EFFECTS IN DOGS OF HYPERVENTILATION AND HYPOTHERMIA ON BODY OXYGEN STORES

BY
M. B. RAVIN AND S. F. SULLIVAN

SUMMARY
Six anaesthetized, paralyzed, hypothermic (30°C) dogs were hyperventilated for 2 hours. During the final 30 minutes, the inspired mixture was altered from oxygen to air. The rates at which alveolar and arterial oxygen concentrations approached their new steady state values were represented by the half-times (t½) of 0.19 and 0.26 minutes, respectively. The turnover rate in venous blood oxygen content proceeded at a considerably slower rate, t½ = 0.90 minutes. The close agreement of results during hypothermia with results obtained during normothermia indicates that hypothermia per se has no significant effect upon oxygen turnover rate.

When the metabolic requirement for oxygen temporarily exceeds the oxygen supplied by ventilation, the immediate oxygen deficit is paid by the oxygen stored in the body. This oxygen reservoir is limited and scarcely contains enough oxygen to supply the body for 5 minutes after gaseous interchange in the lungs has stopped.

Most of the oxygen stored in the body is in the alveolar gas and the blood (Farhi, 1963). The rate at which alveolar and arterial oxygen concentrations are altered can be estimated from the magnitude of alveolar ventilation and cardiac output. Considering that the venous blood is the largest reservoir of oxygen in the body, and the turnover rate of oxygen in venous blood is predominantly dependent upon blood flow (Farhi, 1963), the oxygen turnover rate under different conditions has not been fully documented.

In a previous study of normothermic dogs with controlled ventilation (Sullivan and Ravin, 1968), we determined the rates at which alveolar, arterial, and venous oxygen concentrations approached their new steady-state values when the inspired mixture was changed from oxygen to air. These turnover rates had half-times (t½) of 0.17, 0.23, and 0.75 minutes, respectively. The purpose of the present study is to extend these observations to the hypothermic animal.

METHODS
Six, healthy, adult, mongrel dogs, averaging 10.8 kg (range 8–14 kg) were anaesthetized with intravenous sodium pentobarbitone 30 mg/kg. Their tracheas were intubated with a cuffed endotracheal tube and ventilation was controlled with a ventilator. The dogs were paralyzed with an intravenous drip of 0.1 per cent suxamethonium in 5 per cent dextrose and water (0.5 mg/min) to avoid shivering, muscle movement, or spontaneous respiratory effort. Ventilation was recorded with a 13.5-litre spirometer. A polyethylene catheter was placed in the right ventricle or pulmonary artery via the external jugular vein, using the technique of Lategola and Rahn (1953), so that its tip was within 2 cm of the pulmonary valve. A femoral artery was also cannulated. These catheters sampled mixed venous and arterial blood. A thermistor was introduced into the oesophagus to measure retrocardiac temperature.

The animal was hyperventilated with air (approximately 12 ml/kg body weight at a frequency of 14 per minute) for about 75 minutes while being prepared for study. The dogs were cooled by immersion in crushed ice. When the retrocardiac temperature reached 33°C, the ice was removed and the animal covered with an electronically self-regulating hypothermia blanket. After temperature stabilization at 30°C, the inspired mixture was changed to 100 per cent oxygen for the succeeding 30 minutes. After the...
period of oxygen breathing, arterial and venous blood samples were obtained simultaneously.

Then the inspired mixture was switched to air (FiO₂ 1.0→0.21). End-tidal nitrogen concentration was measured during the period of initial oxygen washout with a nitrogen meter. Additional arterial and mixed venous blood samples were obtained at 0.5, 1, 2, 3, 10, and 30 minutes after breathing air. Blood samples were obtained in heparinized syringes and iced until analysis.

Blood, pH, Pco₂ (Severinghaus and Bradley, 1958), and Po₂ (Clark, 1956) were measured with appropriate electrodes at 37°C. The coefficients of variation for replicates of blood oxygen tension were 0.8 per cent (air) and 1.9 per cent (100 per cent oxygen). Appropriate nomograms (Severinghaus, 1966; Hedley-Whyte, Radford and Laver, 1965) were used to correct measured blood gases for animal-electrode temperature difference.

