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A randomized comparison of total extracorporeal CO_2 removal with conventional mechanical ventilation in experimental hyaline membrane disease

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Abstract. Apnoeic oxygenation (AO) combined with extracorporeal CO_2 removal ($ECCO_2R$), using veno-venous perfusion across a membrane area of 0.1 m^2 has been shown to be feasible in six healthy anaesthetized rabbits. In a further twelve rabbits, $ECCO_2R$ has been randomly compared with conventional mechanical ventilation (CMV) following saline lavage to induce respiratory failure. Blood gases were maintained for up to 6 h within the same range ($PaO_2 = 8-20$ kPa, $PaCO_2 = 4-6$ kPa) in two groups of six by varying airway pressures and the oxygen fraction delivered either to the membrane lung ($ECCO_2R$ group) or to the ventilator (CMV group). The influence of single hourly sustained inflations (SI) on oxygenation was studied. $ECCO_2R$ subjects remained stable and survived. CMV subjects deteriorated and had 80% mortality. Hyaline membranes were absent from $ECCO_2R$ subjects and present in all CMV subjects. The response to SI suggests that a lung volume recruitment is maintained during AO for up to 1 h but is ineffective during CMV.

Key words: Extracorporeal gas exchange – Membrane lung – Apnoeic oxygenation – Hyaline membrane disease

Extracorporeal gas exchange is now established as a mode of therapy for the human newborn with severe acute respiratory failure [1] and promises to reduce mortality in severe adult respiratory distress syndrome (ARDS) [2]. There are two components to this gas exchange: the transfer of oxygen into, and CO_2 out of, the extracorporeal blood. The extent to which these two largely independent components contribute to the success of the technique depends upon its indications and remains to be clarified.

Where oxygenation is the predominant aim of the technique, the term extracorporal membrane oxygenation (ECMO) prevails. A randomized trial of ECMO combined with conventional ventilation was found not to improve mortality in severe ARDS [3], in contrast to the success of ECMO experienced in managing the newborn [4]. Where CO_2 elimination is the main aim, the term extracorporeal CO_2 removal ($ECCO_2R$) is adopted. The Japanese have introduced the term extracorporeal lung assist (ECLA) which emphasizes neither oxygen nor CO_2 transfer [5].

Because the oxygen content of blood leaving an artificial membrane lung cannot exceed the physiological content of arterial blood, the fraction of the body's oxygenation contributed by the membrane lung will be approximately equal to the fraction of the cardiac output it receives. Total ECMO requires the total cardiac output. In contrast to this, blood can be depleted of CO_2 to well below physiological values, such that the total elimination of CO_2 can be accomplished from a blood flow of only 20–30% of the cardiac output. This is technically easier to achieve than total ECMO. At these flows, the extracorporeal lung can provide no more than 20–30% of the body's oxygen requirement, but does permit the cessation of ventilation to the patient's own lungs, through which apnoeic oxygenation (AO) provides the remaining 70–80% of the oxygen uptake.

There is reason to believe that apnoea can facilitate oxygenation of sick lungs when compared with conventional mechanical ventilation (CMV). Early respiratory failure is characterized by an abnormally large hysteresis in the pressure-volume characteristics of the lungs [6] in which a large inflation pressure is needed to recruit alveoli which subsequently require a much lower pressure to keep them patent. By preceding a period of apnoea at a low distending pressure by a single large inflation, the recruitment and

maintenance of lung volume is predicted to provide similar oxygenation at a lower mean airway pressure than can be achieved using CMV. The probable value of volume recruitment by a single inflation of the lungs is strongly supported by experience with high frequency ventilation [7].

There is also reason to believe that the immobility of sick lungs during apnoea will reduce or eliminate the barotrauma associated with CMV. The evolution of hyaline membranes is associated with repeated excursions of the pressure-volume hysteresis [8] which are avoided during AO.

In this study we examined the double hypothesis that AO with low flow $ECCO_2R$ facilitates oxygenation via the subject's own lungs and reduces barotrauma. We adopted a lung lavage model of respiratory failure introduced by Lachmann et al. [9]. The model is characterized by surfactant deficiency and closely resembles the infant respiratory distress syndrome (IRDS). The study is consequently relevant to the question of whether $ECCO_2R$ can replace ECMO in the management of IRDS, permitting an emphasis on oxygenation via the patient's *own* lungs rather than via the extracorporeal membrane lung.

Preliminary results of this study have been presented to the 33 rd meeting of the American Society for Artificial Internal Organs, New York, 1987.

Material and methods

The study was divided into two parts. In part 1, we set out to establish the feasibility of $ECCO_2R$ combined with AO in six healthy rabbits over 6 h each. In part 2, we used a prospective randomized trial in twelve rabbits to compare $ECCO_2R$/AO with CMV over a 6 h period, following induction of respiratory failure.

