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High colloid oncotic pressure priming of cardiopulmonary bypass in neonates and infants: implications on haemofiltration, weight gain and renal function

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Abstract

Objective: To evaluate the influence of high colloid oncotic pressure (COP) priming of cardiopulmonary bypass (CPB) on fluid balances, haemofiltration, capillary leakage and renal function in neonates and infants. **Methods:** Twenty neonates or infants underwent heart surgery using CPB and were randomised in two groups. For group 1 (FFP-group) a blood priming with fresh frozen plasma (FFP, low oncotic pressure) was chosen, for group 2 (HA-group) a blood priming containing FFP and human albumin 20% (HA) to realise higher oncotic pressures was substituted. All patients were monitored before, during and 6 h after CPB. We measured weights, fluid balances, transfusion volumes, colloid oncotic pressures, inflammatory parameters (c-reactive protein, interleukin-6, interleukin-8, thrombocytes, leucocytes) and renal function (creatinine clearances, renal protein losses). **Results:** Patient's demographics and operational procedures were comparable in both groups with no further differences in operation procedures regarding palliation or correction. Colloid oncotic pressures of the priming solutions were higher in the HA-group (28 mmHg $\pm$ 4.9) than in the FFP-group (6 mmHg $\pm$ 1.3, $p < 0.001$). Relative weight gain as a marker of capillary leakage in the HA-group (2% $\pm$ 4.5) was significantly lower 6 h post CPB than in the FFP-group (8% $\pm$ 8.0, $p = 0.015$). Haemofiltration rates were higher in the HA-group (569 ml $\pm$ 197 vs 282 ml $\pm$ 157, $p = 0.002$) on CPB. There were no differences of creatinine clearances 6 h after the end of CPB. Renal protein losses were elevated in both groups without any inter-group differences during and 6 h after CPB. **Conclusion:** Addition of concentrated human albumin to priming fluids in paediatric cardiac surgery leads to less weight gain even after CPB. Supplementing paediatric patients undergoing cardiac surgery with concentrated human albumin does not affect renal function more severely than in paediatric patients undergoing cardiac surgery on CPB with blood priming.

Keywords: Cardiopulmonary bypass; Neonates; Colloid oncotic pressure; Haemofiltration; Renal function

1. Introduction

Many attempts have been made to ameliorate the outcome of cardiac surgery in neonates and small infants undergoing cardiac surgery modifying the cardiopulmonary bypass (CPB). These included modifications of materials i.e. pumps, cannulas, oxygenators and CPB-associated procedures, i.e. pulsatile flow, continuous flow, hypothermia, isolated cerebral perfusion and composition of priming fluids with regards to colloids, blood cells, osmolality, volume and electrolytes. Survival rates have become very satisfying, so investigations have focused on improvement of existing procedures.

CPB remains a high-risk procedure, particularly for neonates and infants. There are nearly as many CPB procedures as cardiac surgery centres [1]. However, clinical trials are hard to conduct. According to Jones and Elliott [2] and Bartels et al. [3] these trials often fail because of the large variability of inborn heart defects, cardiac pathology and surgical techniques. Procedures have been developed using data obtained from animal models or through first-hand experience without statistical evidence.

Major problems of CPB in children are capillary leakage and a significant weight gain during cardiac surgery [2]. This is due to hypothermia [4], haemodilution with subsequent reduction of oxygen carriers and metabolic disturbances [5], renal damage [6], fluid shifts from the intravascular space into tissues or the third space [7] and inflammatory processes [8].

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There were several trials on the influence of colloid oncotic pressure (COP) on CPB and renal function showing conflicting results [9–13]. Therefore, using human albumin to increase oncotic pressure is not practised regularly [1]. Weight gain of only a few hundred grams is often critical, especially in infants or neonates. Depending on the time of CPB and of hypothermia with massive activation of proinflammatory cytokines, composition of priming fluids in regard to oncotic pressure may be of significant importance [14] in order to reduce capillary leakage.

