THROMBIN-INDUCED DISSEMINATED INTRAVASCULAR COAGULATION IN THE DOG

II: CARDIORESPIRATORY CHANGES DURING SPONTANEOUS AND CONTROLLED VENTILATION

J. JASTRZEBSKI, P. HILGARD, M. K. CHAKRABARTI, K. HENRY AND M. K. SYKES

SUMMARY

Disseminated intravascular coagulation (DIC) was induced in anaesthetized dogs by the infusion of a fibrinolytic inhibitor followed by thrombin. The occurrence of DIC was confirmed by haematological and histological examinations. After the thrombin infusion there was a progressive reduction in cardiac index and systemic arterial pressure, only four of the 14 dogs surviving for 4 hr. Pulmonary artery pressure increased after the thrombin infusion, but decreased subsequently in seven animals allowed to breathe spontaneously. In these animals, there was an increase in respiratory rate, minute volume and deadspace/tidal volume ratio, but there were no changes in the arterial-to-alveolar Pco₂ difference. Arterial Pco₂ and Po₂ decreased, but there were no significant changes in total venous admixture. In seven dogs submitted to controlled ventilation, arterial Po₂ decreased to the same extent, but there were no significant changes in arterial Pco₂, deadspace/tidal volume ratio or venous admixture.

Disseminated intravascular coagulation (DIC) occurs commonly in association with major trauma, haemorrhagic shock, septicemia and septic shock. It has also been reported to occur in patients with a low cardiac output after extracorporeal circulation, and in patients with premature separation of the placenta, amniotic fluid embolism, fat embolism, thromboembolism, and a variety of haematological disorders (McKay, 1965; Hardaway, 1962, 1966). Microthrombi are distributed widely throughout the body, but are particularly evident in the lung and kidneys (Hardaway, 1962; Robb, 1963, 1965; Eeles and Sevitt, 1967; Sevitt, 1970; Bergentz, Ljungqvist and Lewis, 1972; Hoie and Schenk, 1972). The widespread coagulation process causes a consumption of clotting factors. Fibrinogen concentrations are decreased and there is a reduction of the platelet count and of other plasma coagulation factors. The concomitant activation of the fibrinolytic system may lead to hyperfibrinolysis. The result of these processes is a consumption coagulopathy. It has been suggested that DIC may be partially responsible for irreversibility in shock (Crowell and Read, 1955; Hardaway and McKay, 1959a). It has also been suggested that it may cause circulatory and respiratory disturbances (Hardaway and McKay, 1959b; Hardaway et al., 1962; Rådegran, 1971). DIC may be of importance in the aetiology of the "shock lung syndrome" (Blaisdell, Lim and Stallone, 1970); it may contribute also to the respiratory and circulatory complications associated with fat embolism (Saldeen, 1970a,b). In all these conditions, DIC may produce its effect by mechanical obstruction of the circulation, by release of vasoactive substances from the platelets and other formed elements in the blood and from the vessel wall, and by an increase in the permeability of vessels. DIC can be produced in the experimental animal by intravenous infusions of thrombin (Jastrzebski et al., 1975), protamine, endotoxin or catecholamines, by the transfusion of platelet-
CARDIORESPIRATORY CHANGES WITH INTRAVASCULAR COAGULATION

rich plasma, and by the induction of acidosis or haemorrhagic shock.

The circulatory and respiratory effects resulting from DIC in the experimental model are similar to many of those seen in patients (Olsson, Rådegran and Taylor, 1970; Rådegran, 1971; Swedenborg, 1971). Although Arfors and his colleagues (1972) have documented some of the respiratory effects of experimental DIC, their studies did not include measurements of deadspace or venous admixture. Furthermore, the observations were made during spontaneous ventilation. The purpose of the present studies was to determine the extent of possible changes in deadspace and venous admixture produced by DIC, and to evaluate the role of controlled ventilation in the prevention of these changes.

METHOD

The experiments were performed on 17 greyhound dogs weighing 22–34 kg. Anaesthesia was induced with thiopentone 20 mg/kg body weight, and a cuffed endotracheal tube was passed. Anaesthesia was then maintained with pentobarbitone, a total dose of 20 mg/kg being given over the study period of 6–7 hr. One litre of 0.9% sodium chloride was also infused during this period. One group of seven animals was allowed to breathe air spontaneously, whilst the second group of seven dogs was ventilated mechanically with air by a volume preset ventilator (Cape) at a frequency of 20 b.p.m., the tidal volume being adjusted initially to produce an end-tidal carbon dioxide concentration of 4.5–5.5%.

