PRIMING OF CARDIOPULMONARY BYPASS WITH HUMAN ALBUMIN OR RINGER LACTATE: EFFECT ON COLLOID OSMOTIC PRESSURE AND EXTRAVASCULAR LUNG WATER

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SUMMARY
We have undertaken a randomized study on 20 patients undergoing coronary artery bypass surgery in order to determine the influence of cardiopulmonary pump prime solutions on colloid osmotic pressure and extravascular lung water. Crystalloid priming with Ringer lactate was compared with an albumin solution of nearly physiological colloid osmotic composition (4%). Measurements of extravascular lung water were performed by a modified, highly sensitive thermal dye technique, with additional detection of tracer signals in the pulmonary artery. In the Ringer lactate group, a significantly greater decrease in colloid osmotic pressure occurred immediately after onset of cardiopulmonary bypass. The more pronounced decrease in colloid osmotic pressure and in transcapillary gradient (difference between colloid osmotic pressure and pulmonary capillary wedge pressure) in the Ringer lactate group was associated with a significant increase in extravascular lung water (by 60%) in the postoperative period; the human albumin group, however, showed only a slight tendency to increased lung water. There were no differences in haemodynamic or respiratory states after operation.

KEY WORDS

One factor which might contribute to respiratory dysfunction after open heart surgery is accumulation of extravascular lung water [1–9]. The intravascular colloid osmotic pressure is an important determinant of transcapillary fluid movement and therefore should be maintained in the physiological range, in particular when capillary permeability is increased [10]. However, with the onset of cardiopulmonary bypass, the plasma is diluted by the prime volume of the machine and colloid osmotic pressure may decrease considerably, depending on the composition of the priming solution [1, 2, 6, 11–14]. Addition of colloids to the pump prime solution has been advocated, therefore, by several groups. However, in most studies the added amounts of albumin or hydroxyethyl starch were not sufficient to result in a physiological colloid osmotic pressure in the prime solutions [1, 11–14]. Furthermore, the results on postoperative accumulation of extravascular lung water were controversial: while some studies failed to show an increase in lung water [12], others demonstrated a significant increase in lung water at different times after operation [13, 15, 16].

The aim of this study was to compare the effect of a high colloid osmotic priming solution (4% albumin) with a pure crystalloid priming solution (Ringer lactate) on postoperative extravascular lung water. In addition, we examined the time at which water was most likely to accumulate in the postoperative period by frequent measurements using a newly developed, sensitive method for measurement of lung water with detection of dye and temperature time courses in the pulmonary artery in addition to the aorta.
PATIENTS AND METHODS

We studied 20 patients undergoing aortocoronary venous bypass surgery. The study was approved by the Committee for Medical Ethics of the University and accepted by the German Research Foundation, SFB 330-Organ Protection. Each patient gave full informed consent at the time of the preoperative visit. No patient had a history of congestive heart failure or valvular heart disease. All patients had ejection fractions greater than 50%.

Patients were premedicated with flunitrazepam 2 mg orally 1 h before arrival in the operating room. When leaving the ward they received additionally promethazine 50 mg and piritramide 15 mg i.m. When they arrived in the operating room, ECG leads were attached; under local anaesthesia the left radial artery was cannulated and a central venous catheter was inserted via the left cubital vein. General anaesthesia was induced with fentanyl 0.5 mg and etomidate 20 mg, and pancuronium 8 mg was given to facilitate tracheal intubation. Artificial ventilation was maintained with an $F_{1O_2}$ of 0.5 in air or in nitrous oxide when systolic arterial pressure exceeded 100 mm Hg.

Patients were allocated randomly to two groups. In one group (Ringer lactate (RL) group) ($n = 10$) crystalloid solutions only were used for priming of the cardiopulmonary bypass: a 2000-ml solution contained Ringer’s lactate 1400 ml, 5% glucose 500 ml and bicarbonate 100 ml. The second group (human albumin (HA) group) ($n = 10$) also received a 2000-ml priming solution, in which 400 ml of Ringer’s lactate was replaced by 20% human albumin 400 ml, producing a concentration of 4% human albumin in this priming solution (Table I). In all patients a membrane oxygenator was used (Maxima, Medtronic).

