Original Article

Hemorheology and renal function during cardiopulmonary bypass in infants

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Abstract *Background:* Acute renal failure is an occasional complication after cardiopulmonary bypass in infants. Whereas it is well known that postoperative hemodynamics inflict acute renal failure, the influence of extracorporeal circulation on the kidney is less clear. Moreover, changes in blood viscosity occur during and after surgery, which may influence renal dysfunction. For this reason, we investigated the impact of blood viscosity on renal function during cardiopulmonary bypass. *Methods:* In 34 patients weighting less than 10 kg, we performed repeated analysis of urine, blood, and plasma viscosity. *Results:* Polyuria and proteinuria that appeared during cardiopulmonary bypass indicated an elevated transglomerular filtration gradient, which recovered within 24 hours. The appearance of N-acetyl-β-D-glucosaminidase in the urine, and elevated excretion of sodium, were additionally indicative of mild tubular damage. Elevation of blood viscosity during hypothermic perfusion showed a statistical correlation with proteinuria and N-acetyl-β-D-glucosaminidaseuria. With hypothermia, the relation of blood viscosity to plasma viscosity became stronger, while the relation to the hematocrit decreased compared to normothermia. *Conclusions:* During cardiopulmonary bypass perfusion, the kidney can be stressed by proteinuria and mild tubular damage. Our data provide evidence that the kidneys can be protected by improved blood viscosity during cardioplegia, but this needs confirmation in a prospective interventional study.

Keywords: Congenital cardiac disease; infant cardiopulmonary bypass; blood viscosity; plasma viscosity

ACUTE RENAL FAILURE IS AN OCCASIONAL complication after cardiopulmonary bypass for correction of congenital cardiac malformations in infants.[1,2] Despite postoperatively decreased cardio-circulatory function, which may cause acute renal failure,[3–5] there is evidence that the alteration of renal function commences at the time of cardiopulmonary bypass.[6,7] Renal function particularly depends upon blood flow. Recent experimental studies have discussed the involvement of blood viscosity and glomerular blood flow in the pathogenesis of chronic glomerular kidney disease produced by long-standing functional disorders.[8,9] On the other hand, enhancement of the conditions underscoring viscosity is known to improve the properties of flow of blood in the kidney.[10,11] The aim of this study was to investigate renal function in infants during surgery involving cardiopulmonary bypass with regard to hemorheology.

Material and methods

Selection of patients

We studied 34 consecutive infants weighing less than 10 kg who underwent correction of congenital cardiac malformations using cardioplegia and cardiopulmonary bypass (Table 1). Patients with renal diseases, as diagnosed by routine ultrasound, were excluded. During the period of study, 10 patients

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Table 1. Patients and bypass data.

Age (month)	3.1 (0.2–16.3)	
Body weight (kg)	4.4 (2.6–9.9)	
Bypass time (min)	117 (44–479)	
Aortic cross-clamping (min)	59 (17–121)	
Rectal body temperature during aortic cross-clamping (°C)	30.7 (18.0–36.2)	
Mean blood flow during CPB (ml/min/kg)	189 (115–277)	
Diagnoses	**Patients no.**	**Type of surgery**
Ventricular septal defect and/or atrial septal defect	14	Corrective
Atrioventricular septal defect	6	Corrective
Transposition of great arteries	6	Arterial switch
Tetralogy of Fallot	2	Corrective
Pulmonary atresia	2	Corrective
Bland-White-Garland syndrome	2	Corrective
Common arterial trunk	1	Corrective
Aortic stenosis	1	Commissurotomy

n = 34; Data are given as median (minimum–maximum); CPB: cardiopulmonary bypass

were excluded. Analysis of creatinine revealed levels below 0.8 mg/dl in the serum of all participating patients.