Anaesthesia and monitoring

Eighteen New Zealand rabbits with a mean weight of 2.5 kg (range 1.8–3.2 kg) were premedicated with Hypnorm (fentanyl 0.315 mg ml^{-1}, fluanisone 10 mg ml^{-1}; Janssen) 0.3 ml kg^{-1} i.m. Anaesthesia was induced 20 min later with halothane 0.5–2.0% in oxygen via an Ayre's T-piece with mask and bag. Tracheostomy was performed and a 2.5–3.0 mm i.d. endotracheal tube introduced 10–20 mm into the trachea. Artificial ventilation was commenced. Animals lay supine throughout the experiments on a warming blanket.

A 23 gauge intravenous cannula was introduced into an ear vein and an infusion of Hartmann's solution begun (enriched with potassium as required). Anaesthesia was maintained with an infusion of pentobarbitone 6–12 mg h^{-1} and muscle relaxation achieved with alcuronium 0.5–1 mg h^{-1}. Arterial blood pressure was monitored from a 19 gauge cannula advanced into a carotid artery. This was also used for blood sampling. A urinary catheter (4–6 FG) was passed.

In addition to the arterial pressure, we monitored airway pressure, rectal temperature, urine volume and, in some experiments, electrocardiograph and train-of-four twitch response. Arterial samples (0.2 ml) were analysed for blood gases and pH using an ABL2 laboratory (Radiometer, Copenhagen). Activated clotting time was measured on 0.4 ml samples (Hemochron, International Technidyne Corp., Edison, N.J.); plasma sodium and potassium were measured electrochemically (Instrumentation Laboratory 501, Birchwood, Warrington, 0.2 ml), and haematocrit was obtained by centrifugation of a capillary tube of blood (0.05 ml).

Animals were infused with crystalloid at a rate of 5 ml kg^{-1} h^{-1} plus a sufficient volume to prevent a marked rise in haematocrit. Donor blood and/or Haemaccel (Hoechst) was given to replace sampling losses and treat hypotension below 70 mm Hg systolic pressure. Sodium bicarbonate was given to correct metabolic acidosis. Animals were sacrificed after 6 h, using a bolus of 180 mg pentobarbitone.

Extracorporeal circuit

Following heparinization (250 iu kg^{-1}), cannulae (1.5–2.0 mm i.d.) were introduced into the internal jugular veins: on the right a cannula for drainage was passed into the inferior vena cava or right atrium; on the left a cannula for return flow was advanced 10–20 mm into the vein. Cannulae were silicone rubber or polyurethane coated. Those for drainage carried lateral ports.

The membrane lungs were of a form previously described [10], differing only in respect to the number of parallel blood channels incorporated. For these experiments we adopted a two channel lung with a gas exchange area 0.097 m^2 of dimpled microporous polypropylene membrane, across which secondary flows were generated in the blood phase with a pulsatile Reynolds number (Re_p) of either 9 or 70. Re_p is a dimensionless measure of the intensity of the sinusoidal oscillations in blood flow which were imposed upon an otherwise steady flow of blood through the lung [10].

In part 1, blood flowed from the subject to a collapsible silicone rubber reservoir (20 ml) situated 0.6 m below the animal, using gravity drainage as found effective in dog perfusion [11]. The total circuit volume was 80 ml. For part 2, we modified our circuit to reduce the variability of circuit volume by eliminating this reservoir, mounting the whole bypass circuit at the same elevation as the subject, and reducing circuit volume to 60 ml. In part 2, drainage was to a semirigid silicone rubber reservoir (2 ml).

The circuit comprised, in the direction of flow, the reservoir with pump cut-off, an occlusive roller pump and the membrane lung.

Components were interconnected with silicone rubber tubing 2.5 mm i.d. Temperature control was achieved by warming the environment of the membrane lung. Blood flow was estimated from the prior calibration with blood of the occlusive pump. The circuit was primed with blood from either one or two litter mates of the main subject, following Hypnorm premedication, halothane anaesthesia and intravenous administration of 2000 iu (part 1) or 1000 iu (part 2) of heparin. Heparin was administered to the main subject with the aim of maintaining ACT 300–500 s (part 1) and 200–300 s (part 2).

Part 1

In six healthy rabbits total $ECCO_2R$ was established with apnoea for 6 h.

A constant airway pressure (CAP) of 7 cm H_2O was applied by delivering to the endotracheal tube pure dry oxygen via a one way valve and calibrated variable-orifice flow meter, from a reservoir receiving 200 ml min^{-1} of oxygen and held at constant pressure with a PEEP valve (AMBU International, Copenhagen).

The membrane lung was supplied with a concentration of 50% oxygen in nitrogen, measured at inlet (Vickers Medical 251, Basingstoke, U.K.) Gas flow was 2 l·min^{-1} ATP, and entered the lung at 50 mm Hg below ambient pressure. Re_p was 70. Blood flow was adjusted to maintain the arterial CO_2 partial pressure (P_{aCO_2}) within the target range 4–6 kPa.

Part 2

In twelve sick rabbits $ECCO_2R$/AO was randomly compared with CMV over a 6 h period.