After induction of anaesthesia, a specially designed balloon-tipped catheter with an additional fiberoptic lead for intravascular dye measurements was placed into the pulmonary artery via the right internal jugular vein. A second combined fiberoptic-thermistor catheter was inserted into the left femoral artery and advanced into the aorta to the thoracic part of the descending aorta (fig. 1). Arterial and mixed venous blood samples were obtained for measurement of haemoglobin and oxygen content and colloid osmotic pressures (IL 186 Weil Oncometer, semi-permeable membrane with 95% rejection of albumin). In addition to standard haemodynamic variables (heart rate, pulmonary and aortic pressures), extravascular lung water, central blood volume and cardiac output were measured by a double indicator dilution technique [17, 18]: 10 ml of an ice cold dye bolus (indocyanine green 12.5 mg) was injected into the proximal lumen of the pulmonary artery catheter. The resulting dye and temperature dilution curves in the pulmonary artery and aorta were detected by the fiberoptic-thermistor catheters, which were connected to special optoelectronic devices (IVS 4000, Fa. Schwarzer, München, FRG). The analog signals

![Fig. 1. Positions of the combined fiberoptic-thermistor catheters in the pulmonary artery (A) and the thoracic aorta (B).](https://academic.oup.com/bja/article-abstract/66/1/73/245155)
of the curves were digitized on-line and stored on hard disk by an IBM-compatible computer. Measurements were performed after induction of anaesthesia (a.A), after cannulation for cardiopulmonary bypass (a.C), during cardiopulmonary bypass (I-IV CPB), after decannulation (a.CPB), at the end of surgery (ES) and 1, 2, 3, 4, 5, 6, 9, 12 and 24 h after operation.

Cardiac output was measured from aortic and pulmonary thermodilution curves according to the Stewart Hamilton procedure. The average of both values was used for further calculations.

Conventionally, measurement of extravascular lung water is based on calculation of mean transit times for dye and heat from aortic dilution curves. This is possible only after elimination of indicator recirculation by monoexponential extrapolation [11-16]. This approach involves assumptions that have not been verified [19] and have been shown in animal experiments to bear a systematic additive error and possess limited accuracy [18]. In contrast, we chose a more complex mathematical approach, which eliminates the effects of indicator recirculation by additional measurement of tracer signals in the pulmonary artery. Thus assumptions about the indicator kinetics at the entrance to the pulmonary system, including the possibility of recirculating indicator, are not required. The theoretical principles of this technique have been described in more detail in previous publications from our group [17-18] and by Zierler [19]. In brief, a mathematical algorithm termed the “convolution integral” is used for numerical description of the tracer passage through the vascular bed of the lung:

$$c_{σ0}(t) = \int_{0}^{\infty} h(t - u) c_{pul}(u) du$$ (1)

The convolution integral (equation (1)) describes the concentration–time course of an aortic tracer curve ($c_{σ0}(t)$) depending on the tracer concentration–time course in the pulmonary artery ($c_{pul}(t)$) and indicator dispersion during lung passage specified by a transport function ($h(t)$; $u$ is a dummy variable for integration). This transport function may be considered the aortic concentration–time course of a tracer, which would result after an ideal indicator bolus (infinite short duration without any recirculation) is injected into the pulmonary artery.

In the present study the transport functions for temperature and dye were determined by iterative convolution of the pulmonary artery dye and temperature dilution curves with a lagged normal density function [20]. This function has been shown previously to represent an accurate model for physiological tracer dispersion in the pulmonary vascular system [21].

A non-linear least square procedure was used to perform the iterative convolution of the curves and to adjust the parameters of the lagged normal density function until the best fit of computed and measured aortic tracer kinetics was achieved [22]. The mean transit times, which are essentially necessary for calculation of extravascular lung water, may then be derived algebraically from the calculated parameters of the function without extrapolation procedures [20, 21]. Total lung water (including intravascular water) and pulmonary blood volume may be calculated from the product of cardiac output with the mean transit times of heat and protein bound dye, respectively. Extravascular lung water is the difference between total lung water and pulmonary blood volume.

