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Continuous arteriovenous haemofiltration and respiratory function in multiple organ systems failure

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Abstract. *Objective:* To determine what change in respiratory function occurred following prolonged and efficient continuous arteriovenous haemofiltration (CAVH) in a group of patients with multiple organ systems failure (MOSF). *Design:* A retrospective assessment using patient notes and ICU charts. *Setting:* The Intensive Care Unit of a large University Teaching Hospital. *Patients:* All ICU patients satisfying the following criteria: (i) Failure of more than one organ system; (ii) Treatment with CAVH; (iii) Removal of more than 10 l of ultrafiltrate per day; (iv) Continuous haemofiltration for at least 5 days. Thirteen patients satisfied these criteria and 14 episodes of CAVH were analyzed. *Measurements:* All data were recorded from the patient notes and ICU charts apart from the A-aDO_2 and PaO_2/FiO_2 (PF) ratio which were calculated from available values. A mean of 3.5 different organ systems failed during the period of stay. The mean daily ultrafiltrate volume obtained was 23.7 (SD 0.95) l and the mean duration of treatment 9.6 (SD 4.3) days. Significant improvements occurred in the values for the PF ratio and ventilatory modality ($p < 0.05$), and the FiO_2 and A-aDO_2 ($p = 0.001$). The mean PEEP value remained unchanged at 4.8 cmH_2O. Ten of the 13 patients subsequently died (77% mortality). *Conclusions:* A significant improvement in respiratory function occurred in patients with MOSF who had undergone a prolonged period of intense CAVH. Haemofiltration may therefore be a useful treatment for respiratory failure in this patient group. Unfortunately the overall mortality of the group remained high.

Key words: Respiratory insufficiency – Hemofiltration – Multiple organ failure – Mortality

Severe respiratory dysfunction is a common problem in intensive care patients with multiple organ system failure (MOSF) [1–5]. Primary lung pathology with secondary infection may make the patient vulnerable to developing this syndrome [6, 7], but more often the deterioration in lung function occurs as a consequence of the pathophysiological processes set in motion by an unrelated primary insult [4, 5]. For many years the treatment has been mainly supportive involving manipulations of intermittent positive-pressure ventilation (IPPV), positive end-expiratory pressure (PEEP) and fluid balance. However, recently there have been several reports of improvement in lung function with continuous arteriovenous haemofiltration (CAVH) [8–11]. Experimental work has shown it to be effective in reducing extravascular lung water following acid-induced pulmonary injury [12], and this has been supported by studies demonstrating an improvement in respiratory function in patients with cardiogenic pulmonary oedema following a short period of ultrafiltration [13, 14]. Further clinical experience involving the use of CAVH in the treatment of the adult respiratory distress syndrome has demonstrated it to be effective in treating either acute respiratory dysfunction alone or respiratory dysfunction as part of the MOSF syndrome [15–17].

Our own anecdotal experience is that some patients with MOSF undergoing CAVH demonstrate an improvement in respiratory function. The aim of this retrospective study was therefore to identify changes in respiratory function in a group of patients with MOSF undergoing a period of intense CAVH, in an attempt to confirm this observation and the findings of these previous studies.

Patients and methods

The admission notes and intensive care charts of the first 40 patients to undergo CAVH on the Adult Intensive Care Unit at the University Hospital, Nottingham between 1986 and 1990 were reviewed. All patients were categorized according to the admitting speciality, and the nature of the main problems leading to admission. An Apache II score had been calculated retrospectively from data obtained during the first 24 h of stay as an indicator of the severity of illness and this was noted [18]. A further retrospective assessment of the severity of illness of the patients was made by determining both the total number of different organ systems to fail and the total number of episodes of systems failure that had occurred during their admission. The definitions of organ systems failure were those of Knaus et al. [19] and are shown in Table 1.