After tracheostomy, subjects were ventilated with a positive end expiratory pressure (PEEP) of 3 cm H_2O, peak pressure (PP) 20 cm H_2O, inspiratory: expiratory (I:E) ratio 1:2, and inspired oxygen fraction (FiO_2) 0.5, using a time-cycled, pressure-limited ventilator (Bear Cub, Intermed, Riverside, California). The respiratory gas flow ($8\,l\cdot min^{-1}$) was humidified (Intermed WE 530) and the ventilatory rate adjusted to achieve a $PaCO_2$ between 4 and 6 kPa.

Following cannulation and priming of the extracorporeal circuit, FiO_2 was raised to 1. Perfusion was established *without gas flow to the membrane* lung at 60 ml min^{-1}, $Re_p = 9$ for 20 min. Blood gases were measured immediately before commencing perfusion, at 5 min, and at 20 min to look for any hypoxic effect of perfusion itself, in the absence of gas exchange. The flow was then reduced to 20 ml min^{-1} prior to the lavage procedure.

Lung compliance was measured before saline lavage. Using a hand-held syringe, 10 ml boluses of oxygen were introduced stepwise into the endotracheal tube (after allowing full passive expiration) every 2 s up to a maximum airway pressure of approximately 35 cm H_2O, and then withdrawn in similar steps.

The subjects' lungs were lavaged with normal saline (0.9%) at 37 °C using 20 ml kg^{-1}. The saline was delivered, after full passive expiration, by syringe into the endotracheal tube over 15 s or at a rate so as not exceed an airway pressure of 35 cm H_2O. The saline was withdrawn by syringe over a further 20–30 s. Lavages were repeated at 10 min intervals until a minimum of three had been performed and the next PaO_2, measured 5 min after a lavage, was less than 50 kPa on the ventilation described above. At this end-point, a further lung compliance measurement was made.

Subjects were immediately randomized to either CMV or $ECCO_2R$/AO by drawing from a lottery of two sets of six assignments. Our approach was to aim to maintain *similar blood gases* within both groups for up to 6 h, and compare the two groups with respect to survival, changes with time in airway inflation pressures, delivered oxygen fractions, lung compliance, and postmortem lung histology.

CMV subjects were managed for up to 6 h as follows. Ventilation was begun with PEEP at 3 cm H_2O, PP 20 cm H_2O, I:E ratio 1:1 and a rate to maintain $PaCO_2$ 4–6 kPa. FIO_2 was increased as required to 1 and thereafter PEEP increased from 3 cm H_2O to maintain PaO_2 8–20 kPa, the *target range of PaO_2 for both treatment groups*. The respiratory rate was adjusted to maintain $PaCO_2$ 4–6 kPA, the *target range of $PaCO_2$ for both groups* (up to the maximum rate of 130 bpm which could be achieved with the ventilator). The peak airway pressure was made a function of respiratory rate according to Table 1. Where this ventilatory protocol did not permit maintenance of *both* PaO_2 and $PaCO_2$ in the specified ranges, PaO_2 was given priority. In all CMV subjects the extracorporeal perfusion was maintained throughout at a flow of 20 ml min^{-1}, with $Re_p = 9$, *without* gas flow to the membrane lung.

Table 1. The protocol for relating peak airway pressure to respiratory rate for subjects allocated to CMV

Respiratory rate (min^{-1})	Peak airway pressure (cm H_2O)
0–30	20
30–45	25
45–60	30
over 60	35

$ECCO_2R$/AO subjects were managed for up to 6 h as follows. Apnoea was instituted, initially at a CAP of 7 cm H_2O as described for part 1. PaO_2 was kept in the target range of 8–20 kPa by first varying the oxygen fraction (F_{MLO_2}) in the gas supplying the membrane lung ($2\,l\cdot min^{-1}$ ATP as part 1) and then the CAP. $F_{ML}O_2$ was increased as required from a minimum of 0.21 (air) to 1 and thereafter CAP increased from 7 cm H_2O to maintain PaO_2 8–20 kPa. The extracorporeal blood flow was adjusted to maintain $PaCO_2$ 4–6 kPa with $Re_P = 70$ throughout.

In both groups, hourly measurements of lung compliance were made, followed immediately by a sustained inflation (SI) to 35 cm H_2O with oxygen for 10 s. The hourly performance of the compliance measurement and SI constituted the only deviation from absolute apnoea in the $ECCO_2R$ group. Measurements of blood gases were made at intervals of between 3 and 15 min to permit frequent adjustments to the target ranges and to follow the effects on PaO_2 of SI. Airway pressure measurements were recorded every 15 min.

In the event of a technical failure of pulmonary ventilation or extracorporeal gas exchange, we preplanned to change to the second ventilatory mode rather than terminate the experiment. Two such failures occurred, one in each of the two treatment groups.