To allow measurements during spontaneous ventilation, a non-rebreathing valve was connected to the endotracheal tube and the expired gas was collected in a Douglas bag. The resistance of the valve to inspiratory and expiratory gas flow was 0.7 cm H₂O at a flow of 30 litre/min, and the deadspace was 20 ml. During controlled ventilation a pressure-operated collect valve was interposed between the ventilator-patient connection port and the endotracheal tube, to separate expired gas from the gas compressed within the ventilator tubing (Sykes, 1969). The expiratory resistance of the valve was 1.3 cm H₂O at a flow of 60 litre/min and the deadspace was 20 ml. The expired gas from this valve passed through a mixing unit (Sykes, 1968) to a calibrated dry gas meter. End-tidal and mixed expired carbon dioxide concentrations were monitored by a rapid infra-red analyser (Hartmann-Braun URAS.4). The mixed expired carbon dioxide tension was also measured by a carbon dioxide electrode. The mixed expired oxygen concentration was measured with a paramagnetic oxygen analyser (Servomex 101A) and duplicate gas samples were checked on an oxygen electrode. All gas samples were collected into oiled, glass and metal syringes. Catheters for pressure recording and blood sampling were inserted into the abdominal aorta and inferior vena cava via the right groin, whilst similar catheters were inserted via the left groin into the femoral artery and pulmonary artery to permit dye injection and sampling for cardiac output measurements by the dye dilution method. A catheter was also floated into the pulmonary artery from the jugular vein for pressure recording and blood sampling. The position of both pulmonary artery catheters was checked by wedging and withdrawal into the right ventricle before final placement in the pulmonary artery. Their position was further checked by a withdrawal trace at the end of the experiment. In three additional dogs a left thoracotomy was performed and a pressure recording catheter was inserted into the left atrium, the chest being left open during the experiment. In these experiments an end-expiratory positive pressure of +5 cm H₂O was applied to prevent lung collapse. The data obtained from these three dogs has not been included in the general results. All pressures were recorded by strain gauges, the outputs of which were fed to a four-channel heated stylus recorder (Devices Ltd) and display oscilloscope (Airmec Ltd). During controlled ventilation the fourth channel monitored airway pressure, which was measured at the level of the endotracheal tube catheter mount. The transducers were calibrated repeatedly against a column of saline, the zero reference point being the junction of the posterior three-fifths and anterior two-fifths of the anteroposterior diameter of the chest. All measurements were made with the animals in the supine position. Both arterial and pulmonary artery blood samples were collected into heparinized plastic syringes during the middle period of the expired gas collection and were analysed using a Radiometer electrode system maintained at 37°C. The oxygen electrode was checked daily for linearity with nitrogen, air and 100% oxygen. The blood-gas factor was determined daily with tonometered blood samples (Adams and Morgan-Hughes, 1967), the blood-gas difference varying between 4% and 6% of the reading during these experiments. The Severinghaus carbon dioxide electrode was standardized with carbon dioxide and oxygen mix-
tures which had been analysed using a Haldane apparatus, and each blood sample was preceded and followed with a known carbon dioxide mixture. The pH electrode was set up with precision buffers and checked with a standardized serum preparation (Adams, Morgan-Hughes and Sykes, 1967, 1968). Haemoglobin concentration was measured by a spectrophotometric method using a cyanmethaemoglobin standard. Dye-dilution measurements were made with indocyanine green using a densitometer and computer (Gilford Instruments). Duplicate or triplicate measurements were made and random curves replotted and checked by planimetry to confirm the computer results. The method had been checked previously against the Fick method using oxygen contents determined using the Van Slyke apparatus.

Ten minutes before each set of cardiorespiratory measurements, the lungs were hyperinflated. The first set of measurements was made when all the preparations had been completed and a steady state had been achieved as shown by a constant end-tidal carbon dioxide concentration. Initial measurements on spontaneous ventilation were not made until the end-tidal carbon dioxide concentration had decreased to less than 6%.