In this study we examined the impact of high oncotic pressure priming by the addition of human albumin 20% on weight gain, fluid balances, haemofiltration and capillary leakage and its affect on renal function.

2. Methods

2.1. Study Design

After authorisation by the ethics committee of Albert Ludwigs University, Freiburg and the written approval of patients' parents, 20 patients were allocated to this study. Blind randomisation was conducted by the Centre of Clinical Studies, University of Freiburg. Every 10 patients were assigned to the FFP-group (FFP, fresh frozen plasma), or the HA-group (HA, human albumin). The primary endpoint of the study was whole body weight gain after CPB. The secondary endpoints were renal function defined by creatinine clearance, renal protein losses and inflammatory response. Newborns and infants weighing less than 6.5 kg or with a maximum cardiac output rate of 1.1 l/min were included in this study. Children with metabolic disturbances, infections or emergencies were excluded from the study. Defined abortion criteria were the use of heart assist devices, or adverse allergic reactions to human albumin.

Clinical, serum and urine parameters were obtained beginning one day before surgery until 6 h post CPB. The serum analysis included interleukin-6 (IL-6), interleukin 8 (IL-8), c-reactive protein (CRP), leucocytes, thrombocytes, haemoglobin (Hb), creatinine and lactate. Urine analysis and renal function surveillance was performed by measuring protein excretion, albumin, microalbumin, α_1-microglobulin, *N*-acetyl-β-D-glucosaminidase, immunoglobulin G and creatinine [15]. Weights were recorded by a digital scale (HD 300, My Weigh, Nevada, USA).

2.2. CPB

CPB was performed using a modified children's device (oxygenator and attached hard shell reservoir D 901 Lilliput 1), an arterial filter (D 736, all Dideco, Sorin Group, Munich, Germany), cardioplegia heat exchanger (CSC14, Cobe, Sorin Group, Munich, Germany) a haemofilter (DHF 0.2) as well as the coated tube systems (SIII PHISIO coated system, all Dideco, Sorin Group, Munich, Germany). After clamping the aorta, 30 ml/kg blood cardioplegia according to Beyersdorf and Buckberg [16] were administered and repeated every 20 min during CPB (10 ml/kg). If deep hypothermia was necessary, we performed selective cerebral perfusion. The α-stat management for maintaining adequate pH on CPB was executed.

Table 1
Composition of priming fluids: FFP-group and HA-group with total amounts of added fluids

	FFP-group	HA-group	*p* value
Priming volume (ml)	339 ± 50.2	373 ± 39.3	0.052
HA 20% (ml)	0	100 ± 7.16	<0.001*
FFP (ml)	122 ± 13.2	52 ± 18.6	<0.001*
Mannitole (3 ml/kg)	14 ± 4.4	16 ± 4	0.28
Ionosterile (ml)	95 ± 43.8	86 ± 36	0.739
Packed red blood cells (ml)	90 ± 12.9	95 ± 15.8	0.353
Trasylol (30,000 kIE/kg, ml)	13 ± 5.5	16 ± 4	0.356
Sodium bicarbonate 8.4% (ml)	5.7 ± 0.8	7.1 ± 1.7	0.043*
Heparin 5000 IE/ml (ml)	0.15 ± 0.05	0.15 ± 0.05	1.0
Colloid oncotic pressure (mmHg)	5.8 ± 1.32	27.9 ± 4.87	<0.001*

Differences are significant in FFP-volume, HA-volume and sodium carbonate added to priming fluids. Colloid oncotic pressures are significantly different in both groups. Units are indicated in the table. The asterisk marks significantly differing values.

During CPB, haemofiltration was conducted intermittently to reduce the concentrations of proinflammatory cytokines and to prevent excessive haemodilution and subsequent fluid shifts to extravascular spaces [6].

All children were operated on by the same surgeon.