Table 1. Definitions of organ system failure (OSF)

Cardiovascular failure:
1. Heart rate ≤ 54/min
2. Mean arterial blood pressure ≤ 49 mmHg
3. Occurrence of ventricular tachycardia and/or ventricular fibrillation
4. Serum pH ≤ 7.24 with a $PaCO_2$ of ≤ 6.5 kpa

Respiratory failure:
1. Respiratory rate ≤ 5/min or ≥ 49/min
2. $PaCO_2 \geq 6.7$ kpa
3. A-$aDO_2 \geq 47$ kpa
4. Ventilator dependence on the fourth day of OSF

Renal failure (since hospital admission):
1. Urine output ≤ 479 ml/24 h or ≤ 159 ml/8 h
2. Serum creatinine ≥ 300 mmol/l

Haematologic failure:
1. WBC $\leq 1 \times 10^9$/l
2. Platelets $\leq 20 \times 10^9$/l
3. Haematocrit $\leq 20\%$

Neurologic failure:
Glasgow coma score ≤ 6 (in the absence of sedation at any one point during the day)

Organ systems failure was deemed to have occurred on that day if any of the individual criteria were met during the 24 h period. Hepatic failure was included if patients had documented liver disease with hepatic encephalopathy and/or abnormal liver function tests. Only patients who were in MOSF were included in the review. We also documented the number of episodes of organ systems recovery that occurred during the same period.

To enable us to confidently assess changes in respiratory function with CAVH we developed a set of criteria that needed to be satisfied before a patient could be included in the assessment group. These ensured that only the results of those patients who were haemofiltered efficiently and for a reasonable duration of time were analyzed.

1) Respiratory systems failure was present at the time CAVH was instituted.
2) More than 10 l/day of filtrate was removed.
3) Haemofiltration continued uninterrupted for at least 5 days.

These criteria were established by examining previous studies involving CAVH and following either their practice or recommendations, so that valid comparisons could be made [21, 31, 32].

Changes in respiratory function with CAVH were determined by examining ventilatory modality (VM), inspired oxygen concentration (FiO_2), alveolar-arterial oxygen difference (A-aDO_2), the PaO_2/FiO_2 ratio (PF), and PEEP for each patient. Ventilatory modality was either continuous mandatory ventilation (CMV), synchronized intermittent mandatory ventilation (SIMV) or spontaneous ventilation (SV). Patients were ventilated with CMV mode unless gas exchange had improved sufficiently to allow weaning, in which case they would be on either SIMV or SV mode. For the purpose of analysis the VM was assigned a numerical value. These were as follows: CMV = 1, SIMV = 2, SV = 3. Alterations in the FiO_2 were dependent on the value of the PaO_2 following routine blood gas analysis. If the PaO_2 was less than 8 kPa then the FiO_2 was increased incrementally until this was corrected. Similarly, if the PaO_2 was above 10 kPa then the FiO_2 was decreased incrementally to maintain a value of between 8 and 10 kPa. Values for all the parameters were obtained immediately prior to and as close as possible to the end of the CAVH period. As a number of patients died while CAVH was still in progress, assessment was made by taking the last available value. The A-aDO_2 was calculated by:

$$\text{A-aDO}_2 = \left((94 \times \text{FiO}_2) - \frac{\text{PaCO}_2}{0.8} \right) - \text{PaO}_2 \ .$$

Arteriovenous access was established either via the femoral vessels or a Scribner forearm shunt. The femoral vessels were cannulated with 10 FG Desilet silicone catheters (Vygon). In the majority of patients a Fresenius AV 600 filter was used in conjunction with its disposable CAVH lines. These were flushed and primed with 2 l of heparinized saline (2000 IU/l heparin) and connected to the patient. Prior to the commencement of therapy baseline activated partial-thromboplastin time (APTT) and clotting block measurements were obtained, and a loading dose of heparin of 20 IU/kg body weight was given either via the integral heparin line or the infusion port on the arterial side. A maintenance infusion of 10 IU/kg was administered and adjusted according to the clotting times, which were kept at twice the baseline value.

The priming fluid was infused into the patient at the initiation of treatment unless fluid balance was critical. Free-drainage of filtrate was allowed in all cases, with the collecting bag being kept well below the filter to maximize the effects of negative pressure on filtration rate. The replacement fluid used was Hemofiltrasol 22 (Gambro), a potassium-free solution with the following composition: Na 140 mmol/l, Ca 1.6 mmol/l, Mg 0.7 mmol/l, Cl 100 mmol/l and lactate 45 mmol/l.

Data are given as mean $\pm$ SD. The FiO_2, A-aDO_2, PF ratio and PEEP values were analyzed using a paired samples *t*-test, and the VM values using the Wilcoxon rank sum test.

