1966). The maximum interval between sampling and analysis for all samples was 15 min and, since arterial samples were analysed first, was considerably shorter for those with high $P_O_2$ values. Corrections for differences in temperature between the patient and the electrode were not applied. $P_CO_2$ and pH were determined using conventional electrodes (Radiometer).

Inspired and expired oxygen concentrations were measured with a paramagnetic analyser (Servomex) which had been calibrated with air and 100% oxygen. The volume of the expired gas was measured at room temperature with a dry gas meter and subsequently converted to BTPS using standard equations. Expired carbon dioxide analysis was performed on the electrode system. Haemoglobin concentration was measured on the first specimen obtained and the value obtained was used in all subsequent calculations of blood oxygen content.

At high inspired oxygen concentrations, alveolar
<table>
<thead>
<tr>
<th>Subject</th>
<th>$F_{O_2}$</th>
<th>$P_{A}O_2$ (kPa)</th>
<th>$P_{V}O_2$ (kPa)</th>
<th>$Q_{va}/Qt$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.260</td>
<td>12.5</td>
<td>4.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.990</td>
<td>59.0</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.595</td>
<td>38.2</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.354</td>
<td>23.5</td>
<td>4.30</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.289</td>
<td>12.0</td>
<td>4.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.993</td>
<td>57.0</td>
<td>3.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.395</td>
<td>24.8</td>
<td>3.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.778</td>
<td>45.0</td>
<td>4.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.544</td>
<td>34.0</td>
<td>3.80</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.995</td>
<td>71.0</td>
<td>4.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.695</td>
<td>53.0</td>
<td>4.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.315</td>
<td>22.0</td>
<td>4.39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.491</td>
<td>35.0</td>
<td>4.53</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.993</td>
<td>59.0</td>
<td>3.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.517</td>
<td>33.0</td>
<td>3.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.309</td>
<td>21.0</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.756</td>
<td>49.0</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.432</td>
<td>31.5</td>
<td>3.60</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.436</td>
<td>28.6</td>
<td>5.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.289</td>
<td>14.0</td>
<td>4.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.995</td>
<td>72.0</td>
<td>4.75</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.720</td>
<td>56.0</td>
<td>5.98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.543</td>
<td>42.0</td>
<td>6.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.345</td>
<td>20.5</td>
<td>5.47</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.302</td>
<td>14.6</td>
<td>3.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.991</td>
<td>55.0</td>
<td>3.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.754</td>
<td>49.0</td>
<td>4.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.512</td>
<td>32.5</td>
<td>4.59</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.315</td>
<td>23.5</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.990</td>
<td>67.0</td>
<td>4.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.625</td>
<td>44.0</td>
<td>4.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.452</td>
<td>30.0</td>
<td>4.50</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.309</td>
<td>13.6</td>
<td>5.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.982</td>
<td>49.9</td>
<td>4.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.664</td>
<td>41.0</td>
<td>6.61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.525</td>
<td>21.0</td>
<td>5.52</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.483</td>
<td>22.5</td>
<td>5.29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.985</td>
<td>57.0</td>
<td>6.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.739</td>
<td>46.5</td>
<td>5.58</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.319</td>
<td>19.0</td>
<td>6.14</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0.500</td>
<td>28.2</td>
<td>5.30</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.990</td>
<td>61.0</td>
<td>5.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.715</td>
<td>48.0</td>
<td>6.94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.300</td>
<td>17.5</td>
<td>6.57</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0.470</td>
<td>31.5</td>
<td>4.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.990</td>
<td>65.0</td>
<td>4.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.750</td>
<td>46.0</td>
<td>4.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.315</td>
<td>23.0</td>
<td>5.09</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0.510</td>
<td>34.0</td>
<td>4.45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.740</td>
<td>50.0</td>
<td>4.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.995</td>
<td>68.5</td>
<td>4.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.315</td>
<td>24.0</td>
<td>5.47</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0.340</td>
<td>8.9</td>
<td>5.87</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.995</td>
<td>15.5</td>
<td>4.89</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.765</td>
<td>12.1</td>
<td>5.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.525</td>
<td>10.1</td>
<td>5.88</td>
<td></td>
</tr>
</tbody>
</table>
Patient 1 Patient 2