The composition of the FFP priming fluid was: FFP, mannitole, ionosterile, packed red blood cells, trasylole, sodium bicarbonate 8.4% and heparin. In the HA-group 100 ml of FFP was replaced with human albumin 20%. (Fresenius Kabi, Germany). A COP between 25 and 30 mmHg was given in the HA-group. The total priming volume of both groups was aimed at 350 ml (Table 1). COP was measured using a BMT 921 oncometer, Thomae, Germany with a 20,000 kDa membrane.

2.3. Statistics

Data were analysed using SPSS 10.0, SPSS Inc., Washington, USA. Due to the small number of patients, we used the non-parametric Mann–Whitney *U*-test for significances. Results were considered as significant when *p* was lower than 0.05. Data are given as mean values with standard deviation of the mean unless otherwise identified.

3. Results

Patient's demographics and intraoperative data were comparable in both groups (Table 2). All 20 patients survived. Priming fluids for CPB were obtained as described in Table 2.

Table 2
Demographic and intraoperative data

	FFP-group	HA-group
Age (days)	130 (4–257)	119 (3–513)
Weight (kg)	5.3 (1.9–7.1)	5.9 (3.7–7.8)
Length (cm)	59.5 (44–67)	63 (50–71)
Sex (m/f)	6/4	8/2
CPB time (min)	128 (39–236)	87 (31–272)
Lowest temperature during CPB (°C)	33.5 (20.3–35.7)	34.1 (22–36)
Procedure (palliation/correction)	3/7	2/8
Isolated cerebral perfusion (DHCA)	2	2

Median and range of values. No significant differences were found between the two groups using the Mann–Whitney *U*-test.

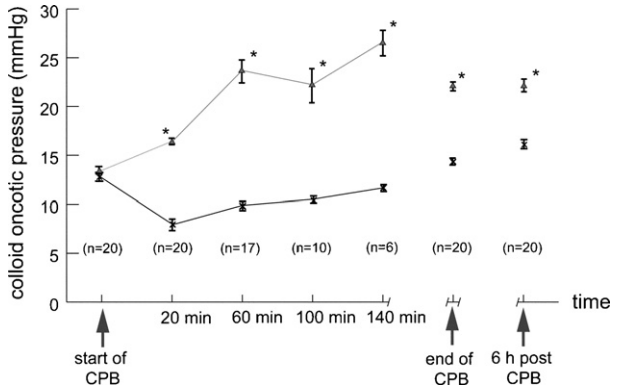

Fig. 1. COP during and 6 h after CPB: FFP-group is shown in black, HA-group in light grey. *N* indicates total number of patients at indicated time on CPB. Error bars indicate standard errors of the mean. COP was measured every 20 min. HA-group has significantly ($p < 0.05$) higher COP than the FFP-group after 20 min on CPB, during operation and 6 h post CPB. In the HA-group, all COP after 40 min on CPB are within physiological range. Arrows indicate beginning, end, and 6 h after CPB.

The use of HA led to higher oncotic pressures of the priming fluid in the HA-group (28 mmHg $\pm$ 4.9 vs 6 mmHg $\pm$ 1.3, $p < 0.001$) and to a slight rise of the absolute prime volume that was not significant (373 ml $\pm$ 39.3 vs 339 $\pm$ 50.2, $p = 0.052$). The use of sodium bicarbonate had to be augmented due to the lower buffering capacity of albumin in the HA-group (7.1 ml $\pm$ 1.73 vs 5.7 $\pm$ 0.82, $p = 0.043$) to reach physiological pH between 7.37 and 7.44. During and 6 h after CPB, oncotic pressures were significantly different in both groups. The course of COP during and after CPB is shown in Fig. 1. COP of the HA-group was higher throughout CPB time and 6 h after CPB. COP in the FFP-group was far below physiological values and reached only lower than normal values 6 h after CPB. This is reflected by fluid balances. Total haemofiltrate volume was 569 ml $\pm$ 197 in the HA-group compared to 282 ml $\pm$ 157 in the FFP-group ($p = 0.002$) (Fig. 2). This in part was counteracted by transfusion of FFP, packed red blood cells and crystalloids during surgery by the anaesthesiologist to maintain adequate blood pressure. Yet no significant difference in total volume was observed

