THE CARDIORESPIRATORY EFFECTS OF HAEMORRHAGE AND OVERTRANSFUSION IN DOGS

BY


SUMMARY

Changes in cardiorespiratory function resulting from haemorrhage and overtransfusion were measured in forty-seven dogs during controlled ventilation. In the animals bled to a mean arterial pressure of 70 mm Hg there were significant reductions in arterial Pco₂, carbon dioxide output and oxygen consumption, cardiac output and total venous admixture. In the animals transfused to a mean central venous pressure of 15 mm Hg there was a significant fall in total thoracic compliance and arterial Po₂ and significant increases in the alveolar-arterial Po₂ difference and carbon dioxide output.

There have now been a number of reports which indicate that cardiorespiratory function during mechanical ventilation is affected by the pattern of ventilation employed. However, most of these studies have been performed on patients or animals with relatively normal respiratory and circulatory systems. In the present experiments an attempt has been made to study the effects of different patterns of ventilation under two conditions met clinically, namely haemorrhagic shock and cardiac failure. Unfortunately, it proved difficult to induce a stable state of cardiac failure in acute experiments in greyhounds. A combination of overtransfusion and the administration of propranolol was tried but it was found that propranolol produced no detectable cardiovascular changes when the blood volume was increased. For this reason the experiments were restricted to observations on the effects of different patterns of ventilation in the normo-, hypo- and hyper-volaemic state. The present paper summarizes the cardiorespiratory effects of alterations in blood volume during controlled ventilation with a standardized waveform. Subsequent papers detail the effects of changing patterns of ventilation in each of the different states of blood volume.

METHODS

To minimize the incidence of transfusion reactions the studies were performed on greyhounds of 20–30 kg body weight. These animals were watered and fed under supervision for 2–7 days before the experiment. A total of 24 dogs were submitted to bleeding and a further 24 to overtransfusion. However, only 23 of the bled dogs are included because of a possible error in blood-gas analysis in one of these experiments.

The pooled results quoted in this paper were compiled from the studies on 16 dogs ventilated with a +0 waveform as produced by a Cape ventilator (Sykes et al., 1970), a further 15 dogs ventilated with a sinusoidal flow pattern (Adams et al., 1970), and 16 dogs ventilated with a 1:2 inspiratory:expiratory ratio on the Barnet ventilator (Finlay et al., 1970). These results represented the control values in each of the studies mentioned and, although the inspiratory flow pattern was slightly different, the inspiratory:expiratory ratio of 1:2 and the frequency of 20 b.p.m. were common to all groups of dogs.

Anaesthesia.

This was induced with 5 per cent thiopentone (25–30 mg/kg i.v.) and a large-bore endotracheal tube was then passed under direct vision. The


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cuff was inflated and mechanical ventilation with room air was started immediately. The respiratory rate was standardized at 20 b.p.m. and the tidal volume was adjusted to maintain an end-tidal carbon dioxide concentration of 4–6 per cent. This was monitored with a rapid infra-red analyzer. Anaesthesia was maintained in two of the earlier experiments with chloralose (60–80 mg/kg i.v.) and in the later experiments with sodium pentobarbitone (20–30 mg/kg i.v.). Half of the sodium pentobarbitone was given in 500 ml of 5 per cent dextrose solution during the first 1–2 hours of the experiment whilst the remainder was given slowly in a further 500 ml of 5 per cent dextrose during the remaining 4–5 hours of the procedure. The dogs lay in the supine position in a V-shaped trough which could be heated to maintain the rectal temperature close to 37°C.

**Preparation.**

After inserting catheters into the abdominal aorta, right atrium and right ventricle from the groin, a catheter was floated from the jugular vein into the pulmonary artery (Fife and Lee, 1965). The position of this catheter was checked by wedging and by obtaining a withdrawal trace at the end of the experiment. The catheters were connected to strain gauges and the output from the strain gauge amplifiers was fed to a 4-channel heated-stylus recorder and display oscilloscope. Two channels were used for blood pressure recordings, a third for e.c.g., and a fourth for recording airway pressure. The transducers were repeatedly calibrated against a water column, the zero reference point being the junction of the posterior three-fifths and anterior two-fifths of the anteroposterior diameter of the chest (Guyton and Greganti, 1956).

Whilst the cannulations were being performed the trachea was exposed and two string ligatures were passed round it. The endotracheal tube cuff was deflated, the ligatures tied tightly round the trachea above and below the position of the cuff and the cuff then reinflated. The absence of leaks was checked before each measurement by observing the expiratory pressure plateau developed during occlusion of the expiratory tube of the ventilator.