**RESULTS**

Table II contains details of the blood-gas measurements and the determinations of venous admixture undertaken in the 13 patients. In five patients from whom we obtained paired samples of pulmonary arterial (PA) and central venous (CV) blood, there was a good correlation between the values of venous admixture calculated using the different venous specimens, but the central venous blood tended to give a higher value (fig. 2).

Similarly, following an alteration in $F_{1\text{O}_2}$, $Q_{\text{va}}/Q_{\text{t}}$ changed in the same direction whether estimated from pulmonary artery or central venous blood. Again, the size of the change in $Q_{\text{va}}/Q_{\text{t}}$ tended to be greater when calculated from central venous blood (fig. 3).

In the patients monitored with pulmonary artery catheters, we have used the pulmonary arterial values of $Cv_{\text{O}_2}$ for all subsequent analyses and graphical representations.

In table III we have documented the mean values of other variables which could have affected venous admixture. Analysis of variance failed to demonstrate any significant differences in mean arterial pressure, cardiac output, $P_{\text{aCO}_2}$, or $P_{\text{vO}_2}$ in the four ranges of fractional concentration of oxygen, neither were there any significant metabolic acid-base disturbances. To investigate further the relationship between cardiac output and $Q_{\text{va}}/Q_{\text{t}}$, the directions of change of the two variables were calculated on 43 occasions when the $F_{1\text{O}_2}$ had been altered. Associated with 22 increases in cardiac output were 11 increases and 11 decreases in $Q_{\text{va}}/Q_{\text{t}}$, while the 21 reductions in

---

**PO$_2$** was calculated using the classical “Alveolar Air Equation”, but at the lower fractional concentrations (< 0.80), an equation which is suitable for use in the presence of nitrous oxide (Filley, Macintosh and Wright, 1954) was applied. Oxygen content of the blood samples was derived from the corrected blood gas values using the Kelman algorithm (Kelman, 1966) and an oxygen combining factor of 1.34. The standard “shunt” equation was used to calculate venous admixture (Berggren, 1942). The equations which form the basis for the various correction factors and content calculations have been described fully in an earlier study from this department (Foëx, Meloche and Prys-Roberts, 1971).

**Statistical techniques**

The results were analysed using Fisher’s exact test, Friedman’s two-way analysis of variance and linear regression analysis. Pooled data are presented in the text and tables as the mean ± SD and $P$ values of < 0.05 were considered significant.
HYPEROXIC SHUNTING DURING N₂O ANAESTHESIA

TABLE III. Mean values (± SD) of arterial pressure, cardiac output, mixed venous Pₒ₂ and arterial Pₐ₉ in the four ranges of F₁ₒ₂

<table>
<thead>
<tr>
<th>F₁ₒ₂</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Cardiac output (litre min⁻¹)</th>
<th>Mixed venous Pₒ₂ (kPa)</th>
<th>Arterial Pₐ₉ (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2–0.39</td>
<td>90.9 (14.5)</td>
<td>3.77 (1.17)</td>
<td>6.43 (1.31)</td>
<td>4.89 (0.89)</td>
</tr>
<tr>
<td>0.4–0.59</td>
<td>84.5 (15.1)</td>
<td>3.59 (1.12)</td>
<td>6.38 (1.24)</td>
<td>4.70 (0.79)</td>
</tr>
<tr>
<td>0.6–0.79</td>
<td>88.7 (19.5)</td>
<td>3.68 (1.16)</td>
<td>6.98 (1.33)</td>
<td>4.98 (1.15)</td>
</tr>
<tr>
<td>0.8–0.99</td>
<td>92.7 (12.7)</td>
<td>3.42 (1.18)</td>
<td>6.57 (0.77)</td>
<td>4.53 (0.91)</td>
</tr>
</tbody>
</table>