Technique for cardiopulmonary bypass

After a bolus injection of heparin to achieve an activated clotting time of more than 480 seconds, non-pulsatile cardiopulmonary bypass was initiated with a microporous polypropylene membrane oxygenator that was selected according to the size of the patient and the requirements for flow (Safe Micro, Polystan, Vaerlose, Denmark; Lilliput D-701 or D-902, Dideco/Sorin, Mirandola, Italy) and an arterial filter (D736, pore size 40 μm, Dideco/Sorin). The extracorporeal circuit consisted of medical grade polyvinylchloride tubing except for silicone tubing in the raceway of the arterial non-pulsatile roller pump (Stöckert, Munich, Germany). The bypass circuit was primed with Jonosteril and pre-bypass filtrated (R3802 0.2 μm Pall Biomedical, Dreieich, Germany). The priming volume of 350–550 ml consisted of isotonic electrolyte solution, which was partially replaced by 120 ml of fresh frozen plasma in the newborn. We added 50 ml of 20% albumin. One hundred to 300 ml packed red blood cells to maintain a calculated hematocrit value over 15%, and if necessary blood was buffered with 8.4% sodium bicarbonate. In one patient, we were able to use a bloodless prime. During bypass, the flow was routinely set at 3 l/min/m², temporarily reduced only with decreased venous return or at the request of the surgeon. Flow was controlled according to the venous oxyhemoglobin saturation measured on-line, and values of arterial blood gases. During the period of rewarming, higher flows were required to meet the increasing metabolic demands. Cooling was

performed in the first 15–20 min of cardiopulmonary bypass (Table 1). Arterial tension of carbon dioxide was maintained throughout hypothermic cardiopulmonary bypass at 35–45 mmHg, uncorrected for temperature according to alpha-stat management. After cross-clamping the aorta, cardiac arrest was induced by injection of 50–100 ml Cardioplegin-N® cardioplegic solution (Köhler, Alsbach-Hähnlein, Germany), followed by an infusion of Hamburg-Eppendorf® colloidal solution (Fresenius, Bad Homburg, Germany), with magnesium and procaine as cardioplegic agents. Colloid cardioplegic solution was then re-infused every 20–30 min. Systemic rewarming was initiated shortly before de-clamping the aorta. Median duration of bypass was 106 min (Table 1). Circulatory arrest was not used. After termination of cardiopulmonary bypass, modified ultrafiltration was performed uniformly in all patients according to the method introduced by Naik and Elliott.[12] The aortic cannula was left in place, and blood from the aorta was passed through a hemoconcentrator (DHF 02, Dideco, Italy), the oxygenated blood being returned through a "Hot-Line" transfusion line (Smith Ind., Rockland, USA) to the right atrium to prevent a drop in temperature, particularly in neonates and small children. In the steady state period of cardiopulmonary bypass, after achieving full flow until the start of the weaning period, the mean flow for cardiopulmonary bypass was calculated from data recorded every 5 min. Colloid osmotic pressure was measured with the Onkometer 923 (BMT, Germany).

Anesthesia

Patients were pre-medicated with midazolam, at a dose of 0.5 mg/kg, 30 minutes before the operation.

Anesthesia was induced with midazolam at 0.2 mg/kg, sufentanyl at 1 μg/kg, and pancuronium at 1 mg/kg. After insertion of an endotracheal tube, and placement of arterial and central venous catheters, anesthesia was maintained by the continuous infusion of sufentanyl at 1–2 μg/kg per hour, the use of an inhalational agent before the initiation of cardiopulmonary bypass, and an additional dose of midazolam at 30 mg/kg during and after cardiopulmonary bypass. Prednisone, at 30 mg/kg, and mannitol at 0.5 g/kg, were given prior to cardiopulmonary bypass. During cooling and rewarming, all the patients received a continuous infusion of nitroprusside at 0.1–5 μg/kg per minute.

Periods of investigation

Hemodynamic, renal and hemorheologic analyses were performed over five time periods:

- onset of general anesthesia – start of cardiopulmonary bypass,
- start of cardiopulmonary bypass – end of aortic cross-clamping,
- start of reperfusion – stop of cardiopulmonary bypass,
- four hours following the cardiopulmonary bypass, and
- 8–24 hours after the end of cardiopulmonary bypass.