Results

Thirteen patients satisfied the criteria for inclusion in the assessment group and a total of 14 different haemofiltration episodes from these patients were subsequently analyzed. Demographic data along with details of diagnosis, severity of illness, duration of stay and outcome are shown in Table 2. The mean total number of episodes of organ systems failure was 3.9 per patient, compared with a figure of 3.5 for the mean number of different organ systems to fail during the period of ICU stay. The commonest systems to fail were the cardiovascular and respiratory systems (both 29% of the total number of different organ systems to fail), closely followed by the kidney (27%). All patients suffered failure of these 3 systems at some time during their stay. There was a mean of 1.4 episodes of organ systems recovery during the same period, and this was usually the cardiovascular system (44%). There were 4 episodes of respiratory system recovery (22%). General surgical patients with surgery-related problems, were those most commonly filtered (46% and 38% respectively).

The main indication for CAVH was acute renal failure (77%) and only 2 patients were filtered specifically for ARDS, though as previously mentioned all patients at some time suffered renal system failure. Arteriovenous access was established via the femoral route in all but one of the patients. The mean commencement time of treatment was 4.4 (SD 4.1) days after admission and the mean duration of filtration was 9.6 (SD 4.3) days. An average of 23.75 (SD 9.50) l of ultrafiltrate was removed each day, allowing the daily positive fluid balance to drop from 3710 (SD 2357) ml to 689 (SD 997) ml. The mean number of filters used was 6.9 (SD 5) with a maximum of 17. All patients received total parenteral nutrition (TPN) during their stay and the mean commencement time of TPN was 4.1 (SD 1.8) days after admission.

The pre- and end of haemofiltration values for the respiratory variables other than VM are outlined in Table 3. As the PF ratio is an exponential function the natu-

Table 2. Demographic and ICU data

Patient	Sex	Age	Admission diagnosis	Apache score	Duration of ICU stay (days)	No. of OSF	No. of OSR	Outcome
1	M	61	Pneumonia/RF/ARF	30	7	3	0	D
2	M	70	Ruptured AAA	26	10	3	0	D
3	F	63	Laparotomy for peritonitis	18	19	5	3	D
4	M	74	Ruptured AAA	24	14	4	1	D
5	M	54	Leaking small bowel anastomosis	14	16	4	1	D
6	M	17	Multiple trauma	23	33	4	3	D
7	M	48	Hepatic coma/septicaemia	35	14	5	0	D
8	M	17	Multiple trauma	16	27	3	2	D
9	M	31	Multiple trauma	10	17	3	1	D
10	M	72	Small bowel perforation	27	10	3	3	S
11	M	18	Diabetic ketoacidosis/pneumonia	31	8	3	1	S
12	M	54	Multiple trauma	11	34	3	1	S
13	F	50	Staphylococcal septicaemia	12	32	3	2	D

AAA, abdominal aortic aneurysm; ARF, acute renal failure; D, died; OSF, organ systems failure; OSR, organ systems recovery; S, survived

ral log of its value was calculated and used for the statistical analysis. There was a significant change in the values of PF ratio and VM ($p<0.05$), and FiO_2 and A-aDO_2 ($p = 0.001$) following the period of haemofiltration. The mean PEEP value remained unchanged. Figure 1 shows the individual pre- and end of treatment values for A-aDO_2, FiO_2 and PF respectively. Prior to treatment 13 patients were on CMV mode and 1 patient was on SIMV mode. At the end of treatment only 8 patients were on CMV mode, 2 were on SIMV mode and 4 patients had been weaned to spontaneous ventilation.