TABLE IV. Directions of change in F₁ₒ₂ and subsequent direction of change in Qva/Qt (a) in all subjects, (b) in those in whom both F₁ₒ₂ were greater than 0.4 and (c) in those in whom at least one F₁ₒ₂ was less than 0.4. Figures in parentheses are those derived from measurements on pulmonary artery (as opposed to central venous) blood

<table>
<thead>
<tr>
<th>Qva/Qt UP</th>
<th>Qva/Qt DOWN</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F₁ₒ₂ UP</td>
<td>11 (6)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>F₁ₒ₂ DOWN</td>
<td>6 (1)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>(b) Both F₁ₒ₂ &gt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F₁ₒ₂ UP</td>
<td>4 (3)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>F₁ₒ₂ DOWN</td>
<td>3 (1)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>(c) At least one F₁ₒ₂ &lt; 0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F₁ₒ₂ UP</td>
<td>7 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>F₁ₒ₂ DOWN</td>
<td>3 (0)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

Cardiac output were accompanied by seven increases and 14 decreases in Qva/Qt.

In total we examined the effect of 43 changes in F₁ₒ₂ in the 13 patients. On 15 occasions F₁ₒ₂ was increased from its previous value and in the remaining 28 it was reduced. There was a highly significant correlation between the direction of change in F₁ₒ₂ and the direction of change in Qva/Qt (P < 0.001) and this correlation held irrespective of whether F₁ₒ₂ was increased or decreased. If one considered only those changes of F₁ₒ₂, where one of the fractional concentrations was less than 0.4, then the significance of this relationship was lost although the tendency remained. In the remaining patients—involving changes in F₁ₒ₂ above 0.4—there was again a highly significant correlation between the direction of change in F₁ₒ₂ and the direction of change in Qva/Qt. These relationships are shown as contingency tables in table IV.

We identified three patterns of response to a changing F₁ₒ₂. Six patients demonstrated a curvilinear relationship between F₁ₒ₂ and Qva/Qt. In four of these six patients, Qva/Qt was highest at the lowest F₁ₒ₂, decreased as F₁ₒ₂ was increased to 0.4–0.6 and then increased again as F₁ₒ₂ approached unity. Patient 1 (fig. 4) typifies this pattern of response. Four patients demonstrated a

Fig. 4. Relationship between Qva/Qt and F₁ₒ₂, for patient 1. In figures 4, 5 and 6, values are plotted in order of ascending F₁ₒ₂, rather than in order of collection (see table II).
progressive increase in venous admixture as the fractional concentration of oxygen was increased and this is illustrated by the response of patient 3 (fig. 5). The final pattern was shown by three subjects in whom there was a sigmoid relationship between $F_{I_{O_2}}$ and $Q_{va}/Q_{t}$, as is seen in the case of subject 10 (fig. 6).

In figure 7 we have expressed $Q_{va}/Q_{t}$ as a percentage of the value which we obtained at the highest $F_{I_{O_2}}$. As can be seen, on all occasions $Q_{va}/Q_{t}$ at this $F_{I_{O_2}}$ was greater than that measured when the fractional concentration was in the range 0.6–0.79 and in eight of the patients it was also greater than that measured in the range 0.4–0.59. We obtained the highest estimate of $Q_{va}/Q_{t}$ during ventilation at the highest $F_{I_{O_2}}$ in eight of the 13 patients and in the remaining five patients the maximal $Q_{va}/Q_{t}$ was seen at some other $F_{I_{O_2}}$—usually in the range of 0.2–0.39.