Evaluation of renal function

Renal function was evaluated by analysis of protein and enzymes in urinary samples collected at specific times as previously described.[13] Clearances of creatinine, and the excretion of sodium, were calculated with standard formulas.[14]

Evaluation of hemorheology

The hematocrit and hemoglobin were measured using a Coulter counter model Celldyn 3500® (Abbott, Illinois, USA). Viscosity was measured using a cone and plate viscometer (Wells-Brookfield, Massachusetts, USA) at shear rates of 225 per second, which represented the shear conditions in arterial vessels at temperatures that corresponded to the central body temperature during collection of blood samples as previously described.[15]

Statistical analysis

Results are expressed as medians and ranges in the tables and for graphic presentation as mean plus and minus the standard error of the mean. For statistical analysis, we used the Mann-Whitney-U test for unpaired samples, the Wilcoxon-test for paired samples, and the Fisher exact test for comparison of numerical variables between groups. A Spearman's correlation coefficient of greater than 0.5 was interpreted as correlation between two different parameters, and p values less than 0.05 were considered to be statistically significant.

Results

Analysis of renal function

When compared with the initial period of the operation, diuresis increased during the period of perfusion on cardiopulmonary bypass, and remained elevated for the first 24 hours after surgery (Fig. 1). The clearance of creatinine was elevated at the onset of cardiopulmonary bypass, and decreased below the preoperative values after cardiopulmonary bypass (Fig. 1). It remained lower for up to 24 hours. At the end of cardiopulmonary bypass, none of the patients was anuric, but three patients developed acute renal failure with oliganuria or anuria in the subsequent 24 hours. These patients were excluded from the subsequent postoperative analysis. Glomerular alteration, as indicated by elevated excretion of protein and albumin, was observed during the reperfusion period of cardiopulmonary bypass and in the early hours postoperatively. This disappeared within 24 hours in all patients (Fig. 1). Tubular alteration, as revealed by elevated urinary activity of the N-acetyl-β-D-glucosaminidase, and elevated urinary excretion of sodium, became obvious during the reperfusion period of cardiopulmonary bypass, and in the first hours postoperatively. It normalized within 24 hours in all patients (Fig. 1).

Hemorheology during cardiopulmonary bypass

When compared with the basal values, the hematocrit was diluted during cardiopulmonary bypass (Fig. 2). Plasma viscosity was elevated during hypothermic perfusion, but blood viscosity did not increase, and was slightly reduced during the period of reperfusion (Fig. 2). The flow during hypothermic perfusion, and the period of reperfusion, were in a comparable range (Table 2).