Epsilon amino caproic acid (EACA) 150–170 mg/kg (Epsikapron, Ab Kabi, Stockholm) was then administered into the left jugular vein over 20 min, using a constant speed syringe. When all the pressures had returned to pre-existing values, an infusion of thrombin was started. The doses of thrombin topical 1,000 NIH units/ml (Parke Davis) varied between 150 and 180 NIH units/kg and were given by a constant speed syringe over a period of 20 min, into the left jugular vein. Repeat sets of cardiorespiratory measurements were then made at hourly intervals after the start of the thrombin infusion for 4 hr or until the death of the animal.

Calculations.
All blood-gas tensions were corrected to the dog's oesophageal temperature (Kelman and Nunn, 1966). End-pulmonary capillary (Cc'\textsubscript{O2}) and arterial oxygen content (Ca\textsubscript{O2}) were derived from the Severinghaus (1966) dissociation curve, 1 g of haemoglobin being assumed to contain 1.39 ml of oxygen when fully saturated. The arterio-mixed venous oxygen difference (Ca\textsubscript{O2}−C\textsubscript{V}O2) was calculated from the oxygen consumption and the cardiac output (measured by dye dilution) in order to obviate errors resulting from unknown shifts in the dissociation curve. Total venous admixture was then calculated from the equation:

\[
\frac{Q_{va}}{Qt} = \frac{Cc'_{O2} - Ca_{O2}}{(Cc'_{O2} - Ca_{O2}) - (Ca_{O2} - C\textsubscript{V}O2)}
\]

These and other calculations were performed on an Elliot 4100 computer using standard equations in the program described by Adams (1970).

All statistical comparisons were based on Student's paired t test.

Haematology.
EDTA blood samples for duplicate platelet counts, fibrinogen concentrations and fibrinolytic activity on unheated fibrin plates were taken 30 min after the infusion of the EACA, and 30 min after the end of the thrombin infusion.

Histology.
Blocks were obtained, from the non-dependent portions of the lungs of four of the dogs submitted to controlled ventilation, and fixed in formal-saline. In a fifth dog the trachea was clamped during inspiration and the lungs and trachea were removed from the thorax. The lungs were then fixed in the inflated position by infusion of formal-saline into the trachea. The material obtained from these animals was embedded in paraffin wax in the routine manner and the sections stained with haematoxylin and eosin, phosphotungstic acid-haematoxylin and haematoxylin elastic Van Giesen.

RESULTS
Only two dogs out of each group of seven survived for more than 4 hr after the start of the thrombin infusion. There was a continuous increase in the oesophageal temperature during the experiment, the mean value being 37.5°C before the thrombin infusion and 39°C at the end of the experiment.

Cardiorespiratory measurements.
The changes occurring during spontaneous and controlled ventilation are shown in tables I and II. A typical pressure record is shown in figure 1. Control measurements of mean arterial pressure (MAP) and mean pulmonary artery pressure (MPAP) were higher than normal in the dogs which breathed spontaneously, although cardiac index (CI) was the same in both groups. EACA produced an increase in systemic and pulmonary artery pressure, which returned to normal in 10–15 min. After the thrombin infusion there was a pro-
TABLE I. Cardiorespiratory changes associated with DIC: spontaneous ventilation.