At post mortem, the lungs from both groups were prepared for histology as follows. The right lung was inflated, via the main bronchus, with oxygen to a pressure of 20 cm H_2O. The bronchus was then tied off, severed proximal to the tie, and the lung immersed in 10% formal saline. The left lung was then inflated via the main bronchus, this time with 10% formal saline to a pressure of 20 cm H_2O, similarly tied and severed, and immersed in formal saline. One of the authors (MSD) examined three sections from each lung under light microscopy whilst unaware of the allocations. Each subject was scored for the absence (0) or presence (1) of each of the three features oedema, haemorrhage and congestion; also for the absence (0) or severity (1 or 2) of each of the two features polymorphonuclear leucocytes and hyaline membranes.

Statistical analysis

All data are presented as means ± sample standard deviation unless otherwise stated. Student's *t*-test was used for comparison of the differences between means of the parametric data. Wilcoxon's rank sum test was used for the non-parametric histological data.

Results

Part 1

In six healthy rabbits blood gas values remained stable over 6 h: $PaO_2 = 28.7$ (± 12.3) kPa, $PaCO_2 = 4.49$ (± 1.11) kPa.

The extracorporeal blood flow required for total $ECCO_2R$ was 67 ± 17 ml $\cdot min^{-1}$ ($n = 6$ subjects, hourly readings) and the endotracheal oxygen consumption was found to be 20.5 ± 7.4 ml(ATP) min^{-1} ($n = 3$ subjects, hourly readings). The mean values correspond approximately to a blood flow of 25 ml $\cdot kg^{-1} min^{-1}$ and a pulmonary oxygen uptake of 8 ml(ATP)$kg^{-1}min^{-1}$. Blood gas and pH measurements from samples at inlet (i) and outlet (o) of the membrane lung ($n = 6$ subjects, single readings) gave the following values (kPa):$PiCO_2 = 2.9 \pm 0.6$, $PiO_2 = 12.8 \pm 12.4$, $pH_i = 7.57 \pm 0.13$; $PoCO_2 = 1.8 \pm 0.2$, $PoO_2 = 41.9 \pm 13.3$, $pH_o = 7.74 \pm 0.12$.

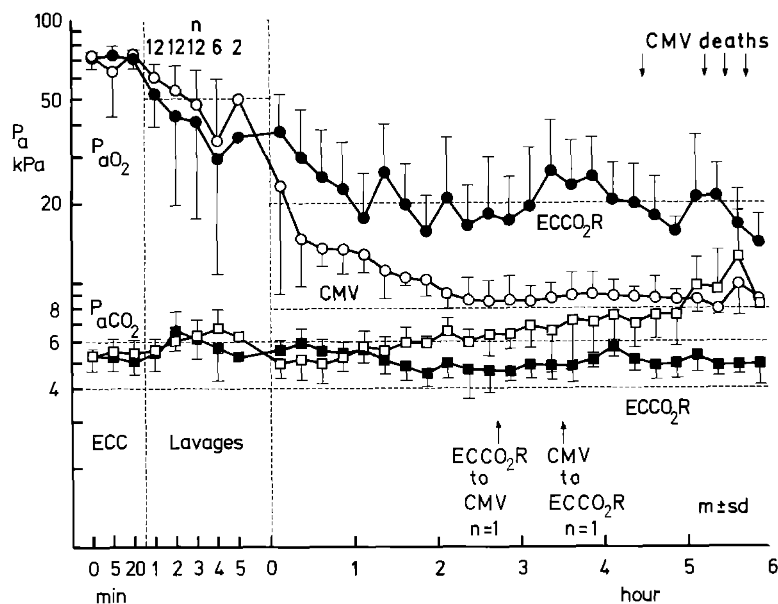

Fig. 1. Arterial partial pressures of oxygen PaO_2 (*circles*) and CO_2 $PaCO_2$ (*squares*) for twelve sick subjects undergoing either CMV (open symbols) or $ECCO_2R/AO$ (*closed symbols*) for up to 6 h. Values are given prior to, and during 20 min of extracorporeal circulation (ECC) without gas flow to the membrane lung and with $FiO_2 = 1$; also following each of between three and five lung lavages, prior to randomization to one of two groups of six. The target ranges of PaO_2 (8–20 kPa) and $PaCO_2$ (4–6 kPa) are depicted by *dashed lines*. Times of changes of ventilatory management for one subject in each group are marked with *arrows*, as are times of death of four CMV subjects

Part 2

Figure 1 shows the blood gas values before ECC, during 20 min ECC without gas exchange, following each of between three and five lavages, and during the subsequent 6 h. Application of a paired t-test to both individual groups of six and the total of twelve subjects reveals no significant difference, even at the 0.1 level, between PaO_2 prior to ECC and at 5 and 20 min ECC.

Up to five lavages were required to reduce PaO_2 to below 50 kPa on $FiO_2 = 1$. The mean and distribution was identical in both groups: 3.67±0.82. The lavages alone increased the required ventilatory rate from 17.1±2.9 to 34.2±5.1 min^{-1} ($n = 12$), and this doubling of rate corresponded with an approximate halving of lung compliance measured at a volume of 20 ml (see below).

