NON-CARDIOGENIC PULMONARY OEDEMA AFTER TRANSFUSION WITH GRANULOCYTE ANTIBODY CONTAINING BLOOD: TREATMENT WITH EXTRACORPOREAL MEMBRANE OXYGENATION

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SUMMARY
A 45-yr-old man developed severe non-cardiogenic pulmonary oedema after a blood transfusion reaction which was resistant to standard therapy. We describe its successful treatment with extracorporeal membrane oxygenation.

KEY WORDS

Extracorporeal membrane oxygenation (ECMO) may be suitable for treatment of severe, but self limiting, disorders of pulmonary gas exchange, but it has failed to find firm indications in adults. We describe its use in treatment of non-cardiogenic pulmonary oedema following transfusion with blood containing an antigranulocyte antibody.

CASE REPORT
A 45-yr-old, 80-kg water bailiff and gamekeeper with an 8-month history of disabling angina presented for coronary artery surgery. His past medical history was unremarkable, with no previous operations and no history of allergy. He did not smoke and was a reformed drinker. Current medication comprised atenolol 50 mg day\(^{-1}\) and aspirin 300 mg day\(^{-1}\), which controlled his symptoms well. Physical and laboratory examinations were normal. Angiography showed good left ventricular function with antero-apical hypokinesia and an ejection fraction of 68%, an occluded right coronary artery, and severe stenoses in the left anterior descending and circumflex arteries. In view of his age, extent of disease and desire for an active lifestyle, it was decided to proceed with surgery.

After premedication with oral nitrazepam and atenolol the evening before surgery and lorazepam, transdermal glyceryl trinitrate and i.m. papaveretum and atropine in the morning, anaesthesia was induced and maintained with midazolam, alfentanil and pancuronium. Nitrous oxide was used until aortic cannulation, after which the lungs were ventilated with oxygen-enriched air. Monitoring was facilitated with radial arterial and internal jugular venous canulae.

The chest was opened via a midline sternotomy and, after full heparinization and cannulation, cardiopulmonary bypass was established and the patient cooled to 28 °C. Saphenous vein was grafted to the first obtuse marginal and posterior descending branches, and the left internal mammary artery was grafted to the left anterior descending coronary artery. Bypass time was 97 min and cross-clamp time was 62 min. After rewarming, the patient was weaned easily in sinus rhythm without inotropic support and treated with an infusion of glyceryl trinitrate 10 µg min\(^{-1}\), producing a systemic arterial pressure of 105/
65 mm Hg, heart rate 75 beat min⁻¹ and central venous pressure (CVP) +7 mm Hg; \( P_a_o \) was 57 kPa and \( P_a_c_{o_2} \) 4.9 kPa, with \( F_i_o \) 1.0 and minute volume 9.5 litre min⁻¹.

Thirty minutes after bypass, protamine 600 mg had been given, the blood from the pump restored to the patient, one unit of whole blood administered, and an infusion of gelatin solution was in progress. The patient was stable, with unchanged haemodynamic variables.

After a further 15 min, arterial pressure decreased to 95/50 mm Hg, CVP increased to +12 mm Hg and heart rate was 85 beat min⁻¹. These changes were followed closely by the appearance of frank pulmonary oedema from the tracheal tube, accompanied by an increase in peak airway pressure from 11 to 36 cm H₂O. Arterial blood-gas analysis with a minute volume of 9.5 litre and \( F_i_o \) 0.5 showed \( P_a_o \) 7.3 kPa and \( P_a_c_{o_2} \) 6.3 kPa. Treatment was commenced with adrenaline, infusion of dopamine, chlorpheniramine, frusemide, aminophylline and methylprednisolone. Minute ventilation was increased, positive end expiratory pressure (PEEP) applied, and \( F_i_o \) increased to 1.0. Further investigation with flow directed pulmonary artery (PA) catheterization via the right atrium revealed PA pressures of 38/20 mm Hg and wedge pressure 10 mm Hg.