**Measurements.**

After the ventilation had been stabilized a blood sample was withdrawn for acid-base determination and any non-respiratory acidosis was corrected by the administration of sodium bicarbonate solution. When a stable Pco₂ had again been achieved, the lungs were inflated by occluding the expiratory tube until a pressure of 30 cm H₂O was reached. (Blood pressure changes in response to this manoeuvre are termed “response to Valsalva” in the results section.) The hyper-inflation was repeated three times and a pause of several minutes was then made to allow the circulation to stabilize once again. During this period the Douglas bag was washed out twice with expired gas. The sample to the infra-red analyzer (60 ml/min) was then discontinued and expired gas was collected for a period of 5 minutes. Five ml blood samples from the femoral and pulmonary arteries were collected into heparinized plastic syringes during the middle 2–3 minutes of the gas collection and records of blood and airway pressures were made. Gas samples from the Douglas bag were taken into 100-ml oiled, glass and metal syringes and the expired gas volume was measured using a calibrated dry gas meter (Adams et al., 1967). Rectal temperature was recorded by a mercury-in-glass thermometer and a similar thermometer was used to record the temperature of the expired gas issuing from the gas meter during measurement of the gas volumes. The end-expired carbon dioxide level was measured before and after the gas collection by the infra-red analyzer and the mean reading taken.

**Ventilators used.**

Three ventilators were used during these studies. The first was a Barnet ventilator fitted with a pressure-operated collect valve (Sykes, 1969). The second was a Cape ventilator (Waine and Fox, 1962) modified with a solenoid-operated collect valve (Sykes et al., 1970) and the third was a waveform generator of our own design which gave a sinusoidal inspiratory flow pattern.
(Adams et al., 1970). All ventilators had an inspiratory:expiratory time ratio of 1:2 and functioned as volume preset machines (Hunter, 1961).

**Bleeding and transfusion.**

Blood was removed through a cannula (4 mm i.d.) inserted through the jugular vein into the right atrium. Bleeding was continued until a mean systemic pressure of 65–75 mm Hg was obtained. This usually required the withdrawal of 1–2 litres of blood. Before each change to a new pattern of ventilation the animal was returned to the control pattern and further increments of blood were withdrawn until the blood pressure once again stabilized at 65–75 mm Hg mean.

The blood withdrawn from the bled animals was taken into ACD solution and stored at 4°C; it was then used for transfusion into the other group of animals on the next day. The transfused blood was warmed by passage through a plastic coil submerged in a water bath at 37–39°C, the base deficit having been corrected by the addition of sodium bicarbonate, 15–20 m-equiv/500 ml blood. Each 500 ml of blood was alternated with 500 ml of 10 per cent dextran and the transfusion was continued until the central venous pressure stabilized at about 15 mm Hg. Since the venous pressure varied with the inflation pressure, and since a small continuous transfusion was required to maintain a given venous pressure, the animals were restabilized on the control inflation pattern between each of the other patterns of ventilation. The average transfusion required to produce a central venous pressure of 15 mm Hg initially was 2.5 litres. A further litre was usually transfused during the remainder of the experiment. This degree of hypervolaemia resulted in great engorgement of all the tissues.

**Analyses.**

Expired gas samples were analyzed in duplicate on a para-magnetic oxygen analyzer and a Severinghaus type carbon dioxide electrode the output of which was read on a Vibron C33B meter. These analyses were checked on a Po electrode and Haldane gas analyzer. Blood-gases were determined in duplicate immediately after sampling with a micro-oxygen electrode, standardized on air and nitrogen, and on the carbon dioxide electrode. The latter was standardized on CO₂ and oxygen mixtures which had been analyzed on a Haldane apparatus. A blood-gas factor of 4 per cent was applied to readings obtained on the oxygen electrode. Both electrodes were checked daily by tonometered blood samples and the results were not accepted if the blood-gas factor was below 2 per cent or above 6 per cent (Adams and Morgan-Hughes, 1967). pH was measured with a micro-glass electrode. This was standardized against precision buffers and checked against a second electrode system (Adams, Morgan-Hughes and Sykes, 1967, 1968). All the electrodes were maintained at 37 ± 0.1°C. Haemoglobin was measured by a spectrophotometric method using a cyanmethaemoglobin standard (Lewis, 1967).