Blood Po₂ was corrected for the electrode blood-gas difference by tonometry at 37°C using a sample of the animal's blood (Ravin and Briscoe, 1964). Utilizing a polypropylene membrane, the relationship of electrode response to gas and blood of the same Po₂ was relatively constant. In this study, mixed venous oxygen tension varied from 30 to 50 mm Hg and, in this range of blood Po₂, the gas-blood correction factor was 1.026 ±0.004 (mean ± SE).

Haemoglobin concentration was determined by spectrophotometry from the first and last arterial sample. The nomogram of Rossing and Cain (1966) was used to derive haemoglobin oxygen saturation from the corrected values of measured Po₂ and pH. Blood oxygen capacity was estimated using the corrected haemoglobin concentration. The oxygen content of the blood was calculated as
\[ (C_o) = (\text{oxygen saturation} \times \text{oxygen capacity}) + \text{amount oxygen dissolved}. \]
Dissolved oxygen in volumes per cent = Po₂ × 0.0274/760 × 100, where 0.0274 = solubility coefficient of oxygen in the whole blood in ml oxygen per ml blood per atmosphere at 30°C (Rosenhain and Penrod, 1951).

PAn₂ (alveolar nitrogen tension) was assumed to be equal to the end-tidal N₂ concentration measured during the change from oxygen to air breathing. The value of PAn₂ was used in the estimate of PAo₂ (alveolar oxygen tension) during this adjustment.

\[ PAo₂ = P_{iO₂} - P_{ACO₂} - P_{AN₂} - P_{AH₂O} \]

The value of PAo₂ is an approximation during this unsteady state. PAo₂ was assumed equal to PAO₂.

At the end of the 30 minutes of breathing air, mixed expired oxygen and carbon dioxide concentrations were measured using the Scholander method (Scholander, 1947). Oxygen consumption (Vo₂), carbon dioxide production (Vco₂), and the respiratory exchange ratio (R) were computed from the following expressions:

\[ Vo₂ = \text{VE}_{SPD} \left( \frac{1 - F_{Eo₂} - F_{ECO₂}}{1 - F_{iO₂}} \right) - F_{EO₂} \]
\[ VCO₂ = \text{VE}_{SPD} \times F_{ECO₂} \]
\[ R = \frac{VCO₂}{Vo₂} \]

(FEO₂ is the fractional concentration of oxygen in the mixed expired gas.)

The final equilibrium value for alveolar oxygen concentration (FAo₂) was solved graphically with the oxygen-carbon dioxide diagram of Rahn and Fenn (1955), using the derived values of R and the measured Paco₂. Cardiac output (Q) was calculated from Vo₂ and the A-V oxygen difference.

\[ Q = \frac{Vo₂}{(CaO₂ - CVO₂)} \]

During the period of oxygen washout, the changes in FAo₂, CaO₂, and CVO₂ were analyzed in terms of the rate at which each approached its new equilibrium value. A means of expressing the rate of change is the half-time, which is the time for the variable in question to change 50 per cent of its overall change. In this study, the half-time is expressed in minutes.

RESULTS

Blood haemoglobin concentration averaged 13.8 ± 1.1 g/100 ml (mean ± SE) with no measurable change between the zero and 30-minute sample. Oesophageal temperature averaged 30.1(±0.9)°C. Arterial carbon dioxide tension averaged 16.1 ± 1.4 and 15.8 ± 1.8 mm Hg, and the pH averaged 7.49 ± 0.03 and 7.50 ± 0.04 at the end of oxygen and air breathing, respectively.

Table I lists the average values for PaO₂, CaO₂, Pco₂, and Cvo₂ during the adjustment from oxygen to air breathing. The average values for FAo₂ were 0.49, 0.32, 0.24, and 0.20 at 1, 2, 3, and 1 minute, respectively. At 30 minutes, FAo₂ averaged 0.182, Vo₂ averaged 37.1 ml/min, R averaged 0.78, and Q averaged 0.61 l/min.
TABLE I

