POST-TRAUMATIC RESPIRATORY DISTRESS DUE TO ENDOTOXINAEMIA AND INTRAVASCULAR COAGULATION

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SUMMARY

A typical example of respiratory distress syndrome following trauma is presented. This was associated with evidence of endotoxinaemia and intravascular coagulation both at its onset and during subsequent acute renal failure.

It has been recognized for many years that respiratory insufficiency may contribute significantly to the mortality and morbidity of patients who have suffered major trauma, burns, haemorrhage, myocardial infarction or sepsis. A similar condition may follow the use of cardiopulmonary bypass. There have been several recent reviews of this subject and many suggestions have been advanced as to its cause (Collins, 1969; Moss, 1972; Dowd and Jenkins, 1972). These include: bronchopneumonia, pulmonary oedema, over-transfusion, particularly with crystalloid solutions, fat embolism, endotoxinaemia, vaso-active amine release, pulmonary thromboembolism, surfactant depletion, oxygen toxicity, and pulmonary trauma.

Recently attention has been concentrated upon the finding of pulmonary microembolization (Blaisdell and Stallone, 1970; Busch et al., 1971; Mittelmayer and Sandritter, 1971). These microemboli may originate in transfused blood or reconstituted plasma, which are known to contain solid and semi-solid particles such as platelet aggregates and fat droplets, or they may be a manifestation of disseminated intravascular coagulation. In the latter case platelet aggregates originating at the site of injury may be propagated to the lungs where they release vaso-active amines which may alter pulmonary vascular resistance and permeability (Blaisdell and Schlobohm, 1973; Wardle, 1973). In theory the whole picture could also be explained on the basis of endotoxinaemia. This case report describes a patient who developed the syndrome of post-traumatic respiratory insufficiency and in whom investigation revealed the presence of endotoxinaemia and intravascular coagulation.

A simple but sensitive assay for the detection and quantitation of endotoxinaemia (Reinhold and Fine, 1971) has become available, based on the finding that lysates of the amoebocytes of the horseshoe crab, Limulus polyphemus, form a gel after exposure to endotoxin. Already the assay has been applied to the detection of infection and sepsis (Caridis et al., 1972). It has been found that endotoxins of all gram-negative organisms are detectable down to a value of 0.1 nanogram per ml plasma, which is a level insufficient to cause a pyrogen reaction. Staphylococci and Candida may also give positive assays.

This method of endotoxin assay is sensitive, but the levels detected have been shown to relate closely to clinical episodes of bacterial infection (Wardle, 1974). It has been stated previously that only minute amounts of endotoxin are required to cause blood coagulation but substantial levels may be needed to induce significant fibrin thrombosis (Barth and Zimmermann, 1972). Applications of the technique to the study of shock and trauma are in progress in many centres.

CASE REPORT

A 23-year-old demolition worker sustained extensive abdominal and pelvic injuries when a crane gantry weighing 2 tons fell across his lower abdomen. On admission to hospital he was unconscious and had neither palpable peripheral pulses nor measurable arterial pressure. He was placed in a G-suit (Lewis, Mackenzie and McNeill, 1972) and immediate infusion via a subclavian catheter was commenced. This included 2 litres of reconstituted plasma, 1.5 litres of group O Rhesus-negative blood and 1 litre of dextan 70. He was then transferred to the operating room and a laparotomy was performed. This revealed multiple pelvic fractures, one of which extended posteriorly so that the skin of his left buttock was visible from within his abdomen. The visceral injuries included two ischaemic segments of large bowel, a transverse jejunal rupture and a divided left common iliac vein. He was then transferred to the operating room and a laparotomy was performed. This revealed multiple pelvic fractures, one of which extended posteriorly so that the skin of his left buttack was visible from within his abdomen. The visceral injuries included two ischaemic segments of large bowel, a transverse jejunal rupture and a divided left common iliac vein. During the course of the operation he was given 7 litres of blood.