**Calculations.**

All the calculations were performed on an Elliot 4100 digital computer using a programme prepared by the authors (Adams, 1970). Temperature correction factors were those described by Kelman and Nunn (1966) and the dissociation curve incorporated in the programme was that described by Severinghaus (1966). Oxygen tension was converted to content by assuming that 1g of haemoglobin (molecular weight 64,458) would combine with 1.39 ml of oxygen (see Appendix), and a solubility factor for oxygen of 0.003 ml/mm Hg was employed to calculate the dissolved oxygen. The Enghoff (1938) modification of the Bohr equation was used to calculate physiological deadspace and total venous admixture (Qs/Qt) was calculated from the standard mixing equation

\[ \frac{Qs}{Qt} = \frac{(C'c_o - C_{ao})}{(C'c_o - C'v_o)} \]

where \( C_{ao} \) = arterial oxygen content and \( C'v_o \) = mixed venous oxygen content. End-pulmon-

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8 Disodium citrate (monohydrate) 2 g, dextrose (anhydrous) 3 g, water 120 ml.
9 Dextran 110 injection B.P. in 0.9 per cent sodium chloride (Pisons Pharmaceuticals Ltd).
10 Model OA 101 Mk II, Servomex Ltd, Crowborough, Sussex.
11 National Welding Co. Ltd, 218 Fremont Street, San Francisco 5, California, U.S.A.
12 Electronic Instruments Ltd, Richmond, Surrey.
14 Radiometer Ltd, V. & A. Howe, 88 Peterborough Road, London S.W.6.
ary capillary oxygen content (CeO₂) was calculated by assuming that the alveolar and end-pulmonary capillary oxygen tensions were equal, alveolar oxygen tension (P_{A\text{O}_2}) being calculated from the alveolar air equation using gas tensions measured at 37°C:

\[ P_{A\text{O}_2} = P_{1\text{O}_2} - P_{\text{CO}_2} \left( \frac{P_{1\text{O}_2} - P_{\text{E\text{O}_2}}}{P_{\text{E\text{CO}_2}}} \right) \]

where

- \( P_{1\text{O}_2} \) = inspired oxygen tension
- \( P_{\text{E\text{O}_2}} \) = mixed expired oxygen tension
- \( P_{\text{E\text{CO}_2}} \) = mixed expired carbon dioxide tension
- \( P_{A\text{O}_2} \) = arterial carbon dioxide tension.

All gas tensions quoted in the results are at rectal temperature. Cardiac output was calculated from the Fick formula, oxygen consumption being derived from the inspired and expired gas concentrations using the standard calculations.

Sources of error.

Expired volume can be measured with an accuracy of ±1 per cent. The accuracy of Pco₂ determination on gases in the range encountered in expired gas (±1 SD) is ±0.5 mm Hg. Expired oxygen can be measured with an accuracy of ±0.1 per cent oxygen. Analysis of the results with tonometered blood samples obtained during these studies indicated that arterial Pco₂ could be determined with an accuracy of ±1 mm Hg. The SD of duplicate samples of blood analyzed on the oxygen electrode was ±1 mm Hg. Errors arising from the assumption of a blood-gas factor of 4 per cent probably increase the SD to ±2 mm Hg. The SD of duplicate haemoglobin estimations was ±0.16 g/100 ml. The main source of error was the calculation of oxygen content from P_{1\text{O}_2}, pH and Hb. The dissociation curve is known to vary considerably between individuals and after transfusion (Valtis and Kennedy, 1954) and in the venous range small changes in tension produce large changes in saturation and content. Furthermore the assumption of a value of 1.39 ml for the volume of oxygen which will combine with 1 g of haemoglobin is based on the theoretical value derived from the molecular weight of haemoglobin (64,458). Unfortunately, a proportion of the total haemoglobin is present as methaemoglobin which does not combine with oxygen. This would therefore reduce the oxygen content for a given P_{1\text{O}_2}. Observations on a number of the dogs indicated that the proportion of methaemoglobin was probably small. The proportion of sulphhaemoglobin was unknown. Since the measurements were comparisons within the same dog and the shift of the dissociation curve due to transfusion would tend to cause underestimation of shunt, it was concluded that it would be better to use a theoretical value rather than the commonly accepted value of 1.34 ml for the calculations.

RESULTS

The results obtained by averaging the observations from 23 dogs subjected to haemorrhage and 24 dogs subjected to overtransfusion are shown in table I.

Bleeding.

The mean arterial, mean pulmonary arterial (PAP) and mean central venous pressures (CVP) fell. In a previous series of 6 dogs left atrial pressure lines were inserted and the chest was then closed with an underwater drain. Bleeding in these dogs led to a fall in mean left atrial pressure from 6 to 3 mm Hg when mean arterial pressure fell from 110 to 65 and mean PAP fell from a mean of 16 to 9 mm Hg.