Arterial and mixed venous blood oxygen concentrations following step decrease in \( F_{\text{to}} \). Ventilation constant. Values represent mean and SE (6 studies).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>( P_{\text{ao}} ) (mm Hg)</th>
<th>( C_{\text{ao}} ) (vol%)</th>
<th>( P_{\text{vo}} ) (mm Hg)</th>
<th>( C_{\text{vo}} ) (vol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>577.0 ± 14.2</td>
<td>20.57 ± 0.87</td>
<td>44.4 ± 5.1</td>
<td>15.32 ± 1.13</td>
</tr>
<tr>
<td>0.5</td>
<td>209.0 ± 12.6</td>
<td>19.06 ± 0.85</td>
<td>41.1 ± 4.6</td>
<td>14.65 ± 1.11</td>
</tr>
<tr>
<td>1</td>
<td>120.2 ± 6.3</td>
<td>18.74 ± 0.85</td>
<td>38.0 ± 3.9</td>
<td>13.75 ± 0.98</td>
</tr>
<tr>
<td>2</td>
<td>111.8 ± 2.4</td>
<td>18.62 ± 0.86</td>
<td>35.1 ± 3.8</td>
<td>12.92 ± 1.10</td>
</tr>
<tr>
<td>3</td>
<td>112.9 ± 2.0</td>
<td>18.62 ± 0.86</td>
<td>34.7 ± 2.9</td>
<td>12.49 ± 0.94</td>
</tr>
<tr>
<td>10</td>
<td>111.6 ± 2.1</td>
<td>18.62 ± 0.86</td>
<td>35.0 ± 2.6</td>
<td>12.53 ± 0.94</td>
</tr>
<tr>
<td>30</td>
<td>112.5 ± 2.3</td>
<td>18.62 ± 0.85</td>
<td>34.8 ± 2.5</td>
<td>12.50 ± 0.91</td>
</tr>
</tbody>
</table>

The plotted average values of \( F_{\text{ao}} \), \( C_{\text{ao}} \) and \( C_{\text{vo}} \) during the adjustment from oxygen to air breathing are shown in figure 1. After 3 minutes, the washout process is essentially complete. Analysis of these data was made in terms of the rate at which each variable approached its asymptote (figs. 2 and 3). The change in \( F_{\text{ao}} \) and \( C_{\text{ao}} \) is represented by the half-times 0.19 and 0.26 minutes respectively, while the change in \( C_{\text{vo}} \) proceeds more slowly with a half-time of 0.90 minutes. Table II compares values previously obtained at normothermia (Sullivan and Ravin, 1963) with those obtained in the present study (\( T = 30.1^\circ \text{C} \)).

TABLE II

Effects of normothermia and hypothermia on \( R \), \( Q \) and \( t_{\frac{1}{2}} \) 30 minutes after switching from oxygen to air breathing.

<table>
<thead>
<tr>
<th></th>
<th>( 37.5^\circ \text{C} )</th>
<th>( 30^\circ \text{C} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{\text{co}} ) (ml/min)</td>
<td>49.0</td>
<td>28.9</td>
</tr>
<tr>
<td>( V_{\text{o}} ) (ml/min)</td>
<td>53.3</td>
<td>37.1</td>
</tr>
<tr>
<td>( R )</td>
<td>0.92</td>
<td>0.78</td>
</tr>
<tr>
<td>( Q ) (l/min)</td>
<td>0.85</td>
<td>0.61</td>
</tr>
<tr>
<td>( F_{\text{ao}} )</td>
<td>0.186</td>
<td>0.182</td>
</tr>
<tr>
<td>( t_{\frac{1}{2}} ) alv. (min)</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td>( t_{\frac{1}{2}} C_{\text{ao}} ) (min)</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>( t_{\frac{1}{2}} C_{\text{vo}} ) (min)</td>
<td>0.75</td>
<td>0.90</td>
</tr>
</tbody>
</table>
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There are four storage sites of oxygen to be considered: alveolar gas, arterial blood, venous blood, and tissue oxygen stores. The change of $F_{A,0}$ from 0.182 to 0.91 represents at least a six-fold change in $P_{A,0}$. If we assume the resting lung volume of the dog to be 30 ml/kg of body weight (Simmons and Hemingway, 1955), then this 80 per cent increase in $F_{A,0}$ represents an alveolar oxygen store increase of approximately 24 ml oxygen per kg body weight.