**DISCUSSION**

The principal finding of this study has been the demonstration of a consistent relationship between fractional inspired oxygen concentration and venous admixture during mechanical ventilation with mixtures of nitrous oxide in oxygen. In all 13 patients $Q_{va}/Q_{t}$ increased as $F_{I_{O_2}}$ was increased from 0.75 to 0.99. In the middle ranges of $F_{I_{O_2}}$, this tendency for $Q_{va}/Q_{t}$ to increase with increasing $F_{I_{O_2}}$ persisted, but in the lower ranges of $F_{I_{O_2}}$ the trend was reversed. Before considering the implications of this finding in detail, we propose to discuss various aspects of the methodology and experimental design.

**Methodology**

The results of this study are obviously crucially dependent on the accuracy of the measured oxygen tension, and throughout the investigation particular care was devoted to the measurement of this variable. For this reason, we used a dedicated electrode, insensitive to anaesthetic gases and operated by an experienced technician, in preference to an automated or semi-automated electrode system. As we have described in the methods section, a rigid calibration procedure was followed...
before and after every oxygen measurement and correction factors were applied to allow for electrode drift, blood:gas phase differences and elapsed time. Although samples were not taken into glass syringes, the plastic syringes were stored in iced water before use and returned there as soon as the sample had been taken. Decreases in \( P_{O_2} \) from this cause would have been greatest in the samples with the greatest values of \( P_{O_2} \), but are unlikely to have been greater than 1.5 kPa (Restall et al., 1975) because these samples were always analysed first. Corrections for differences in temperature between the patient and the electrode were not applied, since the calculation of content involves reconversion of \( P_{O_2} \) at the patient temperature back to a virtual \( P_{O_2} \) at 37 °C and it was felt that oxygen content would not change with temperature. Overall, in order to produce values of \( Q_{va}/Qt \) at the highest \( F_{IO_2} \) values similar to those obtained at \( F_{IO_2} \) of about 50 %, average \( P_{AO_2} \) on nearly 100 % oxygen would have needed to be more than 10 kPa greater than the corrected values.

The alveolar air equation used to calculate \( P_{A_2} \) was appropriate for use in the presence of nitrous oxide as it makes no assumptions about inert gas exchange (Nunn, 1977). Small errors in the calculation of \( P_{A_2} \) may have been introduced by a temperature difference between the alveoli and the assumed temperature of 37 °C, but these would have been minimal under the experimental conditions (Kerr, 1975). In this study, the effect of altering the \( F_{IO_2} \) upon the calculation of \( P_{A_2} \) will differ depending upon the direction of change. When the \( F_{IO_2} \) was increased (and the \( F_{IN_2O} \), therefore, decreased), nitrous oxide would have continued to pass into the alveoli leading to an overestimate of \( P_{AO_2} \) unless the Filley factor was applied. Only at the highest \( F_{IO_2} \) was this not done, so that the resultant overestimate of \( P_{AO_2} \) would lead to a slight underestmate of venous admixture at the highest value. After increases in \( F_{IN_2O} \) the converse would apply, so that the net effect of reciprocal changes would have been an apparent reduction in the oxygen-dependent increase in venous admixture shown by most of our patients.

The suitability of central venous blood as a substitute for “true” mixed venous blood has been questioned (Dongre, McAslan and Shin, 1977). However, in those patients from whom we obtained paired samples, we were able to demonstrate a good correlation both between the absolute values of \( Q_{va}/Qt \) and between the directions of change in \( Q_{va}/Qt \) which subsequently occurred although, as others have found (Scheinman, Brown and Rapaport, 1969; Tahvanainen, Meretoja and Nikki, 1982), the use of caval blood led to a consistent overestimation of \( Q_{va}/Qt \). For these reasons, we do not consider it likely that the use of central venous blood for calculating \( Q_{va}/Qt \) in those patients in whom pulmonary arterial blood was not available will have misrepresented the behaviour of their lungs when the \( F_{IO_2} \) was changed, although it seems likely that the size of the changes was exaggerated.