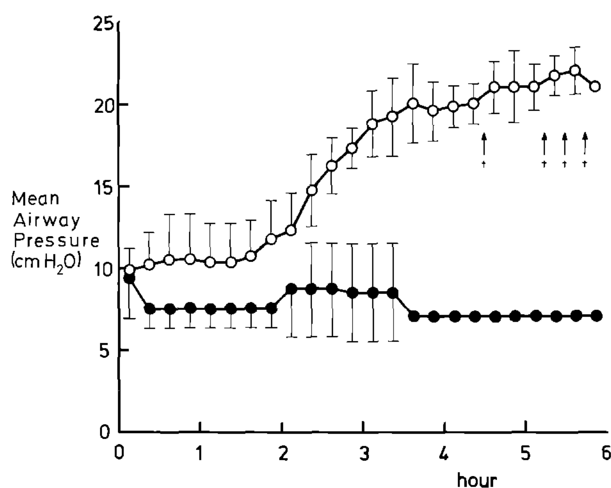

Fig. 2. Mean airway pressures required over 6 h in two groups of six subjects during CMV (*open circles*) or $ECCO_2R/AO$ (*closed circles*), to maintain blood gas values in the range PaO_2 = 8–20 kPa, $PaCO_2$ = 4–6 kPa. The times of death of four CMV subjects are marked with *crosses*

Only one subject survived CMV for 6 h. Five subjects survived $ECCO_2R/AO$ for 6 h. One from each group experienced a technical failure of the ventilatory mode and was transferred successfully to the alternative mode. That from $ECCO_2R/AO$ to CMV (2.75 h) died at 4.75 h; that from CMV to $ECCO_2R/AO$ (3.5 h) survived to 6 h.

Figure 2 shows the mean airway pressures in the two groups. In the CMV group the measurements are derived from the ventilator; in the $ECCO_2R/AO$ group the measurements exclude pressures generated during SI.

Figure 3 shows the oxygen fractions: FiO_2 in the CMV group, $F_{ML}O_2$ in the $ECCO_2R/AO$ group. In the CMV group we can recognize three regions on these graphs. During the first 2 h period, airway pressures remained fairly constant as the FiO_2 had to be raised gradually to 1. PEEP remained close to 3 cm H_2O during this period. In the second 2 h period, elevation of airway pressures was required to maintain PaO_2 in the required range despite FiO_2 being equal to 1. In the third 2 h period, four deaths occurred from circulatory collapse in the presence of high PEEP around 15 cm H_2O and high mean airway pressures of around 20 cm H_2O (all CMV subjects required PP = 35 cm H_2O after 3 h).

In the $ECCO_2R/AO$ group the protocol generated a much greater variability in FiO_2 than in the CMV group. Consequently, standard error of the mean is

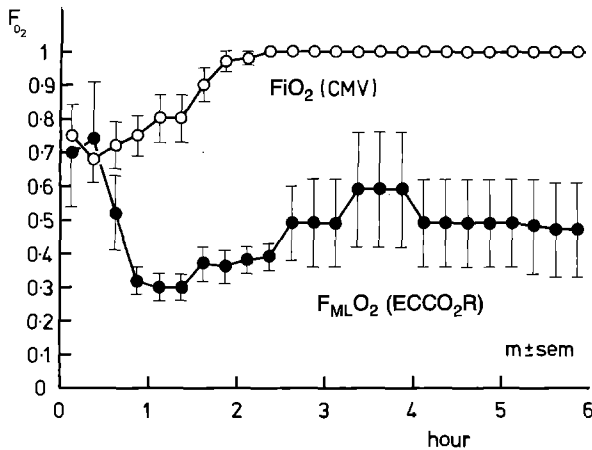

Fig. 3. Delivered oxygen fractions required over 6 h in two groups of six subjects during CMV (*open circles*) or $ECCO_2R$/AO (*closed circles*). $F_{ML}O_2$ is the oxygen fraction delivered to the membrane lung. *Bars* depict standard error of the mean

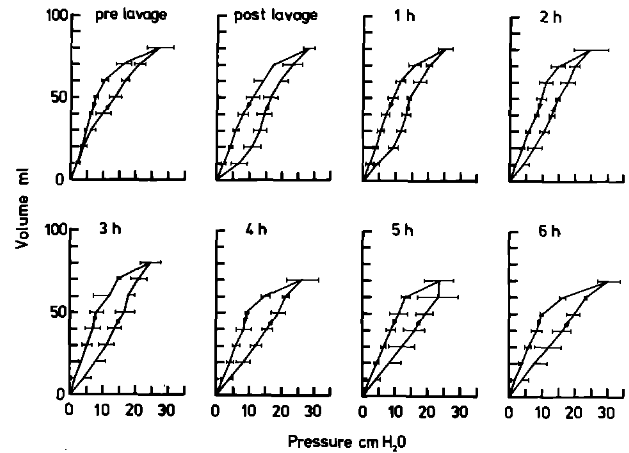

Fig. 5. Pressure volume loop, as Figure 4, but for the $ECCO_2R$/AO group

presented in Figure 3 instead of standard deviation. The pattern of behaviour was as follows. Four subjects retained the minimum permitted airway pressure of 7 cm H_2O for all but the first 15 min of the 6 h period. During the first hour, the mean $F_{ML}O_2$ fell rapidly from a maximum of 0.74 and stabilized at around 0.5 in the second half of the experiment.