Statistics

Two-tailed Student’s $t$ tests for unpaired data were used to compare patient data. The effects of colloid and crystalloid priming solution on all measured data were compared by two-way analysis of variance for repeated measures (ANOVA). If differences between the two groups were significant ($P < 0.05$), post hoc comparisons were performed using the Tukey HSD test with a level of significance $P < 0.05$. All calculated $P$ values are two-tailed. All group data are reported as means (SD).

Table II. Patient data and data on cardioplegia, extracorporeal circulation and ishaemic arrest in the Ringer’s lactate (RL) and human albumin (HA) groups (means (SD)). No statistically significant differences between groups were observed ($t$ test for unpaired data)

<table>
<thead>
<tr>
<th></th>
<th>RL ($n = 10$)</th>
<th>HA ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55.1 (5.6)</td>
<td>56.8 (6.4)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.0 (11.8)</td>
<td>78.1 (11.8)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.71 (0.07)</td>
<td>1.72 (0.08)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.89 (0.18)</td>
<td>1.95 (0.18)</td>
</tr>
<tr>
<td>Number of coronary anastomoses</td>
<td>2.7 (0.67)</td>
<td>3.1 (1.01)</td>
</tr>
<tr>
<td>Total amount of cardioplegia solution (ml)</td>
<td>2075 (109)</td>
<td>2212 (555)</td>
</tr>
<tr>
<td>Duration of ishaemic arrest (min)</td>
<td>56.2 (18.4)</td>
<td>76.0 (36.8)</td>
</tr>
<tr>
<td>Duration of extracorporeal circulation (min)</td>
<td>97.9 (25.7)</td>
<td>116.0 (52.6)</td>
</tr>
<tr>
<td>Time end surgery to extubation (h)</td>
<td>20.2 (6.1)</td>
<td>19.2 (6.8)</td>
</tr>
</tbody>
</table>
RESULTS

There were no differences between the two groups of patients in general characteristics, time of ischaemic arrest and extracorporeal circulation or cardioplegia (table II). Arterial and pulmonary arterial pressures, heart rate and body temperature showed the same time courses for both groups (data not presented). With the onset of extracorporeal circulation, colloid osmotic pressure decreased by more than 50% (from 18.4 (SD 1.3) mm Hg to 9.0 (0.8) mm Hg) with crystalloid solutions (RL group); in the HA group the decrease in colloid osmotic pressure was signifi-
cantly smaller (from 19.3 (2.3) mm Hg to 15.2 (1.1) mm Hg (30%)) (fig. 2). In the postoperative period, both groups showed a continuous increase in colloid osmotic pressure but the preoperative values were not achieved in the RL group; the difference in colloid osmotic pressure between the groups was present for the next 24 h. The difference between colloid osmotic pressure and pulmonary capillary wedge pressure (COD–PCWP) has been suggested as an index of the transcapillary Starling forces regulating fluid transfer [23]. A marked decrease in this gradient was observed in both groups. The change was more pronounced in the RL group and even decreased below zero in this group immediately after cardiopulmonary bypass (fig. 3). Consequently, a significant increase in extravascular lung water by more than 60% occurred in the RL group.

Fig. 4. Time courses of extravascular lung water (EVLW) in the Ringer’s lactate (RL) (○) (n = 10) and human albumin (HA) (●) (n = 10) groups (mean, sd). In the RL group the EVLW increased by more than 60% after cardiopulmonary bypass, whereas the HA group showed only a slight accumulation of pulmonary fluid. P < 0.05 for ANOVA overall difference between group; *P < 0.05 for Tukey HSD post hoc comparison. The difference between both groups remained significant for the first 2 h after surgery.