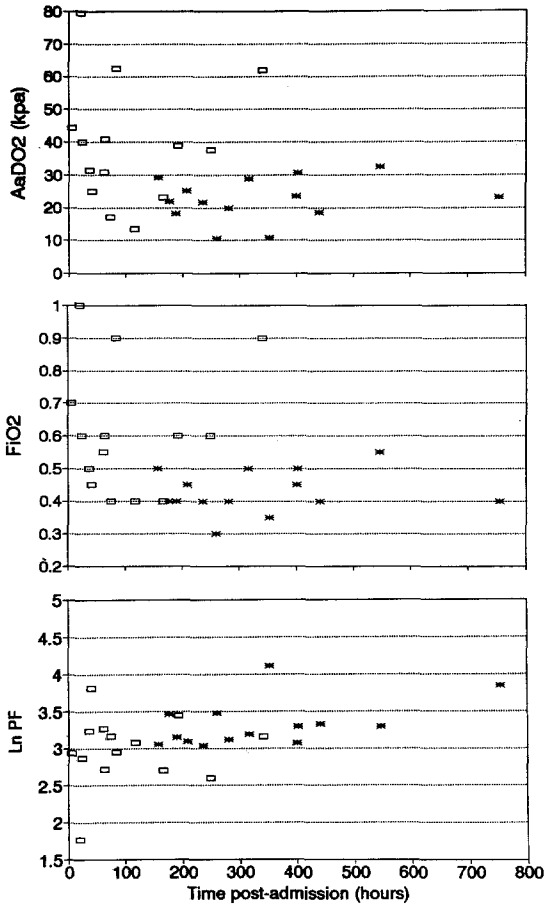

Fig. 1. Pre-treatment (□) and end of treatment (*) values for $AaDO_2$, FiO_2 and ln PF

The calculated mortality of the assessment group was 77%. This is slightly more than the overall mortality of 72.5% for all patients undergoing CAVH in Nottingham. Of the 10 patients who died, 7 underwent post-mortem examination. Respiratory system pathology was given as the cause of death in 3 cases, and as an associated condition in a further 3. Thus only 1 patient had no pathological evidence of respiratory system disease, the cause of death being coronary thrombosis (Table 4).

Morbidity from haemofiltration was uncommon. Of the 40 patients to undergo CAVH only 2 experienced complications directly attributable to the procedure. One developed an arterial embolus that required surgical removal; the second developed a large groin haematoma following the removal of the arterial cannula, which required surgical exploration.

Discussion

Multiple organ systems failure occurs in about 40–50% of ICU patients following a variety of primary insults [1–5]. The respiratory system is commonly involved, but irreversible respiratory failure per se is responsible for death in only about 15% of cases [7]. However, the presence of ARDS does appear to increase greatly the risk of

Table 3. Respiratory function data before and after therapy (mean ± SD)

	Pre-therapy	End of therapy
FiO_2	0.60 ± 0.18	0.43 ± 0.07[a]
A-aDO_2 (kpa)	37.5 ± 17.3	22.5 ± 6.7[a]
PaO_2/FiO_2	22.0 ± 9.4	27.4 ± 7.1[b]
PEEP (cmH_2O)	4.8 ± 4.75	4.8 ± 3.0

[a] $p = 0.001$ (pre-therapy vs. end of therapy)
[b] $p<0.05$ (pre-therapy vs. end of therapy)

Table 4. Postmortem results

Patient	Cause of death	Associated conditions
1	Massive intracranial haemorrhage	Hepatic necrosis RF due to hepatorenal syndrome Lobar pneumonia
4	Massive retroperitoneal haemorrhage	Ruptured aortic aneurysm Coronary thrombosis and IHD
5	Peritonitis	Ulcerative colitis ARDS
6	Respiratory failure	Pulmonary fibrosis ARDS Shock
7	Acute tubular necrosis	ARDS Acute prostatitis Bronchopneumonia
8	Cardiopulmonary failure	Multiple injuries
9	ARDS and bronchopneumonia	Severe chest trauma

ARDS, adult respiratory distress syndrome; IHD, ischaemic heart disease; RF, renal failure

the patient developing the sepsis syndrome, which in this situation is the leading cause of death [5–7]. The combination of respiratory failure due to ARDS and infection leads to MOSF twice as often as ARDS alone, and in 50% of these patients the source of that infection is the lungs [6, 7]. Clearly respiratory failure is an important cause of morbidity and subsequent mortality in adult ICU patients, so there is a need to concentrate support on this system throughout their stay.

The use of CAVH in the management of this group of patients was conceived by Kramer et al. in 1980 [20]. Since then there have been several studies demonstrating the effectiveness of CAVH in aiding the manipulation of fluid balance in ICU patients with acute renal failure [21–27]. Direct and indirect improvements in cardiovascular and respiratory function have been demonstrated [8–11, 13–17], along with an improved ability to provide adequate nutritional support particularly in hypercatabolic patients [28]. There is also evidence to suggest that this and other extracorporeal techniques, when used in conjunction with conventional therapies, may lead to clinical improvement and a reduced overall mortality in MOSF [26, 27, 29]. The mechanism by which CAVH may bring about this improvement remains unclear, but it probably involves the removal of complement activating fractions, vasoactive peptides, and middle molecular weight mediators of lung injury from the circulation [8, 11, 13].