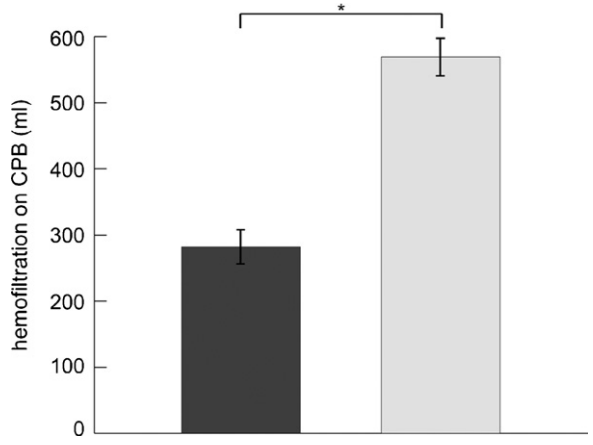

Fig. 2. Haemofiltrate volume on CPB. FFP-group is shown in dark, HA-group in light grey. Error bars indicate standard errors of the mean. Haemofiltrate volume is significantly higher in the HA-group than in the FFP-group.

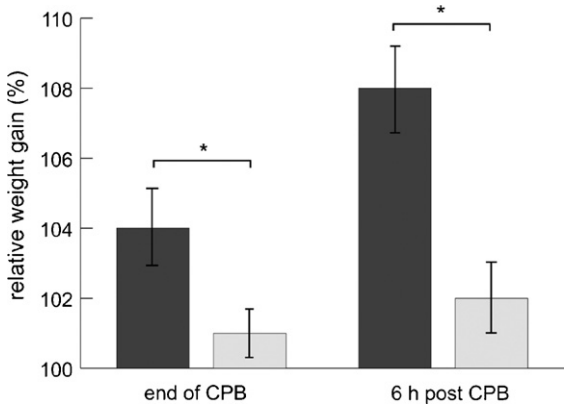

Fig. 3. Relative weight gain. FFP-group is shown in dark, HA-group in light grey. Error bars indicate standard errors of the mean. Weight gain is lower in the HA-group than in the FFP-group directly after and 6 h post CPB ($p = 0.015$).

(439 ml $\pm$ 206 vs 506 ml $\pm$ 433, $p = 0.68$). The difference in fluid balance had a direct impact on weight gain. Whereas the weights rose in both groups, weight gain was significantly lower in the HA-group (2% $\pm$ 4.4 vs 8% $\pm$ 8.0, $p = 0.015$), even 6 h post CPB (Fig. 3). Total volumes administered until 6 h post CPB were comparable in both groups (HA-group 127.6 ml $\pm$ 77.3 vs 128.5 ml $\pm$ 60.5 in the FFP-group). We did not observe severe bleeding or anaphylactic reactions during the stay at the intensive care unit. In both groups, renal function was altered by CPB, as shown in Fig. 4. Creatinine clearances were more physiological in the HA-group 6 h after CPB (HA-group 89.6 ml/min/1.73 m^2 $\pm$ 66.7 vs FFP-group 41.3 $\pm$ 4.3, $p = 0.19$) (Fig. 4a), but showed no statistical significance. Renal protein losses per gram creatinine rose in both groups but showed no significant differences directly after (1.6 g/g $\pm$ 1.2 vs 0.8 g/g $\pm$ 0.7, $p = 0.6$) and 6 h after CPB (3.0 g/g $\pm$ 1.7 vs 3.3 g/g $\pm$ 1.8, $p = 0.39$) (Fig. 4b).