Fig. 5. Time courses of the alveolar–arterial oxygen partial pressure difference (P_{Aa} - P_{Aa}) and arterial oxygen partial pressure (P_{Aa}) in the Ringer’s lactate (○) (n = 10) and human albumin (●) (n = 10) groups (mean, sd). No statistically significant differences between groups.
group. In contrast, in the HA group, there was only a slight tendency to increased extravascular lung water in the postoperative period (fig. 4). The difference between both groups was significant for the first 2 h after the end of surgery. However, the time courses of arterial oxygen pressure ($P_{A,\text{O}_2}$) and of alveolar–arterial oxygen difference ($P_{A,\text{O}_2} - P_{A,\text{O}_2}$) were the same in both groups (fig. 5), as was the average time to tracheal extubation (table II).

DISCUSSION

The results of the present study demonstrate that addition of albumin in a sufficiently high concentration to the priming solution may prevent accumulation of extravascular lung water after open heart surgery. In the HA group there was only a slight tendency to accumulation of extravascular lung water. Although the calculated albumin content of the priming volume was 4% and therefore considerably greater than that used in all previous investigations [11–15], a slight decrease in colloid osmotic pressure was found in this group. In the RL group, the decrease in colloid osmotic pressure was much more pronounced and was accompanied by a marked increase in extravascular lung water.

Accumulation of extravascular lung water after cardiopulmonary bypass may result from several mechanisms. The contact of blood with the foreign surfaces of the extracorporeal circulation activates several inflammatory mediators. Thromboxane B₂, fibrinopeptide, elastase and complement C3a have been shown to be increased in plasma after cardiopulmonary bypass [3, 8, 9, 24, 25]. Neutrophils are activated by mediation of complement C5a and sequestered into the pulmonary circulation with the onset of partial bypass [3, 8, 24]. In principle, all these factors may cause capillary endothelial damage, but accumulation of extravascular fluid does not necessarily occur. In fact, it has been demonstrated in animal experiments that the lymph drainage of the lung can increase markedly and compensate for capillary leaks to a considerable extent [10].

Furthermore, after cardiopulmonary bypass there is not only increased vulnerability of the endothelial barrier, but the intravascular Starling forces regulating transcapillary fluid exchange (intravascular hydrostatic pressure and colloid osmotic pressure) are altered also in an unfavourable manner. Hydrostatic pressure is often increased by left ventricular dysfunction: the left ventricle is compromised by the surgical procedure and may have postischaemic dysfunction because of unavoidable intraoperative ischaemic episodes such as crossclamping and cardioplegia. A greater preload and sometimes inotropic support by catecholamines is required to meet the demands of the circulation. Arterial pressure within the pulmonary circulation is therefore often increased. Additionally, the vascular resistance of the pulmonary circulation is increased, probably because of formation of thromboxane from platelets [24]. As a result, microvascular hydrostatic pressure is increased and this enhances transendothelial fluid transfer. In addition, haemodilution of the blood by the priming volume of the machine causes a considerable decrease in plasma protein concentration and colloid osmotic pressure; thus, after cardiopulmonary bypass, the additive effect of all these mechanisms may lead to exhaustion of the transport capacity of the pulmonary lymph system and extravascular fluid accumulates.

One of the first investigations on the problem of lung water development after cardiopulmonary bypass was performed by Byrick, Colin and Noble [11]. They compared the effects of two types of priming solutions on the postoperative development of extravascular lung water. The machine was primed with either two units of plasma with lactated Ringer's solution or with lactated Ringer's solution alone. In this study, the greatest protein concentration in the prime volume was only 1.2%—far below the physiological range. Thus it is not surprising that no major differences in the time course of changes in colloid osmotic pressure were observed between the two groups. Only a slight increase in extravascular lung water was observed at the end of surgery. In contrast to many other studies, accumulation of extravascular lung water was observed during the first and second days after operation. This finding differs from those of other investigations [12, 13] and of the present study, in which accumulation of extravascular lung water occurred only during the first 4 h after operation. In contrast with most other investigations [1, 2, 12, 13, 15], in Byrick's study [11] colloid osmotic pressure did not reach preoperative values during the first day after operation. Although the immediate postoperative increase of COP to 70–80% of preoperative values is similar to that in other investigations, the COP in Byrick's study remained at these values for the
next 2 days. This suggests postoperative fluid management with larger amounts of crystalloids and this may explain the increased extravascular lung water on the first and second days after operation.