The results of this study demonstrate that an improvement in respiratory function may occur following a prolonged period of intense haemofiltration. More dogmatic statements concerning the responsibility of CAVH for the improvements seen cannot be made in view of the retrospective nature of the study and the lack of any control group. We felt that using the remaining group of patients for this purpose would have been inconsistent as their respiratory parameters were measured over a considerably shorter time period. The reason for this improvement is not clear, but it may have been due to the better control of fluid balance achieved with the commencement of CAVH. The mean daily fluid balance dropped from 3710 ml to 689 ml. This may in turn have had an effect on reducing extravascular lung water (EVLW) with a subsequent improvement in respiratory function. Normally such improvements occur in situations of gross fluid overload when CAVH removes several litres of excess fluid over a short period of time [14]. However, there has been a report of improvement occurring with a continuing net positive daily fluid balance [11]. We were unable to obtain an adequate series of serum albumin concentrations to assess if they were likely to have had an effect on EVLW.

Disappointingly, despite the improvement in respiratory function obtained the overall mortality of the group remained high. This was probably a reflection of persistently poor lung function, resulting in continued ventilator dependence, in a group of patients who were already desperately ill. Of the 4 episodes of respiratory systems recovery to occur, only one occurred in a non-survivor, and they subsequently required re-ventilation. Chronic respiratory system pathology in the non-survivors was confirmed by the post-mortem findings and this is consistent with those of previous studies [6, 7]. A similar retrospective analysis by Koller et al. showed that the greatest improvement in respiratory function and mortality occurred in younger patients with isolated, acute pulmonary dysfunction [15]. Haemofiltration appeared to be less effective in treating patients with concomitant renal failure [15]. This may be a reflection of the different populations of patients treated, the latter group having a higher proportion of sicker post-surgical patients. A more selective study by Maritano et al. involving patients with ARDS demonstrated CAVH to be effective in improving the A-aDO_2 and PaO_2 at a constant FiO_2 [16]. They postulated that CAVH had brought about this improvement by reducing interstitial lung water and alveolar oedema [16]. It may be that haemofiltration is more effective in treating acute permeability-related deteriorations in lung function, and less capable of influencing the eventual outcome when the more chronic, infection-related changes associated with end-stage ARDS are present. Certainly the dramatic improvements in respiratory function seen in patients with cardiogenic and high microvascular permeability pulmonary oedema treated with CAVH seem to support this [8, 13, 14]. The close relationship between ARDS, sepsis and mortality suggests that CAVH may be more important in preventing the development of these chronic changes, than in treating them once they have occurred.

The low complication rate of CAVH amongst our group of patients confirms the findings of earlier studies [21, 24, 26]. However the experience of Klehr et al. suggests that significant morbidity does become apparent when the duration of filtration is increased [17]. In their group of 182 patients the mean duration of treatment was just over 18 days and they recorded a total of 69 complications (38%). Nearly half of these were thromboses and stenoses (19%). Other significant complications included bleeding problems (12%), infections (6%), and discon-

nections (2%). The mean FiO_2 dropped from 0.64 to 0.37% during treatment, suggesting an improvement in respiratory function with filtration. Unfortunately the mortality rate remained high at 78% despite this effect, indicating that factors other than an objective improvement in respiratory function may have a greater influence on eventual outcome [17]. Certainly co-existant acute renal failure carries a very poor prognosis [3, 5, 28, 30, 31].

In summary, our study confirms the finding of previous studies examining the effect of CAVH on respiratory function. It can be stated that patients with MOSF undergoing prolonged and efficient CAVH demonstrated an improvement in respiratory function. Despite this, overall mortality remains high and persistent respiratory system pathology is a common and significant finding on post-mortem examination. Further prospective analysis of CAVH in this role is warranted given its relative ease of use and safety in this situation, and our reliance on mainly supportive techniques to manage severe respiratory failure in the ICU.

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