Severe metabolic disturbances and inflammatory responses were not observed in both groups. Lactate as a marker of hypoxemic tissue damage and IL-6, IL-8 and c-reactive protein levels were elevated as expected after CPB, but did not show any significant differences (Table 3). Furthermore, we did not see a more extensive use of FFP, thrombocyte concentrates or packed red blood cells in either of the two groups during CPB or after admission to the ICU. Interestingly, absolute thrombocyte count in the HA-group

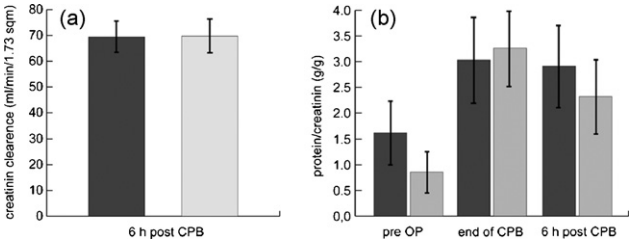

Fig. 4. Renal function: FFP-group is shown in dark, HA-group in light grey. Error bars indicate standard errors of the mean. (a) (Left panel): creatinine clearances 6 h post CPB. (b) (Right panel): protein losses (gram protein per gram creatinine) at points as indicated. There are no significant differences between both groups with regard to protein loss and creatinine clearances. Due to CPB, protein loss is higher during and 6 h after CPB than pre-CPB in both groups. Protein loss normalises earlier in the HA-group than in the FFP-group.

Table 3
Inflammatory, haemotologic and metabolic parameters

	FFP-group	HA-group	p
Lactate (mmol/l)	3.3 ± 1.98	2.76 ± 2.84	0.25
IL-6 (pg/ml)	69.1 ± 43.1	60.2 ± 58.2	0.48
IL-8 (pg/ml)	79.6 ± 97.8	61.1 ± 51.5	0.97
CRP (mg/l)	4.7 ± 4.4	3.4 ± 2.2	0.60
Leucocytes (G/L)	7920 ± 2.662	7300 ± 1946	0.74
Hb (g/dl)	14.1 ± 2.2	12.8 ± 1.87	0.28
Thrombocytes (G/L)	262700 ± 155832	146300 ± 58384	0.12

Metabolic and inflammatory parameters 6 h post CPB. Groups as described previously. There is no difference between both groups. Thrombocyte counts are lower in the HA-group but do not differ significantly.

6 h post CPB was lower than in the FFP-group, but did not differ significantly.

4. Discussion

Fluid balance derangement is one of the major post-operative complications in paediatric heart surgery with cardiopulmonary bypasses. Under CPB with or without hypothermia, fluid shifts from the intravascular space to organs, muscles and other body compartments is a well-known and characterised effect [17]. It remains one of the most important risk factors in cardiac surgery and is still not completely understood. The oncotic pressure of the priming fluid may have some influence on the postoperative outcome after CPB. There are several reports of higher colloid oncotic pressure priming with HAES [18] and albumin, showing tissue protective effects with respect to cardiopulmonary functions [19]. Alternatively, in an animal model by Hindman et al., water content of brain and kidneys seems not to be affected [20]. These observations make the use of human albumin in priming fluids a feasible approach for raising COP and preventing excessive fluid shifts and weight gain in paediatric patients undergoing cardiac surgery. Our data show that albumin as a supplement to priming fluids has a positive effect on haemofiltration during CPB and leads to a reduced weight gain during and throughout the first hours after CPB, as described previously [9].

Even though a higher oncotic pressure theoretically lowers the total haemofiltration volume due to technical limitations of the haemofilter and the technique itself [21], we speculate, that permanent ultrafiltration can be performed more efficiently with physiologic COP. This may be due to a more stable transmembrane pressure and faster fluid redistribution in the patient. It is still debated which procedure, be it modified ultrafiltration (MUF) or continuous ultrafiltration (CUF) is of greater benefit for the patient. Even though data suggest that MUF shows more protective effects and reduces inflammatory cytokines very effectively [22], we decided to perform intermittent ultrafiltration during CPB. Even though data are controversial, to us it appears logical that a continuous haemofiltration may be more efficient in eliminating cytokines and excessive water.