He was returned to the intensive therapy unit with two colostomies and an ileostomy and for 12 hours was maintained inside the G-suit and on positive pressure...
ventilation. Eighteen hours after the initial operation he was conscious, rational, breathing spontaneously, and had an arterial oxygen tension \( (P_{aO_2}) \) of 80 mm Hg breathing room air. His urine output was 1414 ml during this period, his platelet count was 240,000/mm\(^3\) and prothrombin time 78\%. The Limulus plasma assay for endotoxin performed by the method of Reinhold and Fine (1971) gave a value of 0.001 \( \mu g/mL \), but the value was zero 24 hours later.

Forty-eight hours following the injury the patient, who was still fully conscious and alert, began to hyperventilate and it was recognized that he was becoming hypoxic \( (P_{aO_2} 54 \text{ mm Hg and } P_{aCO_2} 30 \text{ mm Hg breathing room air}) \). He also had a non-respiratory alkalosis (base excess +13 m.equiv/l). A chest radiograph taken at this time showed diffuse patchy consolidation (fig. 1). At this point a radiofibrinogen catabolism study was started using a technique previously described (Wardle, 1972). This investigation allows a dynamic assessment of intravascular coagulation to be made. Increased daily breakdown of labelled fibrinogen is shown by its fractional catabolic rate (FCR\%) and if renal failure is present, by the rate of increase of free serum radio-iodine. Although the total body fibrinogen levels were changing in this case, a constant percentage of fibrinogen (about 21\%) is normally catabolized each day. It can be seen from table I that this value was exceeded throughout the period of observation. The results of this study together with the blood gases and the serum concentration of urea and electrolytes are shown in the table and in figure 2.

From this time the patient's clinical condition slowly deteriorated. Endotracheal intubation became necessary on the third day following the injury and a tracheostomy was performed on the fourth day. Despite positive pressure ventilation with oxygen-enriched air (50\% \( O_2 \)), it became increasingly difficult to maintain the arterial oxygen tension at an acceptable level and the alveolar to arterial oxygen tension difference \( (P_{aO_2} - P_{aCO_2}) \) increased progressively. The radiographic appearances became worse and by the sixth day the lung fields were uniformly opaque.

On the eighth day after the accident a lung biopsy was taken by Dr R. A. L. Brewis, because it was considered necessary to exclude infection as the cause of the patient's pulmonary condition. Repeated bacteriological examination had given negative results, and he had been receiving antibiotic therapy, first with gentamicin and later with cephalothin since admission to hospital. Photomicrographs of the specimens obtained are shown in figures 3 and 4. The report received from Dr J. A. J. Ferris stated that there was "evidence of alveolar thickening, increased cellularity, with lymphocytic and fibroblastic infiltration, together with hyaline membrane formation". There was no microscopic evidence of fat embolism and at no point during the course of the illness was there any clinical evidence of this condition.

From this point on the patient's clinical condition slowly deteriorated, although his cardiovascular system remained stable until the terminal stages. As the lung biopsy and bacteriological investigation gave no evidence of bronchopneumonia, the patient was given prednisone \( 30 \text{ mg 4-hourly LV.} \) since it has been suggested that steroid therapy may reduce \( (P_{aO_2} - P_{aCO_2}) \) in post-traumatic respiratory insufficiency. However, no improvement was noted and endotoxinaemia again became detectable at 0.001 \( \mu g/mL \).

A blood culture taken on the ninth day after the accident was later found to contain \textit{Bacteroides}, although

![Fig. 1](https://example.com/f1.png)