In principle, results similar to the present investigation have been described by Boldt and colleagues [16], who found a significant increase in post-bypass lung water in those patients who received preoperative haemodilution with Ringer lactate and underwent extracorporeal circulation with a priming volume of 2000 ml of pure crystalloid. A two-stage cannulation technique was used; ligation of the venae cavae was not performed and the total volume of cardioplegic solution entered the systemic circulation via the coronary sinus. The additive effects of preoperative haemodilution, pure crystalloid priming and cardioplegic solution resulted in an extreme decrease of systemic colloid osmotic pressure (to less than 6 mm Hg on average). Consequently, lung water increased significantly immediately after the end of bypass and was even greater 45 min later.

Interestingly, in the study of Boldt and colleagues [16], the control group (with no significant evidence of lung water accumulation) was comparable to the RL group of the present investigation, which had significant accumulation of lung water. In fact, the time courses of colloid osmotic pressures match very well and are in agreement with many other studies in which pure crystalloid solutions were used for cardiopulmonary bypass [2, 11–15]. However, there were some differences. Boldt observed only a slight, insignificant increase in lung water after surgery; furthermore, under control conditions (before surgery) an extravascular lung water of nearly 6 ml kg\(^{-1}\) was found, which is considerably more than in the present study.

These differences result probably from methodological differences; it is known that the conventional technique of lung water measurement with only a single measuring site, blood withdrawal for tracer detection and monoexponential extrapolation of the tracer curves, leads to a systematic error with overestimation of extravascular lung water [18, 26–28]. Two sources of error are mainly responsible for this overestimation: prepulmonary heat exchange with extravascular tissues, and contamination of the aortic temperature curve by recirculation leading to incorrect estimation of mean temperature transit times [18]. The distribution volume for prepulmonary heat exchange is included erroneously in extravascular lung water measurements assessed by the conventional method and therefore results in an additive error. A systematic additive error might also impair the sensitivity of the measuring method, as minor absolute changes in lung water might be relatively small in comparison with baseline measurements. This might explain why Boldt and colleagues, with high control values for extravascular lung water, observed only a slight insignificant increase in lung water after extracorporeal circulation. In the present study, prepulmonary heat exchange was visible by means of a time delay between the temperature and the dye curve in the pulmonary artery. This slight time delay between both pulmonary tracer curves was observed consistently in all measurements of this study.

In the present investigation a deconvolution technique with two sites of tracer measurement (pulmonary artery and descending aorta) was used. By this method, tracer mean transit times can be calculated on the basis of the respective transpulmonary transport functions. In principle, the additional information, which is supplied by the pulmonary artery catheter, is used to eliminate the pattern of the tracer bolus at the entrance to the organ and to compute the tracer curve at the output from the organ, which would result from an ideal impulse input into the pulmonary artery. The deconvolution approach is, therefore, independent of the shape of the input signal. Differences in shape of the pulmonary curves and recirculation of the tracer do not therefore affect the resulting transport functions. Thus the average control value for extravascular lung water in this study (3.8 ml/kg body weight) was considerably lower than the majority of control values reported in the literature. An important effect of avoiding systematic additive errors is increased sensitivity to small changes in lung water.

Although a considerable postoperative increase in lung water occurred in patients without colloid osmotic priming, the clinical significance of this finding remains unclear. Because of expense, it is questionable if an albumin priming should be advocated for all patients. No differences were observed in postoperative pulmonary function between the two groups, indicating that factors other than changes in extravascular lung water may be more important for postoperative recovery of respiratory function. Probably, excessive haem-
odilution has to occur before the resulting lung water accumulation leads to fatal pulmonary dysfunction. We suggest that a priming volume with a high colloid osmotic pressure should probably be used only in those patients who have additional risk factors for postoperative pulmonary dysfunction.

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REFERENCES