<table>
<thead>
<tr>
<th>Time after start of thrombin infusion</th>
<th>Control</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>240±40</td>
<td>230±60</td>
<td>174±44</td>
<td>107±23</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>19.7±4.8</td>
<td>35.6±11.6</td>
<td>23.0±11.6</td>
<td>15.8±12.2</td>
</tr>
<tr>
<td>CI (ml/kg)</td>
<td>192.7±32.7</td>
<td>132.4±47.0*</td>
<td>77.8±18.4§</td>
<td>70.0±8.2§</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>44.5±5.6</td>
<td>37.0±7.6</td>
<td>35.0±8.4↑</td>
<td>31.3±7.6↑</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.33±0.053</td>
<td>7.308±0.033</td>
<td>7.293±0.065</td>
<td>7.263±0.037</td>
</tr>
<tr>
<td>Pv CO2 (mm Hg)</td>
<td>51.3±8.7</td>
<td>44.4±12.4</td>
<td>46.1±6.3</td>
<td>51.4±10.6</td>
</tr>
<tr>
<td>pHV (units)</td>
<td>7.29±0.099</td>
<td>7.276±0.037</td>
<td>7.299±0.071*</td>
<td>7.205±0.032§</td>
</tr>
<tr>
<td>Base excess (m-equiv./litre)</td>
<td>-2.4±1.2</td>
<td>-6.4±2.3§</td>
<td>-8.4±2.8§</td>
<td>-11.7±3.7§</td>
</tr>
<tr>
<td>Respiratory rate (beats/min)</td>
<td>13.3±5.8</td>
<td>36.3±13.0↑</td>
<td>57.9±15.6↑</td>
<td>41.4±23.4*</td>
</tr>
<tr>
<td>Vt (ml/kg) BTPS</td>
<td>22.97±3.32</td>
<td>14.26±3.5↑</td>
<td>11.4±2.1§</td>
<td>14.7±2.9↑</td>
</tr>
<tr>
<td>Ve (litre/min) BTPS</td>
<td>8.2±3.69</td>
<td>13.19±5.54</td>
<td>17.8±5.37↑</td>
<td>16.8±6.82*</td>
</tr>
<tr>
<td>Vd/Vr (%)</td>
<td>35.0±13.2</td>
<td>43.0±20.9</td>
<td>57.7±7.7↑</td>
<td>48.5±5.4*</td>
</tr>
<tr>
<td>Pa CO2−Pv CO2 (mm Hg)</td>
<td>3.4±3.5</td>
<td>4.3±3.2</td>
<td>4.4±3.7</td>
<td>4.1±1.3</td>
</tr>
<tr>
<td>Vco2 (ml/kg) STPD</td>
<td>8.65±1.5</td>
<td>9.2±2.4</td>
<td>8.9±1.7</td>
<td>9.3±2.6</td>
</tr>
<tr>
<td>Vco2 (ml/kg) STPD</td>
<td>9.7±2.0</td>
<td>12.2±2.8*</td>
<td>12.3±2.6↑</td>
<td>10.5±2.7</td>
</tr>
<tr>
<td>Pa O2−Pv O2 (mm Hg)</td>
<td>19.8±9.8</td>
<td>23.8±6.2</td>
<td>34.7±6.5§</td>
<td>42.7±11.9</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>82.3±6.1</td>
<td>79.5±14.3</td>
<td>72.5±8.6*</td>
<td>72.0±16.7</td>
</tr>
<tr>
<td>Pv O2 (mm Hg)</td>
<td>49.4±5.9</td>
<td>41.5±7.9↑</td>
<td>34.2±6.5§</td>
<td>29.6±8.5</td>
</tr>
<tr>
<td>Qva/Qt (%)</td>
<td>13.1±4.0</td>
<td>14.0±13.7</td>
<td>13.6±9.0</td>
<td>16.1±11.2</td>
</tr>
<tr>
<td>Hb (g%)</td>
<td>17.6±3.2</td>
<td>21.7±4.4</td>
<td>23.5±3.9↑</td>
<td>21.6±3.9</td>
</tr>
<tr>
<td>Number of dogs</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

For abbreviations see text. *P=0.05; †P=0.02; ‡P=0.01; §P=0.001.

TABLE II. Cardiorespiratory changes associated with DIC: controlled ventilation.