**TABLE I**

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical event</th>
<th>( P_{aO_2} ) (mm Hg)</th>
<th>( P_{aCO_2} ) (mm Hg)</th>
<th>( P_{aCO_2} ) (mm Hg)</th>
<th>pH</th>
<th>Base excess</th>
<th>Blood urea (mg%)</th>
<th>Free iodide (%)</th>
<th>Fibrinogen fractional catabolic rate %</th>
<th>(from urine)</th>
<th>Endotoxin assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.6</td>
<td>Laparotomy</td>
<td>350</td>
<td>286</td>
<td>27</td>
<td>7.64</td>
<td>+16</td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td>0.001 ( \mu g/mL )</td>
</tr>
<tr>
<td>14.6</td>
<td>Platelets 240,000</td>
<td>350</td>
<td>231</td>
<td>34</td>
<td>7.58</td>
<td>+3</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td>nil</td>
</tr>
<tr>
<td>15.6</td>
<td>Chest X-ray changes</td>
<td>150</td>
<td>80</td>
<td>40</td>
<td>7.46</td>
<td>+9</td>
<td>48</td>
<td>Radio F started</td>
<td>0.001 ( \mu g/mL )</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>appeared</td>
<td>150</td>
<td>54</td>
<td>30</td>
<td>7.54</td>
<td>+13</td>
<td>48</td>
<td>1.9</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.6</td>
<td>Platelets 150,000/mm(^3)</td>
<td>350</td>
<td>58</td>
<td>45</td>
<td>7.48</td>
<td>+8</td>
<td>33</td>
<td>1.2</td>
<td>49</td>
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<tr>
<td>17.6</td>
<td>Platelets 150,000/mm(^3)</td>
<td>350</td>
<td>60</td>
<td>44</td>
<td>7.50</td>
<td>+10</td>
<td>36</td>
<td>2.3</td>
<td>33</td>
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</tr>
<tr>
<td>18.6</td>
<td>Lung biopsy</td>
<td>350</td>
<td>60</td>
<td>49</td>
<td>7.46</td>
<td>+9</td>
<td>52</td>
<td>7.6</td>
<td>28.5</td>
<td></td>
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</tr>
<tr>
<td>19.6</td>
<td>Platelets 100,000/mm(^3)</td>
<td>350</td>
<td>42</td>
<td>49</td>
<td>7.43</td>
<td>+9</td>
<td>93</td>
<td>4.3</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.6</td>
<td>FDP 50 ( \mu g/mL )</td>
<td>350</td>
<td>35</td>
<td>66</td>
<td>7.31</td>
<td>+11</td>
<td>100</td>
<td>36.7</td>
<td>30</td>
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<td>21.6</td>
<td>Septicaemia</td>
<td>350</td>
<td>35</td>
<td>66</td>
<td>7.31</td>
<td>+11</td>
<td>100</td>
<td>36.7</td>
<td>30</td>
<td></td>
<td></td>
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<tr>
<td>22.6</td>
<td>Acute renal failure</td>
<td>700</td>
<td>87</td>
<td>27</td>
<td>7.53</td>
<td>+1</td>
<td>103</td>
<td>94.0</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.6</td>
<td>Platelets 30,000/mm(^3)</td>
<td>700</td>
<td>79</td>
<td>35</td>
<td>7.57</td>
<td>+9</td>
<td>211</td>
<td>98.0</td>
<td>32.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal values</td>
<td>FDP 30 ( \mu g/mL )</td>
<td>(Air)</td>
<td>150</td>
<td>95</td>
<td>40</td>
<td>7.4</td>
<td>-2 to +2</td>
<td>20.0</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Platelets 250,000/mm(^3)</td>
<td>FDP 0-10 ( \mu g/mL )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
Development of Shock Lung

\[ T/2 = 30.0 \text{ hours} \]
\[ T/2 = 100.0 \]
\[ T/2 = 25.0 \]

\[ \log \% \text{ radio-fibrinogen injected} \]

\[ \text{Time (hrs)} \quad 0 \quad 40 \quad 60 \quad 80 \quad 100 \quad 120 \quad 140 \quad 160 \quad 180 \]

\[ \% \text{ iodide} \quad 1.9 \quad 1.1 \quad 2.3 \quad 7.6 \quad 4.3 \quad 36.7 \quad 94.0 \quad 160.0 \]

\[ \text{FCR\% (urine)} \quad 44 \quad 49 \quad 33 \quad 28.5 \quad 29 \quad 30 \quad 32 \quad 32.5 \]

\[ \text{Endotoxin assay} \quad + \quad - \quad - \quad + \quad + \quad + \quad + \quad + \]