Mean airway pressure fell after bleeding. By assuming that airflow had ceased by the end of inspiration and that peak airway pressure therefore represented the pressure overcoming compliance it was possible to calculate values for total thoracic compliance (Ct) in 17 dogs. This increased slightly after bleeding. Tidal volume (Vt) was slightly reduced after bleeding to keep end-tidal carbon dioxide constant. Physiological deadspace (Vd\text{phys}) was unchanged but deadspace/tidal volume ratio (Vd/Vt) increased slightly. However, the difference was not significant in these studies. There was a significant reduction in arterial carbon dioxide tension (P_{A\text{CO}_2}) after bleeding and also a significant fall in carbon dioxide output (V\text{CO}_2) and oxygen consumption (V\text{O}_2). Ideal alveolar oxygen tension (P_{A\text{O}_2}) and arterial oxygen tension (P_{A\text{O}_2}) were practically unchanged after bleeding and, although there was no change in the alveolar-arterial oxygen tension difference (A-aP_{O}_2), there was a significant increase in arteriovenous oxygen content difference (a-vO₂).
### TABLE I

Changes resulting from alterations in blood volume. For abbreviations see text. All gas and blood-gas tensions expressed as at body temperature.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Hypovolaemic</th>
<th>P</th>
<th>Control</th>
<th>Hypervolaemic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td></td>
<td>Mean</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>124</td>
<td>23</td>
<td></td>
<td>70</td>
<td>16</td>
<td>&lt;0.0001</td>
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<tr>
<td>Mean PAP (mm Hg)</td>
<td>12</td>
<td>3</td>
<td>&lt;0.0001</td>
<td>128</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Mean CVP (mm Hg)</td>
<td>1.1</td>
<td>2.6</td>
<td>NS</td>
<td>0.5</td>
<td>3.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean airway pressure (cm H₂O)</td>
<td>4.2</td>
<td>1.6</td>
<td>NS</td>
<td>3.9</td>
<td>1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ct (ml/cm H₂O)</td>
<td>48.5</td>
<td>16.4</td>
<td>NS</td>
<td>52.3</td>
<td>17.1</td>
<td>NS</td>
</tr>
<tr>
<td>Vr (ml BTPS)</td>
<td>455</td>
<td>86</td>
<td>NS</td>
<td>433</td>
<td>74</td>
<td>NS</td>
</tr>
<tr>
<td>V̇ \text{b} \text{phys} (ml BTPS)</td>
<td>237</td>
<td>45</td>
<td>NS</td>
<td>237</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>V̇ \text{b}/V̇ \text{r} (%)</td>
<td>52.4</td>
<td>5.4</td>
<td>NS</td>
<td>55.8</td>
<td>6.6</td>
<td>NS</td>
</tr>
<tr>
<td>PA\text{CO₂} (mm Hg)</td>
<td>37.3</td>
<td>5.8</td>
<td>0.045</td>
<td>33.5</td>
<td>6.5</td>
<td>0.002</td>
</tr>
<tr>
<td>V̇ \text{CO₂} (ml/kg STPD)</td>
<td>6.52</td>
<td>1.19</td>
<td>0.001</td>
<td>5.07</td>
<td>1.03</td>
<td>0.005</td>
</tr>
<tr>
<td>V̇ \text{O₂} (ml/kg STPD)</td>
<td>6.95</td>
<td>1.32</td>
<td>0.002</td>
<td>5.69</td>
<td>1.21</td>
<td>0.009</td>
</tr>
<tr>
<td>PA\text{O₂} (mm Hg)</td>
<td>110.5</td>
<td>7.44</td>
<td>NS</td>
<td>112.6</td>
<td>8.33</td>
<td>NS</td>
</tr>
<tr>
<td>PA\text{O₂} (mm Hg)</td>
<td>96.2</td>
<td>13.37</td>
<td>NS</td>
<td>96.18</td>
<td>11.65</td>
<td>NS</td>
</tr>
<tr>
<td>A-a PA\text{O₂} (mm Hg)</td>
<td>14.2</td>
<td>12.0</td>
<td>NS</td>
<td>16.4</td>
<td>9.3</td>
<td>NS</td>
</tr>
<tr>
<td>Q̇s/Qt (%)</td>
<td>5.9</td>
<td>5.6</td>
<td>0.02</td>
<td>2.9</td>
<td>2.4</td>
<td>0.001</td>
</tr>
<tr>
<td>a-V̇ \text{O₂} (vols %)</td>
<td>4.44</td>
<td>1.32</td>
<td>&lt;0.0001</td>
<td>10.23</td>
<td>3.63</td>
<td>NS</td>
</tr>
<tr>
<td>CO (l./kg/min)</td>
<td>0.166</td>
<td>0.070</td>
<td>&lt;0.0001</td>
<td>0.06</td>
<td>0.016</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>32</td>
<td>12</td>
<td>&lt;0.0001</td>
<td>11</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>152</td>
<td>27</td>
<td>NS</td>
<td>159</td>
<td>35</td>
<td>NS</td>
</tr>
</tbody>
</table>
and a reduction in total venous admixture (Qs/Qt). There was a marked reduction in cardiac output (CO) and stroke volume. This was associated with a slight increase in mean heart rate.