<table>
<thead>
<tr>
<th>Time after start of thrombin infusion</th>
<th>Control</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>170.0±23.1</td>
<td>164.3±26.5</td>
<td>137.1±52.4</td>
<td>106.2±10.8</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>12.6±3.3</td>
<td>23.4±9.6*</td>
<td>21.0±6.5‡</td>
<td>22.4±8.6*</td>
</tr>
<tr>
<td>CI (ml/kg)</td>
<td>199.0±62.5</td>
<td>111.0±29.4↑</td>
<td>80.5±17.1↑</td>
<td>66.2±9.5§</td>
</tr>
<tr>
<td>Pa CO2 (mm Hg)</td>
<td>37.4±4.4</td>
<td>37.5±6.7</td>
<td>42.0±9.2</td>
<td>40.0±9.9</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.359±0.027</td>
<td>7.315±0.066*</td>
<td>7.274±0.087↑</td>
<td>7.29±0.088*</td>
</tr>
<tr>
<td>pH (units)</td>
<td>42.2±3.0</td>
<td>47.1±4.8</td>
<td>50.7±12.9</td>
<td>47.3±16.2</td>
</tr>
<tr>
<td>pH (units)</td>
<td>7.33±0.031</td>
<td>7.269±0.06↑</td>
<td>7.215±0.081↑</td>
<td>7.248±0.087*</td>
</tr>
<tr>
<td>Base excess (m-equiv./litre)</td>
<td>-3.3±1.1</td>
<td>-7.1±2.8↑</td>
<td>-8.4±2.2$</td>
<td>-8.0±2.2$</td>
</tr>
<tr>
<td>Vd/Vr (%)</td>
<td>46.5±6.5</td>
<td>42.8±3.6</td>
<td>46.0±7.8</td>
<td>47.7±6.7</td>
</tr>
<tr>
<td>Pa CO2−Pv CO2 (mm Hg)</td>
<td>3.6±2.8</td>
<td>3.5±2.2</td>
<td>6.4±4.9</td>
<td>4.4±3.4</td>
</tr>
<tr>
<td>Vco2 (ml/kg/min) STPD</td>
<td>6.38±0.127</td>
<td>6.85±1.43</td>
<td>7.01±1.3*</td>
<td>6.67±1.6</td>
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<tr>
<td>Vco2 (ml/kg/min) STPD</td>
<td>7.85±1.86</td>
<td>7.92±1.74</td>
<td>8.3±1.9</td>
<td>7.7±1.1</td>
</tr>
<tr>
<td>Pa O2−Pv O2 (mm Hg)</td>
<td>18.4±3.7</td>
<td>31.1±11.0↑</td>
<td>33.6±14.5↑</td>
<td>29.1±8.1*</td>
</tr>
<tr>
<td>Pa O2 (mm Hg)</td>
<td>86.2±6.3</td>
<td>72.4±7.8↑</td>
<td>67.5±13.8↑</td>
<td>70.3±12.2*</td>
</tr>
<tr>
<td>Pv O2 (mm Hg)</td>
<td>49.5±5.9</td>
<td>40.2±2.8↑</td>
<td>33.7±6.6§</td>
<td>33.6±6.90↑</td>
</tr>
<tr>
<td>Qva/Qt (%)</td>
<td>11.8±3.95</td>
<td>18.5±8.6</td>
<td>21.46±13.08</td>
<td>18.3±11.3</td>
</tr>
<tr>
<td>Hb (g%)</td>
<td>16.6±3.4</td>
<td>19.5±3.6</td>
<td>19.6±3.1</td>
<td>18.8±3.0</td>
</tr>
<tr>
<td>Number of dogs</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

For abbreviations see text. *P=0.05; †P=0.02; ‡P=0.01; §P=0.001.

Progressive reduction in mean arterial pressure and cardiac index in both groups. Mean pulmonary artery pressure increased within a few minutes of starting the thrombin. It remained elevated for 1-2 hr and then declined in the dogs which breathed spontaneously. In the dogs having controlled ventilation, the pulmonary artery pressure remained high until death occurred. The explanation of the differences in pressure between the two groups is probably to be found in the differing arterial carbon dioxide tensions (Pa CO2) observed in each group at different stages of the experiment. Initially the spontaneously breathing animals were breathing slowly and deeply. There was a marked increase in respiratory rate and in minute volume (Ve) after thrombin was infused. There was a significant increase in deadspace/tidal volume ratio (Vd/Vr), but no change in the arterial to alveolar Pco2 difference (Pa CO2−Pv CO2). Despite the increase in deadspace ventilation, arterial carbon dioxide tension decreased. However, mixed venous Pco2 (Pv CO2) and carbon dioxide output (VCO2) were unchanged throughout the period of observation. Oxygen consumption (V02) increased significantly after
thrombin, and there was a marked metabolic acidosis.

In the group on controlled ventilation, there was a small increase in $V_{CO_2}$ and $V_{O_2}$ after thrombin, but little change in $Vd/Vt$ or $P_{A_{CO_2}} - P_{A_{O_2}}$. Therefore $P_{A_{CO_2}}$ changed little during the experiment and there was only a minor degree of metabolic acidosis. Airway pressure increased slightly after thrombin infusion, but then returned to control values. Both groups of dogs developed a significant increase in alveolar-arterial oxygen tension difference ($P_{A_{O_2}} - P_{A_{O_2}}$) and a reduction in arterial oxygen tension ($P_{A_{O_2}}$). Mixed venous oxygen tension ($P_{V_{O_2}}$) also decreased significantly. Although venous admixture ($Qv/Qt$) increased more in the dogs on controlled ventilation, none of the changes was significantly different from the control readings.