Moreover, human albumin seems to have an enduring effect on weight gain and water inclusion in the first hours post CPB, which may also be due to faster fluid redistribution in the patient and water withdrawal. Even though high oncotic pressures are considered nephrotoxic [23], we did not see any significant differences in creatinine clearances or protein losses. The loss of protein via the kidneys is comparable in both groups during and after CPB, being higher than pre-op, but reducing steadily. According to our

Table 4
Heart defects and surgical procedures

Patient	Heart defect	Age (days)	Procedure	DHCA
FFP-group				
1	HLHS	5	Norwood I	Yes
2	TGA, VSD, PDA	4	Arterial switch, VSD patch repair, ductus ligation	No
3	TOF	144	Patch repair, RVOT reconstruction PV commissurotomy	No
4	VSD	257	Patch repair	No
5	HLHS	7	Norwood I	Yes
6	TOF	157	Intraventricular tunnel repair	No
7	TGA, VSD	7	Arterial switch, patch repair	No
8	HLHS	150	Glenn	No
9	AVSD, PHT	116	Patch repair	No
10	MR IV°	145	Valve repair	No
HA-group				
11	Aortic arch hyoplasia	180	Aortic arch repair	Yes
12	TOF, ASD	138	Patch repair	No
13	VSD	99	Patch repair	No
14	VSD, ASD	121	Patch repair	No
15	HLHS	116	Glenn	No
16	TOF	110	Transannular patch repair	No
17	HLHS	6	Norwood I	Yes
18	Aorto pulmonary window	197	Patch repair	No
19	PA, VSD, AP-shunt	513	Conduit placement, patch repair, shunt ligation	No
20	TGA	4	Arterial switch	No

Congenital heart defects and surgical procedures for all patients. The number of patients does not correspond to the order of randomisation. DHCA: deep hypothermic cardiac arrest; RVOT: right ventricular outflow tract; ASD: atrial septal defect; VSD: ventricle septal defect; PDA: patent ductus arteriosus; TOF: tetralogy of Fallot; AVSD; atrioventricular septal defect; MR: mitral regurgitation; PS: pulmonary stenosis; PA: pulmonary atresia; PHT: pulmonary hypertension; AP-shunt; aorto-pulmonary shunt; TGA: transposition of the great arteries; HLHS: hypoplastic left heart syndrome. Surgical procedures extend through the whole range of paediatric cardiac surgery.

results, renal damage on CPB may be a temporary effect, which normalises quickly [15]. The protein loss in the HA-group may also be elevated due to a higher supply in the priming fluid.

Because human albumin is derived from blood there is a given risk of blood transmitted disease. Because all products are examined excessively, the risk of infection is quite low, with an estimated incidence of 1:325,000, taking into account all HCV, HBV and HIV in total [24], and is therefore not higher than other blood products.

Allergic reactions are uncommon when using albumin and have a lower incidence compared to using gelatines or dextrans according to Laxenaire et al. [25].

In our institution, the supplementation of priming fluids with human albumin increases the costs by about 50 €, which appears reasonable compared to the total cost of the operation.

Regarding safety and economics, the risks and costs of albumin are in our eyes tolerable.

5. Limitations of the study

There are some limitations to this study, which may affect the results. The number of patients in this study is small, with only 10 patients in each group. Also, surgical procedures extend through the whole spectrum of inborn heart defects and are therefore different for nearly each patient (Table 4). Yet the positive effects of higher oncotic pressure are consistent in this study and therefore do not limit its significance. Finally, the study is limited by the short interval of observation (6 h). At the same time, water inclusion and capillary leakage are events that happen during CPB and cannot be observed during ICU stay except in conditions such as sepsis, the use of assist devices or fulminant allergic reactions.

6. Conclusion

In the light of our findings, the addition of human albumin to raise oncotic pressure during CPB in neonates and infants should be considered a complementary strategy for two reasons: haemofiltration after CPB is more efficient and weight gain is reduced significantly. There is no significant or permanent renal damage. Infection rate is low, as is incidence of allergic reaction to human albumin. In our eyes, supplementation of priming fluid with albumin is of significant benefit and is safe in neonates and infants. Further investigation is necessary in this field to understand the underlying mechanisms of pathogenesis and to ameliorate the outcome of CPB on neonates and infants.

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