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 ($t_{1/2}$) of 0.19 and 0.26 minutes, respectively. The turnover rate in venous blood oxygen content proceeded at a considerably slower rate, $t_{1/2}$=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 ($t_{1/2}$) 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 concen-
tration 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 PaO (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 (Severing-
haus, 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 animals' 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 measured haemoglobin concentration.
The oxygen content of the blood was calculated as
(CO2) = (oxygen saturation × oxygen capacity) +
(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 atmos-
phere at 30°C (Rosenhain and Penrod, 1951).

PAO2 (alveolar nitrogen tension) was assumed to
be equal to the end-tidal N2 concentration mea-
sured during the change from oxygen to air
breathing. The value of PAO2 was used in the
estimate of PAO2 (alveolar oxygen tension) during
this adjustment.

PAO2 = PAO2 - PACO2 - PAO2 - PAH2O

The value of PAO2 is an approximation during this
unsteady state. PAO2 was assumed equal to PACO2.

At the end of the 30 minutes of breathing air,
mixed expired oxygen and carbon dioxide concen-
trations 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:

\[ V_{O2} = \frac{F_{I2} \times (1 - FE_{O2} - FE_{CO2}) - FE_{O2}}{1 - FIO2} \]

\[ V_{CO2} = \frac{F_{I2} \times FE_{CO2}}{1 - FE_{CO2}} \]

R = 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,
PACO2, 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, 3, 1, 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 \( F_{O_2} \). Ventilation constant. Values represent mean and SE (6 studies).

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>( P_{O_2} ) (mm Hg)</th>
<th>( C_{O_2} ) (vol %)</th>
<th>( P_{V_{O_2}} ) (mm Hg)</th>
<th>( C_{V_{O_2}} ) (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 ±0.85</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 \( FA_{O_2} \), \( CA_{O_2} \) and \( CV_{O_2} \) 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 \( FA_{O_2} \) and \( CA_{O_2} \) is represented by the half-times 0.19 and 0.26 minutes respectively, while the change in \( CV_{O_2} \) 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 (\( T = 30.1^\circ C \)).

![Graph showing oxygen washout](image1.png)

**Fig. 1**

![Graph showing semilogarithmic changes](image2.png)

**Fig. 2**
Oxygen washout. Changes in \( FA_{O_2} \) plotted semilogarithmically versus time.

**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°C</th>
<th>30°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{co_2} ) (ml/min)</td>
<td>49.0</td>
<td>28.9</td>
</tr>
<tr>
<td>( Vo_2 ) (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>( FA_{O_2} )</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} ) ( CA_{O_2} ) (min)</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>( t\frac{1}{2} ) ( CV_{O_2} ) (min)</td>
<td>0.75</td>
<td>0.90</td>
</tr>
</tbody>
</table>
DISCUSSION

There are four storage sites of oxygen to be considered: alveolar gas, arterial blood, venous blood, and tissue oxygen stores. The change of FAO₂ from 0.182 to 0.91 represents at least a six-fold change in PAO₂. 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 FAO₂ represents an alveolar oxygen store increase of approximately 24 ml oxygen per kg body weight.

While PAO₂ 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 FIO₂ approaches 1.0, the arterial oxygen tension will approach the alveolar oxygen tension. In the present study, average PO₂ 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 PAO₂ 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 FIO₂ is 0.21 (Farhi, 1963), assuming one-quarter of the blood volume is on the arterial side of the circulation. When arterial PO₂ 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 Po2 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 oxymyo-
globin 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 hyper-
ventilated. Obviously, any changes noted in
cardiac output must be interpreted upon the back-
ground 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 from the first to second hour of
anaesthesia in the dog breathing air (Gilmore,
1965). In the dog anaesthetized with thiopentone,
cooling to 30°C results in a marked decrease in
heart rate, coronary flow rate, myocardial oxygen
consumption and an increase in venous oxygen
saturation. Diminished cardiac output during
cooling is primarily due to a marked bradycardia
and not to myocardial depression (Gilmore, 1965).

The arteriovenous oxygen content difference
had increased from 5.25 to 6.12 vol. per cent at
the end of our study when compared to the value
30 minutes earlier during oxygen breathing. If
oxygen consumption during the period of oxygen
breathing were equal to that obtained 30 minutes
later, then the cardiac output during the oxygen
period would be about 28 per cent greater than
the latter value.