Three dogs were submitted to thoracotomy for measurement of left atrial pressure, which remained between 5 and 10 mm Hg throughout the experiments.

**Haematology.**

The inhibition of plasma fibrinolytic activity by EACA was demonstrated by the use of unheated fibrin plates. Before the EACA infusion there was slight spontaneous fibrinolytic activity, but this was absent after both the EACA and thrombin infusions. In two dogs (not included in this series) in which thrombin infusion was not preceded by EACA, there was marked plasma fibrinolytic activity after thrombin. There were no significant differences between the platelet counts and fibrinogen concentrations before and after the infusion of EACA. However, the marked reduction in platelet count and fibrinogen concentrations after thrombin infusion provided evidence that DIC had occurred. The haematocrit and haemoglobin concentrations increased after thrombin (table III). The laboratory diagnosis of DIC after the thrombin infusion was established by demonstrating a reduction of the platelet count and the plasma fibrinogen concentrations. The haematocrit and haemoglobin concentration increased (table III).

**Table III. Haematological changes associated with DIC**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>n</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count (x 10^3/mm³)</td>
<td>177.8 ±44.42</td>
<td>54.0 ±22.92</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (mg%)</td>
<td>262.8 ±90.2</td>
<td>86.1 ±44.8</td>
<td>9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>46.4 ±9.0</td>
<td>59.7 ±11.8</td>
<td>9</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Haemoglobin (g%)</td>
<td>17.6 ±3.2</td>
<td>24.4 ±3.6</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Histology.**

Intravascular fibrin thrombi were found in sections from the lungs of two out of the five dogs sampled. In one dog the thrombi were confined to small arterial vessels less than 50 μm in diameter (fig. 2A). The thrombi were relatively few in number, and were found in vessels extending down to capillary level. In the second dog, microthrombi were seen mainly in arteries larger than 50 μm in diameter. In two dogs, one of which had microthrombi, there was a prominent exudation of polymorphonuclear leucocytes into the alveoli, together with marked interstitial and alveolar haemorrhage.
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(2.2). The remaining three dogs showed marked congestive changes and perivascular haemorrhages. These were most marked in the sections taken from the dependent zones of the lungs which were fixed in inflation.

A feature in all the sections was the prominent smooth muscle component in the respiratory and terminal bronchioles. This was probably a species variation in greyhounds.

DISCUSSION

These experiments showed that thrombin infusion produced marked haematological and haemodynamic changes in both groups of dogs. Haemocoagulation occurred, systemic pressure and cardiac output decreased and pulmonary artery pressure increased. The respiratory response was characterized by marked hyperventilation, an increase in the proportion of deadspace ventilation and a reduction in arterial PaCO₂. When ventilation was controlled, there was little change in deadspace and PaCO₂ increased slightly. There was little change in venous admixture in either group, the reduction in arterial Po₂ being mainly a result of the reduction in mixed venous saturation, secondary to the decrease in cardiac output. Arterial Po₂ tended to be higher in the group breathing spontaneously because of the lower PaO₂. There were therefore remarkably few respiratory changes, despite the gross circulatory changes and the clear haematological evidence of severe DIC.

Cardiovascular changes.

There were no significant changes in central venous pressure in these experiments, nor were there any changes in left atrial pressure in the three dogs in which it was measured. This suggests that the decrease in cardiac output was not a result of cardiac failure. Therefore it is necessary to look for an alternative cause, such as peripheral pooling of blood or fluid loss. In the present experiments, the haematocrit increased continuously after the thrombin infusion and, although splenic contraction can add significant quantities of red cells to the circulation in the dog, the continuous nature of the process suggests that fluid loss was probably the cause. This was confirmed by the autopsy findings of fluid in the peritoneal cavity and bleeding into the gastro-intestinal tract. Arfors and colleagues (1972) have described perivascular oedema in the liver and lung and have suggested that DIC may cause increased capillary permeability. Bayley, Clements and Osbahr (1967) have suggested that fibrinopeptides may be released during DIC and that these may cause endothelial damage and fluid loss.

