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ACUTE PULMONARY HYPERTENSION, LEUCOPENIA AND HYPOXIA IN EARLY HAEMODIALYSIS

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Summary

A sheep model is described which produces acute pulmonary hypertension, leucopenia and hypoxia after blood, previously placed in contact with a Cuprophan hollow fibre artificial kidney, re-enters the circulation. Relationships between these manifestations (acute pulmonary hypertension, leucopenia and hypoxia) were examined in normal leucopenic and Indomethacin pre-treated sheep. The degree of pulmonary vascular response, and severity of leucopenia and hypoxia were all directly interrelated and were dependent upon the volume of blood injected. The induction of leucopenia did not affect the pulmonary hypertension or hypoxia. Pre-treating the animals with the cyclo-oxygenase inhibitor, Indomethacin, abolished both the pulmonary hypertension and the hypoxia without any effect on the development of neutropenia. These results suggest that leucocytes do not play a role in the haemodynamic response nor in the hypoxia; activation of the cyclo-oxygenase system is necessary for the development of acute pulmonary hypertension which causes hypoxia subsequent to alterations in ventilation perfusion relationships.

Introduction

Blood-foreign surface interactions, as occur with the use of extracorporeal devices such as the artificial kidney, may result in clinically significant problems. Activation of the alternate pathway of complement, with the generation of C3a and C5a anaphylotoxins results in pulmonary sequestration of leucocytes which has been held responsible for the peripheral leucopenia and arterial hypoxia that frequently occur during the first 30 minutes of dialysis [1,2]. Cuprophan (or dialysate) hypersensitivity is an infrequent but serious consequence that arises following blood-dialysate contact [3,4]. Characteristically, acute chest and back pain, dyspnoea, diaphoresis and occasionally flushing and oedema of the skin occur within the first 10 minutes of commencing haemodialysis. This
has resulted in cardiopulmonary arrest and death [3]. The majority of reports describe the phenomenon in patients dialysed for the first time by a new (not reused) artificial kidney containing a Cuprophan membrane (Enka, West Germany) in a hollow fibre configuration.

We have recently reported the haemodynamic manifestations of blood-dialyser interactions in an animal model [5], some of which showed striking similarities to ‘Cuprophan hypersensitivity’. Acute pulmonary hypertension occurred within the first few minutes of haemodialysis and was associated with a fall in cardiac output, together with electrocardiographic evidence of myocardial ischaemia and arrhythmias [5]. At the same time, peripheral leucopenia and hypoxia were noted; the changes in pulmonary artery pressure and peripheral leucocyte count occurred simultaneously but preceded the maximal decrease in partial pressure of oxygen. In this model, the pulmonary vascular response depended not only on the surface area of the artificial kidney as well as its chemical structure and configuration. Membranes containing regenerated Cellulose or Cuprophan had a significantly greater effect than with Cellulose Acetate, or Polyacrylonitrile [5]. In clinical studies dialysis with membrane containing Cellulose Acetate or Polyacrylonitrile results in less complement activation, leucopenia and arterial hypoxia than with the use of Cuprophan surfaces [6,7].

This raises the possibility that the cardiopulmonary manifestations of ‘Cuprophan hypersensitivity’ may reflect a more severe expression of the phenomena of leucopenia and hypoxia and that changes in pulmonary vascular tone are common. Preliminary results from clinical studies support this concept and have shown that increases in pulmonary vascular resistance index occur [8].

This paper examines the relationship between these three manifestations of blood foreign surface contact.