The course over the next 3 h was stormy, with systemic hypotension (70/40 mm Hg), pulmonary hypertension (38/22 mm Hg) and tachycardia (115 beat min⁻¹) despite filling pressures in both atria of about 12-13 mm Hg, with worsening pulmonary oedema. Cardiovascular function was supported with infusions of noradrenaline 0.08 \( \mu \)g kg⁻¹ min⁻¹ and dopamine 2 \( \mu \)g kg⁻¹ min⁻¹. Cardiac output at this stage was 4.5-5 litre min⁻¹, giving calculated SVR and PVR of 590 and 214 dyn s cm⁻⁵, respectively.

At this stage, despite increasing minute ventilation to 14 litre min⁻¹, resulting in increased airway pressures (40 cm H₂O), and with PEEP of 4 cm H₂O, pulmonary oedema persisted with deteriorating gas exchange. It was thought unwise to increase ventilation further as this might threaten the integrity of the internal mammary graft.

In view of the severe non-cardiogenic pulmonary oedema, it was decided to institute ECMO. This was established after re-heparinization, initially from femoral vein to femoral artery, with a Sci Med 3500 membrane oxygenator with roller pump and reservoir at a flow of 2.5 litre min⁻¹. Activated clotting times were maintained between 300 and 350 s. This produced a marked improvement in gas exchange with \( P_a_o \) 30 kPa and \( P_a_c_{o_2} \) 4 kPa. Unfortunately, the circulation in the leg became compromised with this arrangement and in view of the patient's active occupation and lifestyle, ECMO was instituted between right atrium and ascending aorta. Satisfactory gas exchange was again established and the circulation to the leg restored.

The patient was returned to the intensive care unit 7 h after bypass with the ECMO system in situ through an open median sternotomy. ECMO was maintained throughout the first night after operation with flows of 2.5 litre min⁻¹. The lungs were ventilated with \( F_i_o \) 0.6 at a minute volume of 10 litre min⁻¹ and PEEP of 5 cm H₂O. Cardiovascular support was continued with infusions of dopamine and noradrenaline. Because of heparinization, bleeding was considerable, requiring packs to be changed several times. Total blood loss while on ECMO was at least 5 litre; this was replaced with whole blood, platelets and plasma protein solution. Sedation during this period was maintained with papaveretum and midazolam, and neuromuscular block maintained with pancuronium.

Pulmonary function improved during the first day after operation, and the patient was eventually weaned from ECMO 20 h after bypass, allowing the chest to be closed and coagulation abnormalities to be corrected. Over the following 24 h ventilatory and inotropic support were decreased, the chest x-ray improved, and the trachea was extubated on the second day after operation. \( P_a_o \) 9.5 kPa while the patient breathed air was recorded at this time. He was discharged from the intensive care unit on the third day, and from the cardiac unit on the ninth day. Pulmonary function tests at this stage showed a marked restrictive deficit, but the patient has since returned successfully to his active occupation.

Subsequent investigation revealed a strongly positive anti-granulocyte cross match with the serum from the unit of whole blood administered in the period immediately after bypass. Anti-lymphocyte matches were negative, and immunoglobulin (including IgE) and complement concentrations were unremarkable. It seems likely, therefore, that the patient's complication was caused by an anti-neutrophil antibody present in the unit of whole blood administered after termination of bypass. This accords with an onset...
time of between 30 min and 2 h. The donor of the implicated unit was traced, and was found to be a 41-year-old woman with no history of blood transfusion but a complicated obstetric history. Her first pregnancy was uncomplicated and resulted in the birth of a normal boy, but her subsequent three pregnancies resulted in a neonatal death, followed by two early second trimester missed abortions.