**Overtransfusion.**

Transfusion to a mean central venous pressure of 15 mm Hg produced an increase in mean arterial pressure and an increase in mean pulmonary artery pressure from a mean of 13 to a mean of 28 mm Hg in the 17 dogs in which it was measured. In 6 other dogs in whom left atrial lines had been inserted transfusion to a mean venous pressure of 13 mm Hg increased mean pulmonary artery pressure from 13 to 21 mm Hg and left atrial pressure from 4 to 17 mm Hg.

Mean airway pressure rose and total thoracic compliance fell after transfusion. The close relation between central venous pressure and airway pressure is illustrated in figure 1. Tidal volume fell slightly after transfusion and, although there was a small reduction in Vd/VT, this was not significant. There was no change in Pao2 or VD/VT, but there was a significant fall in Paco2 and increase in Vco2 and A-aPo2. Total venous admixture was increased from a mean of 4.4 to 6.5 per cent but this change was not statistically significant. a-vO2 decreased slightly but the increase in cardiac output was not significant.

**DISCUSSION**

Patients undergoing open-heart surgery often require mechanical ventilation in the postoperative period, the main indications being ventilatory failure and incipient or established pulmonary oedema (Lumley and Sykes, 1970). A number of these patients have a reduced cardiac output due to uncorrected anatomical abnormalities, imperfect surgical repair, heart block, myocardial failure or cardiac tamponade. Such patients usually have a high venous pressure. Occasionally a massive haemorrhage occurs and mechanical ventilation has to be instituted in a hypovolaemic patient with a low venous pressure. Since a reduction in venous return is the most important mechanism by which intermittent positive pressure ventilation causes a reduction in cardiac output (Maulsby and Hoff, 1962), and since such a reduction in output might prove extremely deleterious in patients whose output was already low, it seemed desirable to assess whether the effects of intermittent positive pressure ventilation would differ when venous pressure was altered.

Initially an attempt was made to produce a state of cardiac failure by tightening ligatures around the aorta and pulmonary artery. This produced very unstable conditions. The administration of the beta-blocking drug propranolol was then tried. This failed to produce a high venous pressure. When propranolol was given to dogs transfused to a high venous pressure there was no alteration in any of the pressures measured. For this reason it was decided to limit the experiments to haemorrhage and overtransfusion.
CARDIORESPIRATORY EFFECTS OF HAEMORRHAGE

The technique used for bleeding was adopted because bleeding into a constant-pressure reservoir would have resulted in alterations in blood volume in response to the changes of waveform which it was desired to study. For this reason in both the bleeding and overtransfusion studies a return was made to the control waveform between each study. Increments of blood were then removed or transfused to readjust the arterial or venous pressure to the desired level.

Effects of altering blood volume.
In the animals studied two features emerged. First, a mean systemic pressure of less than 70 mm Hg could not be maintained for long without cardiac arrest. Secondly, large quantities of blood and dextran could be infused without the production of macroscopic signs of pulmonary oedema. Greyhounds were chosen in preference to mongrels because of the lower incidence of incompatibility reactions after transfusion of blood. None were seen during these studies but hypotension did sometimes occur when blood was run in quickly. This could be prevented by slowing the rate of transfusion and administering calcium chloride intravenously.

Compliance.
There have been many conflicting reports on the changes in lung compliance resulting from a reduction in blood volume. Thus Attinger (1960) and Salzano and Hall (1961) both found that compliance fell after bleeding during spontaneous ventilation whilst Gerst, Rattenborg and Holaday (1959) and Lewin and associates (1960) reported that compliance fell when blood volume was reduced in dogs which were being mechanically ventilated. On the other hand, Cahill and Byrne (1964) and Cahill, Jouasset-Strieder and Byrne (1965), working with dogs, and Davidson and Eyal (1968), working with rabbits, all reported an increase in lung compliance after bleeding.

There are three possible explanations for the observed discrepancies. Firstly, it is known that during spontaneous ventilation in the dog there is a tendency for progressive alveolar collapse to occur (Mead and Collier, 1959). If the reduction in blood volume was effected slowly it is possible that the reduction in compliance due to alveolar collapse might have overshadowed any increase in compliance due to the reduction in blood volume. A second possibility is that there might have been a reduction in compliance secondary to airway closure induced by the liberation of histamine in the shocked animal (Marshall, 1969). The third possibility is that the reduction in pulmonary blood flow might have affected the pulmonary vascular bed in such a way that it weakened the structural support of the lung. The suggestion that the distended pulmonary vascular bed provides structural airway support has been made by Giannelli, Ayres and Buehler (1967) on the basis of studies in the isolated, perfused and ventilated lung, but there is as yet no confirmatory evidence that such a mechanism is of importance in the intact animal.