Methods

Specific details of the sheep model have been described elsewhere [5]. In summary, Suffolk sheep of either sex, six to 12 months old, were prepared for haemodynamic monitoring by inserting, via a jugular vein, a triple lumen thermodilution Swan-Ganz catheter (Edwards Lab, Santa Ana, Calif) for subsequent measurement of the pulmonary artery pressure. A carotid artery was cannulated with a polyvinyl catheter (OD 3mm) for blood sampling. A Quinton-Scribner SAF-T shunt (Extracorporeal Medical Specialties, King of Prussia, Pa) was inserted into the femoral artery and vein. The Scribner shunt was connected to a dialyser by standard haemodialysis blood lines. The dialyser could be bypassed by directing flow through a bypass line, or by changing arterial clamps introduced into the circuit. Blood was pumped through a circuit using a Sarns semiocclusive pump (model 550, Sarns Inc, Ann Arbour, Mich). The circuit was primed using 0.9% saline and Heparin 3,000 IU (Hepalean, Organon, Toronto, Canada) was given into the arterial line at commencement of blood flow. Blood was allowed to fill the dialysis circuit containing a Cuprophan hollow fibre artificial kidney (Erika 200 HPF, Erika Corp, Rockleigh, NJ) which was then clamped off. After 10 minutes static contact with this dialyser, 50ml of blood
was withdrawn. The mean pulmonary artery pressure (PAP) was monitored continuously and the neutrophil count, and partial pressure of oxygen were measured prior to and every 20 seconds following reinjection of increasing volume (1, 2.5, 10 and 15ml) of this static contacted blood. The experiments were performed in normal, leucopenic or Indomethacin pretreated sheep (n=5 in each group). Leucopenia was induced with intravenous Mustine Hydrochloride (Merck, Sharpe and Dohme, West Point, Pa) 0.4mg/kg on days one and four. The experiments were performed on days six and seven after confirmation that the total white blood cell count was less than 1 x 10^9/L. Indomethacin sodium trihydrate (2.0mg/kg) was reconstituted in sterile water and given intravenously over 20 minutes.

The basic data are expressed as mean ± SEM using the change from baseline for each parameter (Δ PAP, ΔPaO₂ and per cent fall in neutrophil count). The analysis of variance was used to examine the effects of volume and treatment (leucopenia, Indomethacin) on ΔMean PAP, ΔPaO₂ and per cent fall in neutrophil count.

Results

Figure 1 shows a typical response that occurs following reinjection of a volume (10ml) of blood after static contact with Cuprophan. The pulmonary artery pressure increased from 13 to 43mmHg and coincided with a fall in neutrophil count (5.9 x 10^9/L) within 20 seconds of reinjection of static contacted blood. Maximal hypoxia occurred at 60 seconds (100 to 66mmHg PaO₂). All these events returned to baseline by 300 seconds.

Figure 2 shows the change in mean pulmonary artery pressure (ΔMean PAP), per cent fall in neutrophil count, and the change in partial pressure of oxygen (ΔPaO₂) following reinjection of increasing volumes (1, 2.5, 10 and 15ml) of blood after 10 minutes static contact with a Cuprophan hollow fibre kidney in normal, leucopenia, or Indomethacin pretreated sheep.

In normal sheep, 1 and 2ml of blood reinjected after contact with Cuprophan had little effect on the pulmonary artery pressure; however, reinjection of 5ml after contact caused a 17mmHg increase in mean PAP. The injection of 10 and 15ml after contact caused an even greater elevation in mean PAP (28 and 32mmHg respectively). The changes in arterial oxygenation (ΔPaO₂) and percentage fall in neutrophil count mirrored the degree of pulmonary hypertension with each volume reinjected in normal animals after contact with Cuprophan. The analysis of variance showed a significant effect of the volumes reinjected on the Δ mean PAP (p<0.001), degree of hypoxia (p<0.0005), and per cent fall in neutrophils (p<0.05).

In leucopenic animals, a similar degree of pulmonary hypertension and arterial hypoxia occurred as demonstrated in normals. One ml reinjected caused little effect on pulmonary artery pressure or on arterial oxygenation. Five ml reinjected caused an increment of 34mmHg in mean PAP and a fall in PaO₂ of 32mmHg. Analysis of variance showed a significant effect of the volumes reinjected on the Δmean PAP (p<0.001) and on the degree of hypoxia (p<0.0005).

The use of Indomethacin blocked both the pulmonary hypertensive and
Figure 1. Mean PAP (mmHg), PaO₂ (mmHg), and neutrophil count (x 10⁹/L) following reinjection of 10ml of blood after 10 minutes static contact with a Cuprophan hollow fibre dialyser.
hypoxic responses with all blood volumes reinjected while the percentage fall in neutrophil count occurred to a similar degree as demonstrated in non-Indomethacin pretreated sheep. Examination of the pulmonary and hypoxic responses using analysis of variance indicated that interactions existed between the volumes
of blood re-injected and the use of Indomethacin (p<0.005). On the other hand, Indomethacin was not a significant variable when one examined the effect of re-injection upon the percentage fall in neutrophil count.