DISCUSSION

Fulminant non-cardiogenic pulmonary oedema is a rare but potentially lethal complication of cardiopulmonary bypass. Several causes have been postulated, including endotoxin, protamine, complement activation by pump or oxygenator and, as in this patient, transfusion reaction [1, 2]. White blood cell antibodies or leucoagglutinins have been implicated in both experimental models and a few clinical cases. In these patients white blood cell antibodies have most commonly been found in donor plasma, but occasionally in recipients [3]. Following reaction between antibody and white blood cell there is release of various toxins, including oxygen species, proteolytic enzymes and activated complement. When antibodies are found in donor sera, these are often from multiparous women, arising presumably from sensitization to fetal alloantigens during pregnancy. Potential reactions cannot be detected by conventional cross matching.

The frequency of reaction following passive transfer of leucocyte antibody is estimated at 0.02 % of all transfusions, but may be commoner than is widely appreciated. Leucoagglutinating or lymphocytotoxic antibodies have been shown consistently to be present in around 17 % of pregnant women and to persist for 3 yr thereafter in 55 %. Antibodies have been shown to be present in approximately 3 % of previously transfused male donors. These groups at risk of having such antibodies represent perhaps 1.5 % of the blood donor population [4]. Donations with leucocyte antibodies are dangerous only for patients with the specific leucocyte antigens which would react with them. This is an extremely rare circumstance. If donations are found to have leucocyte antibodies, they may still be used to produce washed red blood cells. Red blood cell concentrates may contain sufficient remaining plasma, and therefore antibody, to cause pulmonary reactions.

Management of non-cardiogenic pulmonary oedema includes prompt recognition. Suspicion is warranted in situations in which there is particular risk such as blood transfusion or cardiac surgery. Indeed, prophylaxis with antihistamine and steroid has been recommended before cardiopulmonary bypass [2]. Appropriate resuscitative measures should include respiratory support with oxygen, bronchodilators, tracheo-bronchial toilet, positive pressure ventilation and PEEP if required. Significant effusions should be drained. The circulation should be monitored with central venous, pulmonary artery or, if possible, left atrial catheterization, filling pressures optimized, and inotropic support given in severe cases. Metabolic derangements must be treated. Specific measures include antihistamines such as chlorpheniramine, pharmacological doses of steroid to minimize pulmonary endothelial damage, and adrenaline to antagonize the effects of histamine and for its bronchodilating, inotropic and vasoactive actions.

Because of its cost in terms of labour, expense and complications, the use of ECMO has so far been limited. It has failed to improve mortality in severe acute respiratory failure, although recent techniques which emphasize elimination of carbon dioxide may be more promising [5]. Indications outside the field of neonatal medicine are not defined [6, 7]. It would appear to be appropriate for the treatment of a short, self limiting illness with a rapidly reversible lung lesion during which support could be applied for as short a period as possible to minimize problems of complications and resources. A recent example is its successful use in the sickle cell syndrome [8].

Non-cardiogenic pulmonary oedema after cardiopulmonary bypass or blood transfusion would seem to be such a situation in which the nature of the lung lesion is severe but transient, and ECMO may be appropriate in the most severe cases in which oxygenation is inadequate, despite medical treatment. In the patient we describe, acceptable gas exchange was achieved with modest flows for the 16-h period before the worst of the pulmonary effects diminished. The major complications encountered were lower limb ischaemia distal to the cannulation site, and bleeding from heparinization. The former could perhaps have been modified by the use of smaller cannulae and therefore slower flow rates, but obviously a balance must be found between cannula size and a flow rate sufficient to maintain oxygen delivery. We chose to use activated clotting times in the
range 300–350 s, which have been suggested for use with our system [9]. It may be possible to minimize bleeding using heparin-bonded extracorporeal systems and lesser degrees of systemic heparinization with careful monitoring of transmembrane pressure [10].

ACKNOWLEDGEMENTS

We thank Mrs Judith Chapman and Dr M. F. Murphy of St Bartholomew's Hospital, London, for confirming the presence of specific anti-granulocyte antibody.

REFERENCES