There seems to be general agreement that pulmonary congestion or oedema decreases lung compliance (Christie and Meakins, 1934; Saxton et al., 1956; Frank et al., 1957; Bondurant, Hickam and Isley, 1957; Hughes, May and Widdicombe, 1958; Sharp et al., 1958; Cook et al., 1959; Larmi and Appelqvist, 1961), although Borst and associates (1957) found relatively small changes resulting from changes of blood flow and pulmonary arterial and left atrial pressure in the isolated lung.

On the evidence provided it seems reasonable to conclude that lung compliance increases with haemorrhage and decreases when pulmonary vascular engorgement is produced by overtransfusion.

$V_{co_2}$ and $V_O_2$.

The average oxygen consumption of dogs anaesthetized with pentobarbitone is quoted as 4.61 ml/kg when the haematocrit is normal (Crowell, Ford and Lewis, 1959). The mean $V_O_2$ of the normovolaemic animals in these experiments was 6.9 ml/kg. Whether this is a difference between mongrels and greyhounds is not known. The reduced $V_O_2$ and $V_{co_2}$ during hypovolaemia is probably due to underperfusion of some tissues with the formation of an oxygen debt. This suggestion is supported by the occurrence of a non-respiratory acidosis during haemorrhage. A similar fall in $V_O_2$ is seen when a reduction in cardiac output is produced by deep halothane anaesthesia or vagal stimulation (Theye and Sessler, 1967).
Although there was no significant increase in $V_{O_2}$ as a result of overtransfusion in the combined results presented here, there was a significant increase in cardiac output and $V_{O_2}$ in the group of experiments performed by Finlay and associates (1970). Theye and Sessler (1967) found that when cardiac output was increased by pacing there was also a significant increase in $V_{O_2}$. It is likely that part of the increased $V_{O_2}$ noted in such circumstances is due to an increased consumption of oxygen by the cardiac muscle but it is also possible that increased tissue perfusion may open up previously closed capillaries and lead to an increased tissue utilization of oxygen.

Deadspace.

The values for $V_d/V_t$ ratio found in the normo-volaemic state (mean 51 per cent) are higher than those reported by some authors in anaesthetized, mechanically ventilated dogs. Thus Williams and Rayford (1956) found a mean $V_d/V_t$ ratio of 37 per cent at shallow tidal volumes and 49 per cent at larger tidal volumes whilst Severinghaus and Stupfel (1957) found $V_d/V_t$ ratios of 40.2 and 42.4 per cent on spontaneous and controlled ventilation respectively. Suwa, Hedley-Whyte and Bendixen (1966), however, found a mean $V_d/V_t$ ratio of 48.1 per cent on spontaneous ventilation and 54.8 per cent on controlled ventilation and they found a good correlation between the increase in $V_d/V_t$ ratio and the decrease in cardiac index and pulmonary artery pressure which occurred when controlled ventilation was started. Severinghaus and Stupfel used chloralose anaesthesia in 4 of the 7 dogs studied whereas most of our own animals, and those in the other studies mentioned, received a barbiturate. Furthermore, most of the animals used in our studies appeared to be old and it is known that $V_d/V_t$ ratio increases with age (Tenney and Miller, 1956; Raine and Bishop, 1963; Cooper, 1967).

The failure to find any marked increase in $V_d/V_t$ ratio after haemorrhage is at variance with calculations based on the data of Cournand and associates (1943) and the results of studies by Gerst, Rattenborg and Holaday (1959) and Freeman and Nunn (1963). Gerst, Rattenborg and Holaday found that $V_d/V_t$ increased from 33 to 55 per cent after bleeding to a systolic pressure which was 25-50 per cent of the control value whilst Freeman and Nunn found a mean $V_d/V_t$ ratio of 78 per cent in 3 dogs after bleeding to a mean arterial pressure of 50 mm Hg. However, it is noteworthy that in the latter study the mean cardiac output in 3 dogs was only 850 ml/min and that halothane, a known myocardial depressant, was used for the anaesthesia. In dogs bled under conditions similar to our own the increase in $V_d/V_t$ (from 45 to 57 per cent) was very similar (Rehder et al., 1965). In humans it would seem that the increase in $V_d/V_t$ ratio is only moderate if deliberate hypotension is accompanied by spontaneous ventilation (Asmussen and Eckenhoff, 1964) and that, even after a head-up tilt and controlled ventilation, the $V_d/V_t$ ratio may still be under 50 per cent (Asmussen and Eckenhoff, 1964). However, the application of high positive airway pressures in this situation may well increase $V_d/V_t$ beyond these limits (Eckenhoff et al., 1963).