Discussion
In sheep transient and acute pulmonary hypertension routinely occurs early in experimental dialysis and the degree to which it occurs varies with the use of artificial kidneys of different surface area, configuration, and composition [5]. Its occurrence coincides with the development of neutropenia and hypoxia. Animals which develop the severe pulmonary hypertensive response become tachypnoeic, dyspnoeic and may even develop subsequent myocardial ischaemia and arrhythmias; occasionally cardiopulmonary arrest occurs [5]. Such dramatic symptoms and signs are similar to those described with the so-called 'Cuprophan hypersensitivity' reaction which occasionally complicates clinical haemodialysis [3,4]. Thus, we hypothesise that acute pulmonary hypertension is of pathophysiological significance in its occurrence. Acute pulmonary hypertension has been reported on at least one occasion in a patient with typical manifestations of this reaction [9]. Furthermore, we have observed increases in pulmonary vascular resistance during the early stages of haemodialysis in patients with acute renal failure [8]. These observations suggest that a range of changes in pulmonary vascular tone occur during early haemodialysis and that the severity of cardiopulmonary symptoms may depend on the degree of acute pulmonary hypertension produced.

The relationship of this pulmonary vascular response to the characteristic leucopenia and hypoxia remains unclear. It has been postulated that in the early stages of haemodialysis the hypoxia is related to complement induced intra-pulmonary leucostasis [1,2]. However, reports have indicated a discrepancy between the intensity of complement activation and severity of leucopenia and hypoxia [10]. Our results show that there is a dose-response relationship between these three phenomena. In normal sheep, the degree of pulmonary hypertension correlates with the severity of leucopenia and hypoxia; the induction of leucopenia does not affect either the pulmonary vascular response or the degree of hypoxia; Indomethacin pretreated animals show no pulmonary artery response nor do they develop hypoxia; however, leucopenia occurs to the same degree as normals. This suggests that leucocytes are unnecessary in either the production of pulmonary hypertension or hypoxia, and that the changes in pulmonary vascular tone cause the hypoxia (by alterations in ventilation perfusion relationships). Furthermore, the haemodynamic response is dependent upon the cyclooxygenase system. Further experiments in our model suggest this reaction requires the presence of a plasma factor which is heat labile, calcium and complement dependent. Further work is necessary to confirm these preliminary observations.

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Open Discussion

RITZ (Heidelberg) Could you tell us how this corresponds to the situation in the human? Can you give us some information on blood pressure and left ventricular function. The reason I am asking this is because there was a presentation at the International Congress of Nephrology* where blood pressures with this model of up to 200mmHg or more have been observed and this has certainly not been seen in dialysed patients.

WALKER If you look in the literature at the few described cases of hypersensitivity reaction you will find that both hypotension, normotension and hypertension have been described. The reasons for this are not known. In the animals we see the same thing but most commonly we see profound hypertension. I am not sure of the reason for this but it is quite possible that there may be some effect of the cyclo-oxygenase system or of the alternate pathway of complement to the anaphylactotoxin C₃a or C₅a on systemic vasculature. The other alternative possibility is that there is a compensatory mechanism with release of catecholamines which may cause the systemic hypertension. I have no data on left ventricular function in sheep or in humans. We believe that it is not a primary left ventricular problem but a primary right ventricular problem, in that you have physical obstruction to blood flow through the lungs which causes acute right ventricular failure and therefore a decreased pre-load on the left ventricle. There is other animal models in the same situation which correlate with this particular problem. In the human I can tell you that we have done invasive haemodynamic monitoring in acute renal failure patients. We have found approximately 30 per cent of them develop acute pulmonary hypertension in the first 15 minutes. In our chronic stable patients we did find a significant number developed a dramatic fall in right ventricular ejection fraction using the radionuclide equilibration technique without any significant change in left ventricular ejection fraction. This was in asymptomatic patients. The

primary effect is on the right ventricle rather than the left ventricle, and the left ventricle suffers only because the right ventricle has failed.

UNKNOWN I ask why you see hypoxaemia occurring with slight complement activation which occurs with polysulphone membranes?

WALKER The problem is that the complement activation or I should say hypoxaemia during haemodialysis, is multifactorial. We believe that the initial hypoxaemia that occurs during haemodialysis is related to complement activation and is subsequent to changes in pulmonary vascular tone which causes acute ventilation perfusion mismatches which results in the hypoxia. There are many causes of hypoxaemia during dialysis such as microemboli or whether the dialysate buffer is acetate or bicarbonate. They tend to lose CO$_2$ across the dialyser as well and so there are many different mechanisms. I am not sure if that answers your question or not.