Pressure-volume loops generated before and after lavage, and hourly thereafter are presented for the CMV group in Figure 4 and the $ECCO_2R$/AO group in Figure 5. The effect of lavage is to introduce a 'knee' into the inflation limb of the loops without markedly changing the deflation limb. In the CMV subjects there is a decrease with time in steepness of both the inspiratory and expiratory limb. Since compliance is proportional to the gradient of these curves, these changes represent a decrease in both inspiratory and expiratory compliances with time. The knee introduced by lavage is not eliminated by CMV.

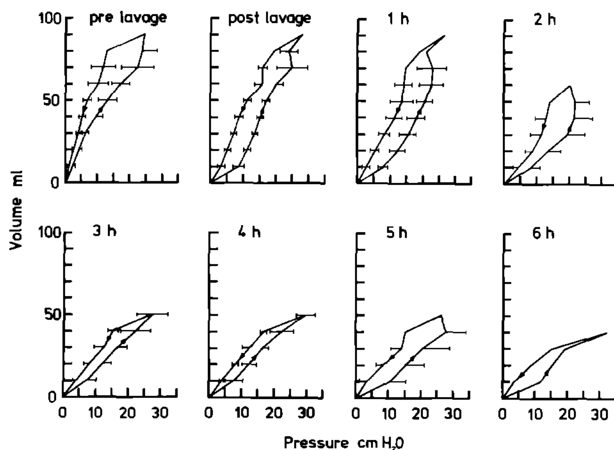

Fig. 4. Pressure volume loops measured before and after lavage, and hourly thereafter in the CMV group. Pressure (cm H_2O) is plotted horizontally and volume (10 ml steps) is plotted vertically. All loops followed an anti-clockwise direction with 2 s between measurements (see text). Loops have been closed at the origin, even though final expiration generated negative pressure in some subjects. *Bars* depict sample standard deviations

Contrast these findings with the $ECCO_2R$/AO group (Figure 5). Here, lavage has a similar effect in introducing a knee to the inspiratory limb, but in this group the inspiratory and expiratory compliances do not decrease progressively with time. Moreover, the knee gradually disappears until at 6 h the inspiratory limb of the pressure-volume curve has become a straight line.

The effect of SI upon PaO_2 is shown in Figure 6. In both the CMV group (18 occasions) and the $ECCO_2R$/AO group (17 occasions) PaO_2 was sampled before SI and for intervals for up to 60 min following SI. The CMV group showed no benefit from the manoeuvre aimed at recruiting lung volume, and increasing PaO_2. In contrast to this $ECCO_2R$/AO showed an immediate doubling of PaO_2, with some elevation in PaO_2 maintained for up to 60 min.

We emphasize that in CMV subjects the SI to 35 cm H_2O for 10 s was followed immediately by momentary 1–2 s disconnection from the source of inflating pressure prior to reconnection to the ventilator. The airway pressure thus fell to zero briefly before reintroduction of PEEP. In $ECCO_2R$/AO subjects, the SI to 35 cm H_2O for 10 s was generated by inflation through the one-way valve (and flow meter), which formed part of the AO system. Consequently no passive expiration was possible, and airway pressure returned to its pre SI setting only as oxygen was taken up from the alveoli by pulmonary blood. The time required for this was noticed to be around 5 min. This was consistent with measurements of en-

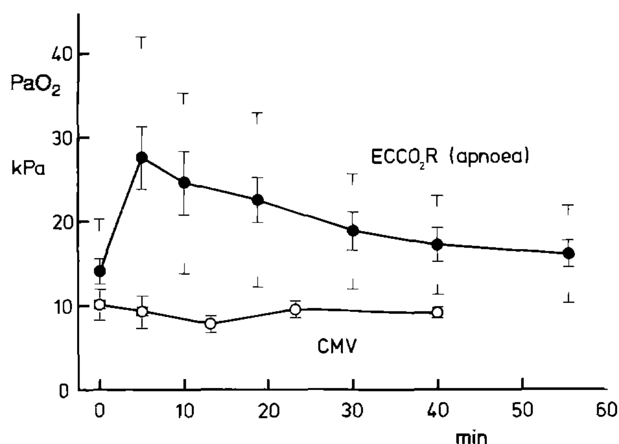

Fig. 6. Arterial oxygen partial partial pressure PaO_2 before, and at times up to 60 min following, sustained inflation of the lungs to 35 cm H_2O for 10 s with oxygen. Data points variably represent between 4 and 18 readings. *Bars* for both sample standard deviation and standard error of the mean are shown

dotracheal oxygen consumption in this group (15.9 ± 2.4 ml(ATP)min^{-1}, $n = 30$ readings) and the observation that inflation to 35 cm H_2O required approximately 80 ml of oxygen (Fig. 6): $80/15.8 = 5.1$ min.

