PATHOPHYSIOLOGY OF DIALYSIS RELATED HYPOXAEemia

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Summary

In order to elucidate the pathogenesis of haemodialysis related hypoxaemia, lung function studies, measurements of intra-thoracic fluid changes, leucocytes and complement activity were made in 12 patients during a routine six hours dialysis using cellulose membranes. Coincidently with the fall in arterial oxygen tension, lung function was significantly impaired, paralleled by a decrease in transthoracic impedance, leucopenia and a decrease in plasma complement activity. It therefore is suggested that blood membrane interaction leads to complement-mediated pulmonary leucostasis evoking mild pulmonary oedema with impaired oxygen diffusion, resulting in hypoxaemia.

Introduction

A distinct fall in arterial oxygen tension (paO₂) occurring in the initial phase of haemodialysis is a well known phenomenon. Although this dialysis hypoxaemia usually is well tolerated by stable dialysis patients it can result in cardiopulmonary decompensation in patients with pre-existing compromised heart and lung function. The aetiology of this dialysis related hypoxaemia is still a matter of controversy. Whereas Craddock et al [1] suggested that acute pulmonary dysfunction secondary to complement-mediated leucostasis in the pulmonary vasculature was the major cause of the marked drop in paO₂ values, other authors [2, 3] implicated hypocapnic hypoventilation secondary to the loss of carbon dioxide (paCO₂) via the dialyser as the pathogenic mechanism.

To elucidate the pathophysiology of this dialysis hypoxaemia serial lung function studies were performed during routine haemodialysis.

Patients and methods

The following investigations were done in 12 stable patients during a routine haemodialysis (HD) using a cellophane membrane repeatedly during the first hour of HD and hourly thereafter.
1. Lung function studies: minute ventilation (MV) was measured by a lammelle spiroceptator, alveolar oxygen tension (pAO₂) paramagnetically (Oxymat M), alveolar CO₂ tension (pACO₂) by ultrareadsorption (Ultramat M CO₂), pAO₂ and pACO₂ by an automatic blood-gas analyser (AVL gas check); AaDO₂ was directly derived from the difference between pAO₂ and pACO₂ values.

2. Measurements of intrathoracic fluid changes by means of changes of transthoracic electrical impedance (Minesota IKG).

3. CH₅₀ as parameter for complement activity was measured by immunohaemolysis; leucocytes were counted automatically (Coulter counter).

Additionally, diffusion capacity for carbon monoxide (DLCO) was measured by the steady state method before the beginning, at 30 minutes after the start and at the end of the six hours dialysis.

Prior to another HD session six of these patients received transfusions of fresh heparinised plasma from healthy donors which was brought into contact with the dialyser cellulose membrane. This was achieved by prefilling a hollow fibre haemodialyser and dialyser tubing with fresh plasma and by circulating this plasma by means of roller pumps for 20 minutes. This plasma was washed out with saline and transfused into the patient. Leucocytes and blood gases were measured after plasma transfusion as well as after the following HD, which was performed on the same dialyser.

Results

Immediately after the beginning of HD there was a significant drop in pAO₂, reaching a maximum at about 30 minutes after the start and with a tendency
Figure 2. Behaviour of arterial carbon dioxide tension ($\text{paCO}_2$) and minute ventilation (MV) during HD

Figure 3. Behaviour of transthoracal electrical impedance ($Z_o$) during HD
Figure 4. Pulmonary diffusion capacity for carbon monoxide ($D_{LCO}$) during HD

Figure 5. Behaviour of white blood cell counts (WBC) and arterial oxygen tension ($p_{A}O_{2}$) after transfusion of 'membrane-activated' plasma and after subsequent HD
towards normal at about one hour. As \( p\text{AO}_2 \) did not change there was a significant rise in \( \text{AaDO}_2 \) inverse to the decrease of \( \text{pAO}_2 \) (Figure 1).

\( \text{pCO}_2 \) and minute ventilation (Figure 2) did not change, therefore giving no evidence for hypocapnia or hypoventilation. Parallel to the drop in \( \text{pAO}_2 \) transthoracic impedance decreased significantly, indicating intrathoracic fluid accumulation (Figure 3). Furthermore impairment of alveolar diffusion was indicated by a significant decrease in \( D_{1,\text{CO}} \) at 30 minutes (Figure 4).

Peripheral leucocyte counts decreased from an average value of 4,300 at the beginning to \( 1,200 \times 10^9 /L \) (\( p < 0.001 \)) at 20 minutes, concomitantly \( \text{CH}_5 \text{o} \) fell from 24.6 to 16.2 mean \( \text{CH}_5 \text{o} /\text{ml} \) (\( p < 0.001 \)).

Transfusion of heparinised fresh plasma which had had contact with the dialyser membrane produced the same significant leucopenia and fall in \( \text{pAO}_2 \) as did the subsequent dialysis (Figure 5).