We deliberately altered the sequence of exposure to the various \( F_{IO_2} \) values from patient to patient for several reasons. First, we intended to minimize any possible time-dependent changes in \( Q_{va}/Qt \), notwithstanding the evidence that such changes appear not to occur (Dueck, Rathbun and Harrison, 1981). Second, we wished to expose the patients to both increasing and decreasing \( F_{IO_2} \) in order to assess the reversibility (or otherwise) of any changes in venous admixture. Finally, by varying the exposure sequence, we hoped that any errors introduced by incomplete mixing during the equilibration period would be self-cancelling. In addition, this practice will have lessened any distortion in the pattern of response produced by our use of the initial haemoglobin concentration throughout the study. Although each 1-g decrease in haemoglobin concentration will cause the value of \( Q_{va}/Qt \) derived from a given set of blood-gas measurements to be increased by a factor of about 1.05 (10 becomes 10.5% and 20 becomes 21%), changes were minimized in our patients by avoiding large crystalloid infusions and transfusing blood early, and by comparing \( Q_{va}/Qt \) values at successive \( F_{IO_2} \) values (table IV) rather than at widely spaced intervals during the operation. In designing the study we also sought to stabilize most of the suggested determinants of venous admixture and thereby isolate the effect of variations in the composition of the inspired gas. In particular, at each fractional concentration of oxygen, the lungs were ventilated at the same tidal volume, neither the cardiac output nor arterial pressure changed significantly and there was little change in either the mixed venous oxygen tension or the arterial \( P_{Co_2} \).

**Physiology**

The increases in \( Q_{va}/Qt \) shown by several patients at the lower values of \( F_{IO_2} \) are similar to those reported by other investigators (Douglas,
Downs and Snook, 1980; Oliven, Abinader and Bursztein, 1980) and probably represent the passive effect of increasing unsaturation of blood from poorly ventilated lung units as the inspired and hence alveolar oxygen tensions decrease, rather than a change in true shunt. As $F_{1O_2}$ is reduced from about 40% towards 20%, the rate of increase of $Q_{va}/Qt$ resulting from a fixed amount of $V/Q$ mismatching accelerates so that any oxygen-dependent effect is likely to be obscured. In a study such as this it is not possible to distinguish between the effects of true shunt and those of low $V/Q$ units but, in a recent study using a multiple inert-gas elimination technique (Lundh and Hedenstierna, 1984), $Va/Q$ distributions remained unaltered when $F_{1O_2}$ was increased from about 30 to 50%.

It has recently been suggested (Dueck et al., 1980) that during nitrous oxide–oxygen anaesthesia the effects of poorly ventilated lung units on oxygen transfer may be camouflaged during ventilation with nitrous oxide in oxygen (60:40) mixtures because the $P_{Ao_2}$ in such units may be increased by rapid $N_2O$ uptake—a second-gas effect. While we accept that such a mechanism may increase $P_{Ao_2}$ transiently, we find it difficult to conceive how enough oxygen can pass into what are, by definition, poorly ventilated alveoli in order to sustain a significant increase in arterial $P_{O_2}$. For this reason we do not believe that our estimates of venous admixture in the $F_{1O_2}$ range 0.3–0.5 were spuriously low.

Similarly, in view of the precautions taken with our measurements of oxygen tension, we feel confident in the accuracy of our determinations of venous admixture at the high $F_{1O_2}$ values, and, thus, are driven to conclude that, in the presence of nitrous oxide, venous admixture often increases as $F_{1O_2}$ is increased in the range 0.5–0.99.

This pattern of response has in fact been observed previously during ventilation with nitrous oxide in oxygen mixtures (Michenfelder, Fowler and Theye, 1966; Bradshaw and Thompson, 1982) and is incompatible with that predicted by the “Critical $Va/Q$” hypothesis. (The latter suggests that, during ventilation with such mixtures, the tendency for poorly ventilated alveoli to collapse and hence to increase $Q_{va}/Qt$ would be largely independent of $F_{1O_2}$ (fig. 1.).) This apparent contradiction can be considered in the light of at least four other observations which are also difficult to reconcile with “Critical $Va/Q$” as being an important mechanism for redistributing ventilation in the face of a changing $F_{1O_2}$:

1. The increase in $Q_{va}/Qt$ observed when $F_{1O_2}$ is increased is readily reversed when $F_{1O_2}$ is decreased again, even when the pattern of ventilation is unchanged (McAslan et al., 1973; Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Reines and Civetta, 1979; Quan et al., 1980; Lundh and Hedenstierna, 1984). This observation, reconfirmed in the present study, requires that lung units, which according to the “Critical $Va/Q$” theory should have become atelectatic in order to contribute to the increased shunting at high $F_{1O_2}$, re-open within a short time (15–30 min) of exposure to a lower $F_{1O_2}$. In view of this rapid reversibility, it could be argued that the subcritical units remained open by inspiring alveolar gas from neighbouring units during the expiratory phase of the rest of the lung (“collateral ventilation”) (Dantzker, Wagner and West, 1975). This appears unlikely as, under these conditions, the lung unit should remain effective for oxygen uptake but ineffective for carbon dioxide elimination and thus should not be detected as venous admixture by our measurements.

2. It might be expected that alveolar atelectasis of the degree required to produce the observed increases in $Q_{va}/Qt$ would be accompanied by detectable reductions in lung volume. However, Suter, Fairley and Schlobohm (1975) failed to demonstrate a progressive decrease in lung volume in spite of steadily increasing $Q_{va}/Qt$ as $F_{1O_2}$ was increased to 90%, although there was a decrease in functional residual capacity (FRC) after ventilation with 100% oxygen. Conversely, Heneghan, Bergman and Jones (1984) were unable to initiate changes in oxygenating efficiency during anaesthesia by altering FRC. Thus, it would appear that significant changes in $Q_{va}/Qt$ can occur independently of changes in lung volume.

3. In most of the studies reported, insufficient time has been allowed after $F_{1O_2}$ changes to permit atelectasis to occur. McAslan and colleagues (1973) found increases in $Q_{va}/Qt$ after 5 min ventilation with 100% oxygen and in most of the other studies equilibration times of between 15 and 30 min have been used. In the absence of $N_2O$, the critical $Va/Q$ theory predicts that considerably longer time periods would be necessary for alveolar collapse to take place, particularly at the intermediate values of $F_{1O_2}$.

4. In most of their patients, Lundh and Hedenstierna (1984) found increasing true shunt as $F_{1O_2}$ was increased from 53 to 85% without demonstrating the presence of lung units with $Va/Q$ ratios in the “critical” range. In one of
their nine patients such units were found, and it appeared that they became atelectatic on ventilation with 85% oxygen and remained so on return to a lower $F_{O_2}$.

Since it seems unlikely that, in most patients, the oxygen-dependent increase in $Q_{va}/Q_t$ can be explained by a passive redistribution of ventilation based on the physical properties of the respiratory gases, an alternative possibility, that of an oxygen-mediated redistribution of the pulmonary blood flow, must be considered as the main cause of this phenomenon. This conclusion has been reached by other investigators (Kerr, 1975; Suter, Fairley and Schlobohm, 1975; Lundh and Hedenstierna, 1984) and is strongly reinforced by the results of this study. The mechanism of the redistribution remains unclear, however, since, unlike pulmonary hypoxic vasoconstriction in man (Bjertnaes, 1978), it occurs in the presence of halothane (Michenfelder, Fowler and Theye, 1966; Drummond, Wildsmith and Masson, 1978; Lundh and Hedenstierna, 1984), and there is no obvious relationship between the change in $Q_{va}/Q_t$ and changes in mixed venous oxygenation.

ACKNOWLEDGEMENTS

We are greatly indebted to Dr C. Hahn for his advice and guidance with the oxygen electrode which was tested and operated by Messrs Scarlett, Morris and Jones. We wish to thank Professor Morris for permission to study his patients and Professor Sykes for his assistance in the preparation of the paper.

REFERENCES


saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation*, 11, 165.