The histological findings on light microscopy are summarized in table 2. The greatest differences observed were with regard to the presence of polymorphonuclear leucocytes, and the formation of hyaline membranes. Both features were pronounced in the CMV group; hyaline membranes were not seen in the $ECCO_2R$ group.

Finally, the blood flow required to maintain total $ECCO_2R$ was 67 ± 9 ml·min^{-1} ($n = 33$ readings), an identical mean to that found in part 1.

Table 2. Mean histological scores from light microscopy of the lungs, performed blind. Each group contains five subjects which completed the protocol without a change of ventilatory mode

		CMV	$ECCO_2R$
Congestion	(0–1)	0.2	0.4
Oedema	(0–1)	0.8	0.2
Haemorrhage	(0–1)	0.8	0.4
Polymorphs	(0–2)	1.8	0.4
Hyaline membrane	(0–2)	1.8	0
Total[a]	(0–7)	5.4	1.4

[a] Differences between means are significant exactly at the 0.01 level on Wilcoxon's rank sum test for unpaired samples (rank sum 15)

Discussion

Part 1 of the study demonstrated the feasibility of total $ECCO_2R$ in 2.5 kg subjects using venovenous perfusion across a membrane of area 0.1 m^2. The blood flow required corresponds to approximately 30% of the cardiac output we have measured in similar experiments in this laboratory at CAP 7 cm H_2O (200–250 ml·min^{-1}). Blood gas values at inlet to the membrane lung revealed a lower P_{CO_2} and higher P_{O_2} than would be expected for mixed venous blood. We take this to be evidence of recirculation of extracorporeal blood within the venous system, which reduces the efficiency with which the membrane lung extracts CO_2 for a given blood flow. The relatively close proximity in these experiments of both drainage and return cannulae to the right atrium is likely to have contributed to recirculation. We have found a femoral cannula difficult to introduce in the rabbit. In situations where its use is possible, more efficient $ECCO_2R$ is likely to be attainable, in relation to blood flow and size of membrane lung.

The circuit priming volume and the extracorporeal blood flow required were closely similar to those of Mook et al. [12] who used a microporous polypropylene hollow fibre membrane lung (0.5 m^2) to perform $ECCO_2R$ in rabbits ventilated at 2 breaths per minute. Jugular venous access was similarly used in their experiments.

Part 2 of the study confirms the addition of a third model of respiratory failure to those of fetal lamb prematurity [13] and meconium aspiration [14], in which $ECCO_2R$/AO has been found to yield a better outcome than CMV. Pesenti et al. [13] performed a controlled study using fetal lambs of 128–130 days gestation (term 145–147 days), having mean weight around 3.3 kg. Using a CAP of 10–15 cm H_2O over a mean duration of 31 h extracorporeal circulation, they achieved a weaning and survival rate of 90% in ten subjects allocated $ECCO_2R$. This contrasted with a survival of 29% in a group of seven subjects allocated to CMV at mean airway pressures in the range 9–13 cm H_2O. These workers apparently did not randomize their subjects. Their protocol was not designed to maintain any one respiratory parameter similar in both groups. All control deaths were from combined respiratory and metabolic acidosis rather than hypoxia. This brings into question the adequacy of the CMV as a comparison for results with $ECCO_2R$/AO, and is a reminder of the difficulty, in studies of this kind, of knowing in relation to which *unchanged* factors *changes* in therapy can be regarded as informative.

In a second model of respiratory failure [14], the Kolobow group randomized fetal lambs of 131–133

days gestation to receive either CMV alone, or CMV followed under certain criteria by $ECCO_2R$/AO, after instillation of sterile meconium into the lungs. 42% of 19 control subjects survived the protocol, compared with 69% of the group allocated possible $ECCO_2R$/AO. Furthermore, a population of subjects with severe respiratory failure was defined, in which the respective mortalities from CMV and $ECCO_2R$/AO were 100% and 60%. These workers emphasized the benefit of lung inflation to 15 cm H_2O to reinflate atelectatic lungs prior to AO at lower airway pressures.

In this study we attempted to minimize bias in our management of the control and treated groups by randomizing *after* induction of respiratory failure. All subjects were connected to an extracorporeal circuit, initially without gas flow to the membrane lung, so that the assigned ventilatory mode could be instituted *immediately* following randomization. The extracoporeal perfusion prior to, during, and following lavage in both groups was designed to control for any unforeseen effects of such perfusion alone. Kawino et al. [15] have, for example, recently made the striking discovery that depletion of polymorphonuclear leucocytes alone, in saline lavaged rabbits, can eliminate the formation of hyaline membranes and reduce the hypoxia associated with CMV. Alterations in white cell count during venovenous perfusion are known to occur in a system of this kind [11]. Only by subjecting both groups to the perfusion can we compare the effects of CMV and AO in isolation.