The systemic hypotension could have been a result of the reduction in cardiac output. However, there is now much evidence which suggests that
vascular changes during DIC can be caused by the release of vasoactive substances from the platelet. Both Rådegran (1971) and Swedenborg (1971) concluded that the dilatation of systemic vessels could be a result of the action of ADP and ATP released from the platelet during the process of aggregation. Serotonin and histamine are also released during aggregation, but dog platelets contain insignificant amounts of histamine (Humphrey and Jaques, 1954). Serotonin is known to cause pulmonary vasoconstriction and terminal airway closure, and could well be responsible for the changes observed during DIC (Stein et al., 1970; Hyman et al., 1971; Woolverton and Hyman, 1973). This view contrasts with the earlier view that the pulmonary hypertension was chiefly a consequence of obstruction of pulmonary vessels by microthrombi (Hardaway, 1962; Allardyce et al., 1969).

**Respiratory changes.**

The most dramatic change was the increase in respiratory frequency which occurred shortly after commencing the thrombin infusion. The tidal volume decreased and the minute volume stabilized at about twice the control value. These changes led to an increase in anatomical deadspace ventilation; the reduction in arterial $P_{CO_2}$ was consequently smaller than would have been expected from the increase in minute volume (Roos, Dahlstrom and Murphy, 1955; Cooper, 1967).

The rapid, shallow pattern of breathing in this group of dogs could have been a result of reflex stimulation from lung receptors or of the effects of DIC on the respiratory centre. McKay (1965) has described central nervous system disorders during DIC in man. Changes suggestive of central nervous system involvement were also observed in the present experiments. Some of the dogs which breathed spontaneously developed convulsions which persisted for up to 30 min before death and could not be abolished by further doses of pentobarbitone. Furthermore, most of the dogs developed a slow, very deep, pattern of breathing 10–15 min before death occurred. The abrupt increases in temperature in some of the animals were also suggestive of hypothalamic involvement.

In the dogs submitted to controlled ventilation, there were no significant differences between the means of the deadspace/tidal volume ratios before and after the administration of thrombin. However, six of the seven dogs showed a reduction in $V_d/V_t$ ratio 1 hr after the start of the thrombin infusion, at a time when there was a significant increase in mean pulmonary artery pressure and a decrease in cardiac index. In some animals $V_d/V_t$ ratios remained below the control values, whilst in others $V_d/V_t$ increased to values which were markedly higher than those present before the thrombin infusion.

The variations in deadspace were probably caused by several different factors. First, a decrease in cardiac output tends to lower pulmonary artery pressure, thus reducing blood flow to the non-dependent alveoli. This causes an increase in alveolar deadspace (Gerst, Rattenborg and Holaday, 1959; Freeman and Nunn, 1963). However, in the present experiments pulmonary artery pressure increased despite a decrease in cardiac output. Since left atrial pressure did not change, pulmonary vascular resistance must have increased. This increase may have been caused by obstruction of the pulmonary vascular bed by microthrombi, or by local or generalized pulmonary vasoconstriction resulting from the release of vasoactive substances.

If the microthrombi had caused regional reductions in pulmonary blood flow, there should have been an increase in alveolar deadspace and deadspace/tidal volume ratio similar to that seen in pulmonary embolism (Jones and Goodwin, 1965; Kafer, 1969). In the present experiments there was little increase in $Pa_{CO_2} - Pa_{CO_2}$ in any of the dogs, and there was no correlation between mean pulmonary artery pressure and $V_d/V_t$. When mean pulmonary artery pressure exceeded 20 mm Hg there were only two occasions on which $V_d/V_t$ increased. There is therefore little evidence to suggest that DIC causes marked regional reductions in blood flow.

There are, however, two mechanisms which might have tended to minimize the effects of regional variations in flow. First, it is known that generalized pulmonary vasoconstriction tends to redistribute flow from the dependent to the non-dependent portions of the lung, thus reducing alveolar deadspace in the latter areas (Fowler and Read, 1963; Haas and Bergofsky, 1967). Similar changes occur when pulmonary vascular resistance increases in the later stages of haemorrhagic shock (Naimark, Dugard and Rangno, 1968; Bø and Hognestad, 1971). Second, serotonin is known to constrict terminal airways as well as the pulmonary vasculature (Stein et al., 1970). If ventilation to individual alveolar units had been reduced when blood flow was reduced by the local release of vasoactive agents, there might have been no increase in measured deadspace although the total area of lung
available for gas exchange would, of course, have been reduced.