If it is postulated that the increased $V_d/V_t$ ratio associated with anaesthesia is due to a reduced pulmonary artery pressure and failure of perfusion of the uppermost alveoli in the lung (Asmussen, 1966), then an increase in pulmonary artery pressure should restore $V_d/V_t$ towards normal levels. Such a fall in $V_d/V_t$ has been shown to occur in exercise (Asmussen and Nielsen, 1956) and in pulmonary congestion due to G-suit inflation (Daly et al., 1964). In the present studies overtransfusion produced a mean increase in mean pulmonary artery pressure from 13 to 28 mm Hg but this only reduced $V_d/V_t$ from 50 to 48 per cent. It is possible that any improvement in the perfusion of previously non-perfused alveoli was offset by increased ventilation/perfusion inequality due to the increased left atrial pressure in the overtransfusion experiments. However, from evidence now being accumulated by one of the authors (M.K.S.) it would seem more likely that the increase in $V_d/V_t$ resulting from the administration of an anaesthetic is not related directly to a fall in pulmonary artery pressure but is rather due to maldistribution at alveolar level, possibly of the "stratified" type (Read, 1969). If this is so, an increase in pulmonary artery pressure would not be expected to reduce $V_d/V_t$.\
Venous admixture.

The calculated venous admixture when breathing air includes the effects of ventilation/perfusion inequalities and intra- and extrapulmonary right-to-left shunts.

The first possible explanation for the observed changes in oxygenation is, therefore, that there might be an alteration in the degree of ventilation/perfusion inequality present in the lung. This might be due to an alteration in overall pulmonary blood flow (ventilation remaining constant) or to a wider scatter of ventilation/perfusion relationships at alveolar level due to the observed changes in pulmonary arterial and left atrial pressures. Niden, Burrows and Barclay (1960), working with both innervated and denervated isolated perfused dog lung preparations, were the first to show that arterial saturation decreased when pulmonary blood flow was increased and vice versa. This observation confirmed the theoretical analysis of Rahn (1949). Gerst, Rattenborg and Holaday (1959) and Freeman and Nunn (1963) have also reported a reduction in venous admixture effect when cardiac output was reduced by haemorrhage. However, West (1969), utilizing mathematical models of lungs with varying degrees of ventilation/perfusion inequality has shown that, even if the overall distribution of ventilation/perfusion inequalities remains unchanged, an alteration in total pulmonary blood flow in the face of constant ventilation will result in changes in measured venous admixture and alveolar deadspace. According to his calculations an increase in pulmonary blood flow will result in an increase in venous admixture and reduction in alveolar deadspace whilst a fall in pulmonary blood flow will produce the opposite effect. To resolve this problem it would be necessary to isolate the effects of changes in pulmonary blood flow, oxygen consumption and left atrial pressure; attempts to do this have so far proved unsuccessful.

The second explanation for the changes in venous admixture is that there might be an alteration in the proportion of blood passing through right-to-left shunts in the lung. The most important sites where right-to-left shunting may occur are the bronchopulmonary veins and subpleural anastomoses, the Thebesian veins and through precapillary shunts. There is general agreement that bronchial artery blood becomes venous in its passage through the lungs and that, in the presence of a normal pulmonary blood flow, this blood passes through the bronchopulmonary veins to mix with the arterialized pulmonary venous blood. Estimates of the venous admixture from this source vary but it seems unlikely that the venous admixture exceeds 1–2 per cent of the cardiac output in the dog (Aviado et al., 1961). It has been estimated that Thebesian vein drainage contributes less than 1–2 per cent of the cardiac output in man (Ravin, Epstein and Malm, 1965) and even less in the dog (Moir, Driscoll and Eckstein, 1964). Our own estimations, derived from left atrial and arterial Po₂ measurements in another series of experiments, agree with these figures. There are no quantitative data which would indicate how these two sources of venous admixture would vary with cardiac output, but it has been shown in the isolated perfused dog lung that a reduction in pulmonary artery flow results in less desaturation of the bronchial flow, thus suggesting that more of the flow passes into anastomoses with the pulmonary capillaries whilst less passes into the bronchopulmonary veins (Aviado et al., 1961).

The evidence for the existence of potential precapillary arterio-venous channels has been discussed by von Hayek (1960). These channels have been called "Sperr" arteries because they form a T-network which would allow blood to flow from the bronchial arteries to the pulmonary arterioles or from pulmonary arterioles to bronchopulmonary veins, according to the tone of their muscular walls. The existence of pulmonary artery-venous shunts has been demonstrated by the injection of glass beads (Prinzmetal et al., 1948; Bostroem and Piiper 1955; Niden and Aviado, 1956) and by cinefluorography (Rahn, Stroud and Tobin, 1952); however, some workers have doubted their existence (Kniseley, Satterwhite and Wallace, 1956). Niden and Aviado made the interesting observation that beads up to 420 μ in diameter passed through the lungs when the pulmonary artery pressure had been increased by emboli and that fewer glass beads passed through the lung when 100 per cent oxygen was inhaled than when 10 per cent oxygen was given.