In addition to these constant factors, we chose to adopt an approach close to clinical practice, which aimed to maintain similar ranges of blood gas values in both groups. We experienced two difficulties in achieving this aim. Firstly, sustained inflations in the $ECCO_2R$/AO group frequently elevated PaO_2 to above 20 kPa (Fig. 6) for around 20 min. Since these were performed hourly (Fig. 1), a sizeable fraction of the 6 h experiment was occupied with a mean PaO_2 over 20 kPa. Secondly, a limitation of ventilator frequency at an I:E ratio of 1:1 to 130 bpm made it difficult to maintain $PaCO_2$ in the CMV group below 6 kPa in the final half of the experiment (Fig. 1). The resulting differences in blood gases between groups serve, however, to emphasize the beneficial effects of $ECCO_2R$/AO, rather than call into question the significance of the difference between the groups.

A beneficial and prolonged effect of SI upon oxygenation has been seen in studies comparing high frequency ventilation (HFV) with CMV [16, 17]. Kolton et al found the rise in PaO_2 after SI to be associated with a rise in lung volume at the same mean airway pressure [16]. This recruitment of lung volume could be maintained by HFV but was rapidly lost during further CMV after the SI. They interpreted this phenomenon to be exploitation of the pathological pressure volume hysteresis seen in early acute respiratory failure.

The same interpretation seems appropriate here. The mean CAP for the $ECCO_2R$/AO group was around 8 cm H_2O. On the inspiratory limb of the pressure volume loop of the $ECCO_2R$/AO group (Fig. 5), this pressure corresponds with a low inspired volume of around 20 ml. On the expiratory limb of the pressure volume loops, 8 cm H_2O corresponds with a volume of around 40 ml. Figure 6 suggests that an increase in lung volume, following an excursion up then down the pressure volume loop, can be maintained in part for up to 60 min during apnoeic oxygenation. If this interpretation is correct, the implications for the management of severe acute respiratory failure are far-reaching. The work of Matamis et al. [6] shows that increased hyteresis is an *early* feature of ARDS, suggesting that $ECCO_2R$/AO (and HFV) are likely to improve oxygenation most effectively when applied early in the course of the disease. Such a hypothesis is supported by the results of Mathe et al. [18], who found that a reduced duration of exposure to high FiO_2 was required in newborns with hyaline membrane disease exposed *early* (before 24 h) to PEEP lying above the knee of the inspiratory limb of the pulmonary pressure volume loop.

The question of alveolar oxygen toxicity arises during $ECCO_2R$. Kolobow et al. [19] have demonstrated equilibration during $ECCO_2R$/AO of alveolar nitrogen partial pressure P_AN_2 with membrane lung nitrogen partial pressure $P_{ML}N_2$. Assuming that both alveolar gas and membrane lung gas are saturated to the same extent with water vapour, and that $P_ACO_2 = PaCO_2$, it follows that P_AO_2 is related to $P_{ML}O_2$ by

$$P_AO_2 = P_{ML}O_2 - PaCO_2 \qquad [1].$$

Equation 1 is the rationale for our use of variable $F_{ML}O_2$ during AO as one factor in controlling blood gases, analogous to FiO_2 during CMV. The equilibrium represented by equation 1 is not rapidly achieved. Experience in dogs [20] shows the time constant to be of the order of 1 h. Consequently, this method of controlling P_AO_2 and hence PaO_2 can only be expected to be precise when apnoea is maintained for longer than 1 h.

For part 1 of this study $F_{ML}O_2$ was chosen to be 0.5, and $P_{ML}O_2$ can be estimated to have been 44 kPa on account of the subatmospheric pressure in the membrane lung gas supply. P_AO_2 is thus predicted by equation 1 to be approximately $44-5 = 39$ kPa. The mean measured PaO_2 was 28.7 kPa. this degree of

alveolar-arterial PO_2 difference is consistent with the presence of a normal pulmonary shunt in these healthy supine subjects. During part 2 of this study, $F_{ML}O_2$ reached a fairly steady mean close to 0.5 in hours 3–6. The hourly disturbance of nitrogen equilibrium by the performance of a compliance measurement will have detracted from the accuracy of equation 1 for these subjects, but the lower mean PaO_2 at this time ($\sim$ 20 kPa), than in part 1, is consistent with a larger pulmonary shunt.

The formation of profuse hyaline membranes after only 5 h of CMV in saline lavaged rabbits has been observed by Hamilton et al. [21), who observed a marked reduction in their severity following HFV. The absence of hyaline membranes in our $ECCO_2R$/AO group provides further evidence that repeated mechanical inflation of surfactant-deficient lungs is one step in the process leading to alveolar exudates. The finding that white cells are also essential for the formation of hyaline membranes raises tantalizing questions about the mechanism [15].

We conclude that, in surfactant depleted subjects, $ECCO_2R$ combined with apnoeic oxgenation can prevent the deterioration of lung function and architecture which results from conventional mechanical ventilation, and provides oxygenation at lower airway pressures and lower alveolar oxygen concentrations.

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