While $P_{A,0}$ values may vary over a physiological range of 50 mm Hg (20–70 mm Hg), the alveolar oxygen may vary by ten times as much when inspired air is replaced by oxygen. Thus, the alveolar carbon dioxide store in man can vary by less than 300 ml as compared with a total stored carbon dioxide of 120 l, whereas the alveolar oxygen store can vary by 2.5 l, a value much higher than the total oxygen stored normally in the body (Farhi, 1963).

In the absence of shunting, as the $F_{1,0}$ approaches 1.0, the arterial oxygen tension will approach the alveolar oxygen tension. In the present study, average $P_{0,3}$ in the alveoli is 697 mm Hg compared with an average arterial tension of 577 mm Hg. Assuming that the average physiological shunt is 2.8 per cent of the cardiac output (Bartels et al., 1955), the magnitude of shunting here is responsible for an arterial blood oxygen content of 1–2 per cent lower than that obtained with no shunting whatsoever. There is no significant difference between the $P_{A,0}$ values obtained breathing 100 per cent oxygen at normothermia or hypothermia (table II).

The oxygen capacity of arterialized blood is approximately 3.8 ml/kg body weight when the $F_{I,0}$ is 0.21 (Farhi, 1963), assuming one-quarter of the blood volume is on the arterial side of the circulation. When arterial $P_{0,3}$ drops to 40 mm Hg near its lowest value compatible with life, oxygen saturation decreases to 75 per cent, and the arterial oxygen content becomes 2.8 ml/kg. When oxygen is breathed the oxygen carried in the arterial blood becomes 4.2 ml/kg. Thus, the arterial component of the oxygen stores is by far the most steady of all compartments, the maximum variation being 25 per cent of the normal value.

The advantage of hyperventilating the animals lies in the rapid exchange of alveolar gas, which aids in distinguishing the venous from the alveolar and arterial changes. During the adjustment from oxygen to air breathing, mixed venous oxygen tension decreased an average of 9.6 mm Hg, which represented a change of 2.82 vol. per cent. If we assume a canine blood volume equal to 10 per cent of body weight and a venous volume equal to 75 per cent of the total blood volume, then there would be 75 ml of venous blood per kg of body weight. In the present study this would represent a change of 2.12 ml oxygen per kg when changing from oxygen to air breathing (2.82 x 0.75). When the rate of change in venous blood is extrapolated to the initial concentration, the intercept is at zero time plus 25 seconds. This can be interpreted to mean that, on the average, the initial change in mixed venous oxygen content requires about 0.42 minute following the alveolar change and presumably represents the average circulation time. Under normothermia the circulation time was.
estimated to be about 13 per cent shorter, and this difference is due in part to the change in cardiac output with hypothermia.

At present it is not possible to measure the body oxygen tissue stores since neither the oxygen solubility factor in tissues nor the Po$_2$ of tissues has been accurately determined. The non-vascular water content of the body is approximately 60 per cent of body weight or 600 ml/kg. If the oxygen dissolved in this tissue (600 ml/kg) decreased 9.6 mm Hg (equal to the decrease in venous blood when switching from oxygen to air breathing), then the quantity of oxygen released would be 0.17 ml oxygen per kg body weight [9.6 x (0.023/760) x 600]. During this period the quantity of oxygen released from mixed venous blood equals 2.12 ml oxygen per kg body weight. Therefore, the quantity liberated from tissues is at most 10 per cent of that made available from the venous reservoir and, in terms of the total body reservoir, is of minimal importance.

Although the amount of oxygen bound to myoglobin in muscle is more than ten times higher than the dissolved oxygen, it is not justified to consider myoglobin in a discussion of oxygen turnover rates since oxygen bound to myoglobin is available only in situ. The shape of the oxymyoglobin dissociation curve effectively prevents oxygen from leaving the muscle until the partial pressure of oxygen drops to extremely low values.

The reported effects of hyperventilation on cardiac output in the dog remain equivocal. Salzano and Hall (1965) report a significant decrease in cardiac output with positive pressure breathing. Other investigators (Rowe, Castillo and Crumpton, 1962; Brown, 1953) report no change in cardiac output when dogs are artificially hyperventilated. Obviously, any changes noted in cardiac output must be interpreted upon the background of anaesthesia, respiratory or metabolic acidosis, and body temperature. One must observe extreme caution in applying the results of animal experimentation to man.