In our previous study at normothermia (Sullivan
and Ravin, 1968), after 30 minutes of air breathing
the arteriovenous oxygen content difference was
6.4 vol. per cent, the Vo2 averaged 53.3 ml/min
and the Q, therefore, averaged 0.85 l./min (table
II). Under hypothermia, but with other conditions
remaining similar, the Vo2 averaged 34.2 ml/min,
the arteriovenous oxygen content difference aver-
gaged 6.12 and, consequently, the Q averaged 0.56
l./min. Under the conditions reported here, the
34 per cent decrease in cardiac output between the
two studies appears to be related to the decrease
in oxygen consumption with hypothermia,
and explains the increase in turnover time in the
oxygen venous reservoir. Our value of a 36 per
cent fall in Vo2 at 30°C is in agreement with the
35 per cent fall reported by Michenfelder and
Theye (1968).

One can describe the pattern of oxygen trans-
port 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.

If FiO2 and Q are kept constant, a change in
alveolar ventilation must cause a readjustment in
PaO2. This will be accompanied by a similar
change in PaO2 and, hence, in oxygen content.
This change will be followed by venous blood,
provided Vo2 and Q are constant. However,
because of the shape of the oxygen dissociation
curve, the blood content changes are usually
minimal and practically all the readjustment of the
stores occurs in the alveolar gas. This implies that
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 $PAO_2$ 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 concentration 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:

$$TC = 0.81 l./0.61 l./min = 1.33 \text{ min}$$

For purposes of illustration the theoretical venous half-time is

$$\log_2 \times \text{time-constant} = 0.92 \text{ min} (0.693 \times 1.33 \text{ min})$$

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


LES EFFETS DE L'HYPERVERVENTILATION ET DE L'HYPOTHERMIE CHEZ LE CHIEN SUR LES RESERVES CORPORELLES D'OXYGENE

SOMMAIRE
Six chiens anesthésiés, paralysés et hypothermiques (30°C) ont été hyperventilés durant deux heures. On remplaça dans le mélange inspiré au cours des 30 dernières minutes, l’oxygène par l’air. Les taux auxquels les concentrations alvéolaires et artérielles d’oxygène se rapprochèrent de leur nouvelle valeur steady-state, sont exprimés par les demi-temps (t½) respectivement de 0,19 et 0,26 minutes. Le taux de turnover dans la concentration veineuse d’oxygène fut considérablement moins rapide, avec un t½=0,90 minutes. Le fait que les résultats durant l’hypothermie correspondent de près à ceux obtenus durant normothermie, indique que l’hypothermie en soi n’influence pas significativement le taux de turnover oxygénique.

WIRKUNGEN VON HYPERVENTILATION UND HYPOTHERMIE AUF DIE SÄUERSTOFFVORRÄTEN BEIM HUND

ZUSAMMENFASSUNG
Sechs narkotisierte und relaxierte Hunde wurden bei Hypothermie (30 Grad C) zwei Stunden lang hyperventilirt. Während der letzten 30 Minuten wurde die Inspirationsmischung langsam von Sauerstoff auf Luft umgestellt. Die Zeiträume, zu denen die alveolären und arteriellen Sauerstoffkonzentrationen ihre neuen Gleichgewichtswerte erreichten, wurden durch die Halbwertszeiten (t½) von 0,19 beziehungsweise 0,26 Minuten ausgedrückt. Der Übergangsprozeß beim Sauerstoffgehalt im venösen Blut vollzog sich in einem beträchtlich längerem Zeitraum, t½=0,90 Minuten. Die annähernde Übereinstimmung der Ergebnisse bei Hypothermie mit den Ergebnissen, die unter Normothermie erzielt wurden, deutet darauf hin, daß Hypothermie alleine keine signifikante Wirkung auf die Sauerstoffkonzentrationen ausübt.

EFECTOS EN PERROS DE LA HIPERVENTILACION E HIPOTERMIA SOBRE LOS DEPOSITOS DE OXIGENO EN EL CUERPO

RESUMEN
Seis perros hipotermicos (30 °C), paralizados y anestesiados fueron hiperventilados durante 2 horas. Durante los últimos 30 minutos la mezcla inspirada fue cambiada de oxígeno a aire. Las velocidades a las cuales las concentraciones de oxígeno alveolar y arterial alcanzaron sus nuevos valores de estado constante fueron representadas por los tiempos medios (t½) de 0,19 y 0,26 minutos respectivamente. La velocidad de intercambio en el contenido de oxígeno en sangre venosa fue mucho más lenta, a saber t½=0,90 minutos. La estrecha concordancia de valores durante hipotermia con los resultados obtenidos durante normotermia indica que la hipotermia por sí misma no tiene ningún efecto significativo sobre la velocidad de intercambio de oxígeno.

EDITORIAL continued from page 731

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.