It is apparent from the above discussion that
there is little evidence that the alteration in total venous admixture is due in whole, or in part, to an alteration in the quantity of blood flowing through right-to-left intrapulmonary shunts. Nevertheless evidence from both human and animal studies (Hedley-Whyte, Pontoppidan and Morris, 1966; Leigh and Tyrrell, 1968; Yamamura et al., 1969) indicates that changes in rightto-left shunt with changes in cardiac output do occur. It must therefore be concluded that any or all of the above mechanisms may be responsible for the changes seen in the present series of studies.

**APPENDIX**

**Oxygen capacity of haemoglobin.**

One gram of haemoglobin has usually been taken to combine with 1.34 ml of oxygen at standard temperature and pressure (0°C, 760 torr). In this paper the constant 1.39 has been taken for the following reasons. The older constant, 1.34, dates from 1894 when Hüfner calculated this value from the carbon monoxide combining power of oxyhaemoglobin after making considerable corrections. Peters and Van Slyke (1931) comment that this value of 1.34 is used without justification to estimate in grams the haemoglobin content of human blood from analytically determined oxygen or carbon monoxide capacities. They calculated a value of 1.36 which was, however, itself based on Hüfner's value of 0.34 per cent of iron in the haemoglobin molecule. The problem in the accurate determination of the factor resulted from the difficulty of recrystallizing haemoglobin without changing part of it to some other derivative in the process (Barcroft, 1928). However, since the exact sequence of amino acids in the haemoglobin molecule has now been established (Braunitzer et al., 1961; Hill, Konigsberg et al., 1962) the molecular weight can be theoretically calculated by arithmetical summation (Braunitzer, 1964). The molecular weight of human haemoglobin has the value 64,458 (anhydrous) by decision of the Standing Committee of the European Society concerning haemoglobinometry (1963). From this molecular weight it can be calculated that the amount of iron in the molecule is 0.347 per cent. The older value was taken as 0.338 per cent.

The calculation of the constant 1.39 is carried out as follows:

Molecular weight of haemoglobin (by amino acid residues) = 64,458

There are 4 atoms of Fe (iron) in the molecule, so

1 g mol. wt. Fe is contained in 16114 g mol. wt. of haemoglobin.

Since the atomic weight of Fe is 55.84,

100 g haemoglobin contains 55.84/16,114 × 100 = 0.347 g Fe;

1 g molecule of oxygen occupies 22,400 ml at STP.

The molar ratio of Fe:O₂ is 1:1;

i.e., 1 g Fe per ml O₂ = 55.84:22,400 = 1:400;

i.e., 1 g of Fe in haemoglobin will combine with 400 ml O₂;

and as 1 g haemoglobin contains 0.00347 g Fe,

1 g gram of haemoglobin will combine with

0.00347 × 400 = 1.39 ml O₂, at STP.

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**LES EFFETS CARDIORESPIRATOIRES DE L’HEMORRHAGIE ET DE LA SURTRANSFUSION CHEZ LE CHIEN**

**SOMMAIRE**

Les modifications de la fonction cardiorespiratoire, qui résultent de l’hémorragie et de la surtransfusion, ont été mesurées chez quarante sept chiens durant une ventilation contrôlée. Chez les animaux saignés jusqu’à une pression artérielle moyenne de 70 mm Hg, on observa des réductions significatives du Po2, artériel, du débit de gaz carbonique et de la consommation d’oxygène, du débit cardiaque et du mélange veineux total. Chez les animaux transfusés jusqu’à une pression veineuse centrale de 15 mm Hg, il y eut une réduction significative de l’amplitude thoracique totale et du Po2 artériel, et un accroissement significatif de la différence alvéolaire-artérielle du Po2, et du débit de gaz carbonique.

**DIE KARDIORESPIRATORISCHEN WIRKUNGEN VON HÄMORRHAGIE UND ÜBERTRANSFUSION BEI HUNDEN**

**ZUSAMMENFASSUNG**

Veränderungen in der kardiopulmonarischen Funktion aufgrund von Hämorrhagie und Übertransfusions wurden an siebenundvierzig Hunden während kontrollierter Ventilation gemessen. Bei den Tieren, denen bis zu einem mittleren arteriellen Druck von 70 mm Hg Blut entzogen worden war, wurden signifikante Reduzierungen der arteriellen Kohlendioxydsättigung, der Kohlendioxidabgabe und des Sauerstoffverbrauchs, des Herzminutenvolumens und der gesamten venösen Beimischung festgestellt. Bei den Tieren, die eine Transfusion bis zu einem mittleren zentralen Venendruck von 15 mm Hg erhielten, ergab sich ein signifikanter Abfall der totalen Thorax-Compliance und der arteriellen Sauerstoffspannung sowie signifikante Erhöhungen in der Differenz der alveolär-arteriellen Sauerstoffspannung und der Kohlendioxydabgabe.