**Discussion**

Our results clearly indicate that dialysis related hypoxaemia is of pulmonary origin. This is indicated by a significant drop in alveolar diffusion as shown by the significant decrease of \( D_{1,\text{CO}} \) whereas \( \text{pCO}_2 \) and minute ventilation remained unchanged excluding hypocapnic hypoventilation as the cause. This is in contrast to the reports of Sherlock [2] and Aurigemma [3] who suggested that a decrease in alveolar oxygen tension owing to a decrease in ventilation secondary to \( \text{CO}_2 \) loss via the dialyser was responsible for hypoxaemia. Their conclusion was reached by calculation of \( \text{pAO}_2 \) values using the alveolar gas equation and cannot be supported by our results, as measured \( \text{pAO}_2 \) in our patients showed a constant behaviour throughout the dialysis procedure. Furthermore hypoventilation is not likely to occur when \( \text{pCO}_2 \) stays at a constant level, a fact already stressed by others [4].

Transient leucopenia is a well known feature of haemodialysis [5, 6] and it was Craddock [1] who first called attention to the temporal relation between leucopenia and dialysis hypoxaemia. Furthermore he suggested that leucopenia was due to complement activation by the cellophane membrane [7] and demonstrated as morphological equivalent for hypoxaemia plugging of leucocytes in the pulmonary vessels, and interstitial pulmonary oedema in animals [1]. That leucopenia and hypoxaemia are related events was demonstrated by our plasma transfusion experiments showing that plasma activated on the dialysis membrane induced simultaneous leucopenia and hypoxaemia when infused into patients, similar to the subsequent haemodialysis. Further evidence for a causal relationship between leucopenia and dialysis hypoxaemia can be derived from the finding that haemodialysis failed to evoke hypoxaemia in an agranulocytotic [1] and a leucopenic patient [8].

The fall in transthoracic electrical impedance indicating intrapulmonary fluid accumulation supports the theory of plugging of leucocytes in the pulmonary vessels and consecutive interstitial oedema as cause of hypoxaemia.
References


Open Discussion

ALJAMA (Cordoba) We showed at the Istanbul Congress that leucopenia and activation of complement are unrelated phenomena. In fact if you use different kinds of membranes such as polyacrylonitrile you will find that in fact there is activation of complement but no leucopenia. On the other hand if you repeat your experiment during isolated ultrafiltration you will get significant leucopenia but not hypoxaemia, so how can you explain these figures?

GRAF Our results are only derived from cellulose membranes. There may be other mechanisms acting with PAN-membranes. They have a rather high ultrafiltration rate so that the ultrafiltration during the first hour overcomes the interstitial pulmonary oedema. The same would be true for ultrafiltration without dialysis on cellulose membranes, so that no initial drop in pao2 may be found.

ALJAMA As far as I know ultrafiltration has nothing to do with complement activation.

GRAF Ultrafiltration removes the interstitial oedema and therefore you cannot see the drop in pO2 seen when one uses cellulose membranes.

ALJAMA I am not happy with your explanation. How can you explain that there is no significant hypoxaemia when you use bicarbonate instead of acetate in the concentrate?

GRAF We have no experience with bicarbonate. If you use bicarbonate in the dialysate then the patient will get a pCO2 load from the dialysate and therefore possibly will get hyperventilation to overcome hypoxaemia.

ALJAMA I think that the change in pH is the same if you use acetate and bicarbonate.

GRAF I think the experiments circulating the plasma and infusing it into the patient are indicative that hypoxaemia is transferable by a soluble factor and that leucopenia occurs at the same time.

ALJAMA It is very suggestive.
LEONARD (New York) I simply want to ask what your controls were? Did you prepare plasma and reinfuse it into the patient without exposure to anything except the bag, and can you also tell me how you prepared plasma from blood. What was the method of separation and was it complete and did that do anything to your system?

GRAF Plasma from healthy donors was obtained by centrifugation.

LEONARD Did you give plasma to the patient putting it in the same blood bank and preparing it in the same way without exposure to the dialyser and run the same tests? Did you do a control?

GRAF No.

SCHMITT (Rostock) Of course you know the paper of Francis Dummler in which he showed last year that hypoxaemia and leucopenia in haemodialysis were unrelated events. You know that he used PAN membranes and reused cellulose membranes within which no leucopenia occurred, but he could observe dialysis-induced hypoxaemia. Have you any comments on this fact?

GRAF My comment is the same as I said to the first questioner. PAN membranes may be different. He possibly failed to see hypoxaemia because of the high ultrafiltration rate.

SCHMITT One additional comment: in our opinion the dialysis-induced hypoxaemia is mainly due to a pulmonary disequilibrium syndrome and only partially the consequence of pulmonary leucostasis.