This hypothesis might also explain the relatively small increase in total venous admixture observed in the present experiments. However Rädegran (1971) has shown that hyperinflation of the lungs abolishes the reduction in compliance which occurs when DIC is induced. In the present experiments the lungs were also inflated three times to +30 cm H$_2$O before each set of measurements. This would have tended to decrease the amount of venous admixture. Another factor which might have minimized the changes in venous admixture is the reduction in shunt which usually accompanies a decrease in cardiac output (Leigh and Tyrell, 1968; Yamamura et al., 1969; Watanabe, 1969). If the measured venous admixture had been corrected for this effect, there would certainly have been a significant increase in both groups of dogs.

In view of the marked reductions in cardiac output in these experiments, it would be unwise to draw any firm conclusions as to the value of controlled ventilation in treatment. However, it is notable that there was no increase in oxygen consumption or in non-respiratory acidosis during controlled ventilation. Further studies designed to evaluate the respiratory changes which occur when fluid loss is replaced will be reported in a subsequent publication.

REFERENCES


COAGULATION INTRAVASCULAIRE DISEMINEE CHEZ LES CHIENS PROVOQUEE PAR LA THROMBINE

II: VARIATIONS CARDIORESPIRATOIRES SOUS VENTILATION CONTROLEE ET VENTILATION SPONTANEE

RESUME

La coagulation intravasaulaire disseminee a ete provoquee sur des chiens anesthesies par la perfusion d’un agent fibrinolytique, suivi de thrombine. Le fait de la coagulation intravasaulaire disseminee a ete confirme par des examens hematologiques et histologiques. Apres la perfusion de thrombine, il y a eu une reduction progressive de l’indice cardiaque et de la tension arterielle generale; quatre chiens seulement sur quatorze ont survu pendant plus de quatre heures. Les injection d’une thrombine arterielle pulmonaire a augmentee apres la perfusion de thrombine, mais elle a diminuee par la suite sur sept animaux que l’on a laisse respirer spontanement. Sur ces animaux, on a constate une augmentation du rythme de la respiration, du volume par minute et du rapport volume d’air de respiration/espace mort, mais il n’y a eu aucun changement dans la difference de pression arterielle alveolaire partielle de CO2. Les pressions arterielles partielles de CO2 et d’O2 ont baisse, mais il n’y a eu aucune variation importante dans le dosage veineux total. Sur les sept chiens soumis a une ventilation controlee, la pression arterielle partielle d’O2 a baisse dans des proportions semblables, mais il n’y a eu aucune variation importante de la pression arterielle partielle de CO2, dans le rapport volume d’air de respiration/espace mort ou dans le dosage veineux.

DURCH THROMBIN HERVERGERUFENE GERINNUNG IN DEN GEFASSEN BEI HUNDEN

ZUSAMMENFASSUNG


COAGULACION INTRAVASCULAR DISEMINADA INDUCIDA POR TROMBINA EN EL PERRO

II: CAMBIOS CARDIORESPIRATORIOS DURANTE VENTILACION ESPONTANEA Y CONTROLADA

SUMARIO

Se indujo la coagulación intravascular disseminada (DIC) en perros anestesiados por la infusión de un inhibidor fibrinolítico seguido de trombina. La formación de DIC se confirmó por medio de exámenes hematológicos e histológicos. Después de la infusión de trombina hubo una reducción progresiva del índice cardíaco y presión arterial sistemática, solamente cuatro de los catorce perros sobrevivieron por 4h. La presión arterial pulmonar aumentó después de la infusión de trombina, pero disminuyó posteriormente en siete animales a los que se permitió respirar espontáneamente. En estos animales, hubo un aumento de la velocidad respiratoria, volumen por minuto y relación espacio muerto/volumen de flujo, pero no hubo cambios en la diferencia de Pco2, arterial-alveolar. El Pco2 y el Po2 arterial disminuyeron pero no hubo cambios significativos en la mezcla de Thor n venosa total. En siete perros sometidos a ventilación controlada, el Po2 arterial disminuyó del mismo modo, pero no hubo cambios significativos en el Pco2 arterial, relación espacio muerto/volumen de flujo o mezcla venosa.