Pentobarbitone results in a 25 per cent decrease in cardiac output in the dog remain equivocal. Salzano and Hall (1965) report a significant decrease in cardiac output with positive pressure breathing. Other investigators (Rowe, Castillo and Crumpton, 1962; Brown, 1953) report no change in cardiac output when dogs are artificially hyperventilated. Obviously, any changes noted in cardiac output must be interpreted upon the background of anaesthesia, respiratory or metabolic acidosis, and body temperature. One must observe extreme caution in applying the results of animal experimentation to man.

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One can describe the pattern of oxygen transport by using Farhi and Rahn's (1968) model for carbon dioxide transport. A reservoir where oxygen is kept at a constant pressure represents the atmosphere. A first resistance connects to the alveolar-arterial reservoir, and a second allows passage from the alveolar-arterial to the venous-tissue reservoirs. The first resistance represents the effects of the ventilation and the second depicts the influence of the cardiac output.
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the changes must be extremely rapid and, in fact, require as little as 0.2 minute for 50 per cent completion. The same holds true when changes in \( P_{A_0_2} \) follow a change in inspired gas mixture.

Separation of the oxygen stores of the body into alveolar, arterial and venous compartments is a gross over-simplification of a highly complex relationship. However, individual compartment analysis does permit an approximation of the relative turnover rates to the volume of oxygen exchanged. When flow and mixing in a compartment are uniform, then the rate of change of the substance in question will proceed at a predictable rate. Then when the substance in question in the compartment, which had previously been at constant concentration, is presented with a step change in the input concentration, the relationship describing the change under these conditions is experimental and the rate may be defined by the time-constant (TC).

\[
TC = \frac{\text{Volume of compartment}}{\text{Flow}}
\]

For example, in the present study the average volume of the venous compartment was assumed to be equal to 75 per cent of the average blood volumes (0.75 \( \times \) 10 l./kg \( \times \) 10.8 kg) or 0.81 l. Cardiac output averaged 0.61 l./min. Therefore, if a step change in concentration were presented:

\[
TC = \frac{0.81 \text{ l./0.61 l./min}}{} = 1.33 \text{ min.}
\]

For purposes of illustration the theoretical venous half-time =

\[
\log_2 (x \text{ time-constant}) = 0.92 \text{ min (0.693 \times 1.33 \text{ min})}.
\]

The observed half-time in venous blood was 0.90 minute and results from the actual physiological fact that although changes in alveolar and arterial oxygen concentrations occur rapidly, the change is not instantaneous. Therefore, a new square oxygen front cannot be presented to the venous compartment.

In conclusion, we have demonstrated that the time-constants for alveolar, arterial, and venous compartments are 0.19, 0.26, and 0.90 minute, respectively. The close agreement of results during hypothermia with results obtained during normothermia indicates that hypothermia per se has no significant effect upon oxygen turnover rate. Furthermore, we have (1) documented the extremely labile and limited nature of the oxygen stores of the body and (2) provided data which will be useful in constructing models to predict changes in body oxygen content during anaesthesia with hyperventilation and hypothermia.

REFERENCES


BRIEF REPORTS

W. H. A. BOSWORTH and M. M. COVENTRY

The influence of hypoxia on the release of ¹³¹Ilabelled
adenine andadenosine from rat liver slices

Three ¹³¹I-labelled adenosine and adenine
slices were incubated in the presence of
an oxygen-deficient atmosphere. After
incubation, the slices were assayed for
¹³¹I-labelled substances.

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It is not intended here to advocate a particular course of action. What is advocated is that anaesthetists should devote thought and discussion to the position of the Faculty and the question of separation. The possibility that independence may be accompanied by a loss of influence cannot be dismissed lightly, and it may be that when the facts of the new Charter are known pressure for independence will be less.

It is extremely difficult at the present time to decide between options and almost impossible to predict the consequences of following a particular line. Whatever may be the ultimate conclusion of these discussions, the harmonious relationship which has existed for so long between anaesthetists and surgeons in the United Kingdom, and which may well have influenced the practice of anaesthesia in other countries, must be maintained.