FIG. 2. The survival of radio-fibrinogen in the patient's plasma is depicted: the half-life in hours of the three components is shown. However, under non-steady conditions the breakdown rate of fibrinogen is more accurately assessed from the FCR\% of isotope in daily urine collections. Declining renal function is evident from the increase of serum radio-iodide. It will be noted that endotoxinaemia was initially present and then reappeared prior to the onset of acute renal failure.

FIG. 3. Lung biopsy X200 stained with Root stain to show the reticulum. This is intact, indicating that the lung anatomy is not destroyed by infection or trauma.

FIG. 4. Lung biopsy X200 stained with haematoxylin and eosin. This shows alveolar thickening, cellular infiltration and hyaline membrane formation. There is no evidence of bronchopneumonia.

this information was not available until after the patient had died.

On the tenth day after the accident the patient went into acute renal failure. An arteriovenous shunt was inserted and haemodialysis was begun.

During the last 24 hours of his life the patient was ventilated with 100\% oxygen. On this regime his arterial oxygen tension was maintained at an acceptable level. However, he showed no clinical signs of improvement and he died on the eleventh day after admission.

At the autopsy, in addition to the surgical findings, it was noted that the patient's lungs were solid in consistency and that there were some areas of bronchopneumonia. However, the microscopic examination of the lung confirmed that there were extensive areas of lung tissue showing the same changes as were identified by the lung biopsy. There was no evidence of pulmonary fat embolism.
DISCUSSION

Post-traumatic respiratory insufficiency has been called "shock lung," to define the clinical conditions in which it arises. However, there is no doubt that in many cases the syndrome is due to bronchopneumonia, fat embolism, oxygen toxicity or overtransfusion, particularly with crystalloid solutions. It is believed that these conditions did not play a significant part in the case which is described.

Evidence was obtained that disseminated intravascular coagulation was occurring at the time when the pulmonary dysfunction first occurred. Moreover endotoxaemia was identified at this time and also later in the course of the disease before a positive bacterial culture was obtained (fig. 5).

Platelet aggregates are detectable in vena cava blood after lower limb injury (McNamara, Molot and Stremple, 1970) and fibrin embolization to the lungs has also been demonstrated (Busch et al., 1971). This makes the theory of pulmonary microembolization attractive (Hardaway, 1973). It is considered that amines released from damaged platelets are capable of causing pulmonary vasoconstriction and increased permeability of the pulmonary capillaries, leading to pulmonary oedema. Pulmonary microthrombi have been identified by Mittelmayer and Sandritter (1971) and Lindquist, Rammer and Saldeen (1972) in post-traumatic respiratory failure.

The alternative (or supplementary) explanation is that the whole clinical process is due to endotoxaemia, which, it is now known, frequently follows extensive trauma (Caridis et al., 1972; Fine, 1973). It is only recently that a simple method for detection of endotoxin has been applied (Levin et al., 1970). The numerous noxious actions of endotoxin include vasoconstriction, increase of vascular permeability and induction of platelet aggregation and disseminated intravascular coagulation. In fact Cuevas and others (1972) have shown in rabbits that the typical features of shock lung can be produced by endotoxin. This is the first recorded case in man in which endotoxin assays substantiate this view. Added to this are the data from the radiofibrinogen catabolism study which give corroborative information in the form of accelerated fibrinogen catabolism both at the onset of the shock lung syndrome and again at the onset of the acute renal failure, at which late stage definite septicaemia was recognized. It is now well known that endotoxin induces disseminated intravascular coagulation in man (Corrigan, Walker and May, 1968; Wardle, 1972). Consideration of the platelet counts, fibrinogen degradation products levels and fibrinogen turnover rates make it clear that this did in fact occur.

REFERENCES