Factors influencing blood viscosity

During normothermia, blood viscosity showed a statistical correlation with the hemoglobin and the hematocrit, while plasma viscosity was not correlated to the blood viscosity by statistical meanings (Table 3). In contrast, during hypothermic perfusion, the body temperature and the plasma viscosity were statistically correlated with the blood
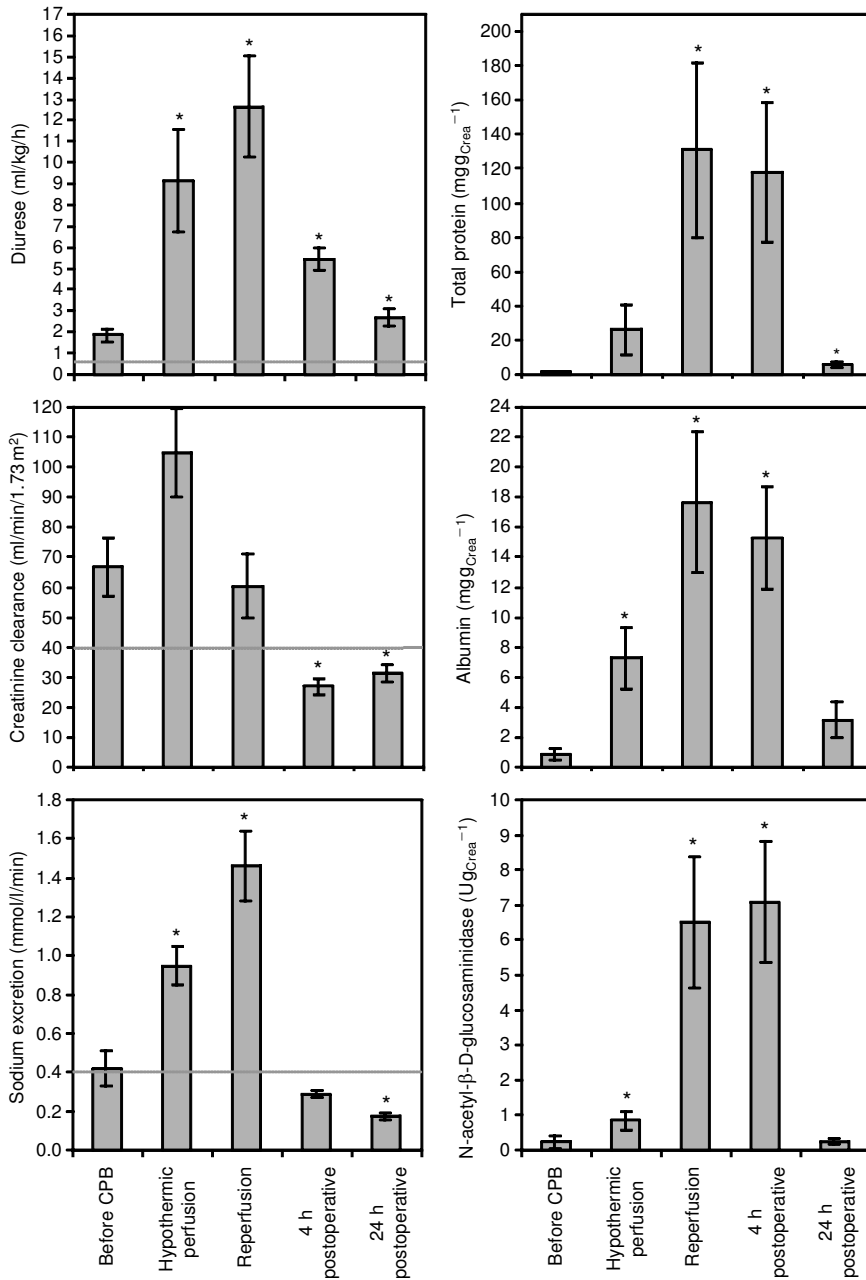
Figure 1.
*Data are given as mean ± SEM. *p < 0.05 compared to first column. The dotted lines show the minimal reference values. The bars represent the analyses at the intra- and postoperative sample periods during cardiopulmonary bypass. While polyuria and elevated excretion of sodium appeared during extracorporeal perfusion (left sided diagrams), proteinuria and tubular impairment occur during the final period of cardiopulmonary bypass (right sided diagrams). The clearance of creatinine was depressed after the operation.*

viscosity, while hemoglobin and hematocrit were not (Table 3).

Comparison of renal function with demographic and cardiopulmonary bypass data

Spearman's correlation analysis showed a relationship between central body temperature during hypothermic perfusion, and albuminuria during the period of reperfusion ($r = -0.615$; $p < 0.0005$). Blood viscosity during hypothermic perfusion was statistically related to albuminuria ($r = 0.705$; $p < 0.0005$) and to urinary values of N-acetyl-β-D-glucosaminidase ($r = 0.548$; $p = 0.001$) during the period of reperfusion (Fig. 3).

Comment

This study focusses on two main topics. First, renal function was analyzed during the different periods of cardiopulmonary bypass and, secondly, on the basis of the rheological conditions. Our data demonstrate proteinuria and impairment of tubular cellular function during extracorporeal circulation and shortly after the period of cardiopulmonary bypass. The question is whether our findings indicate only
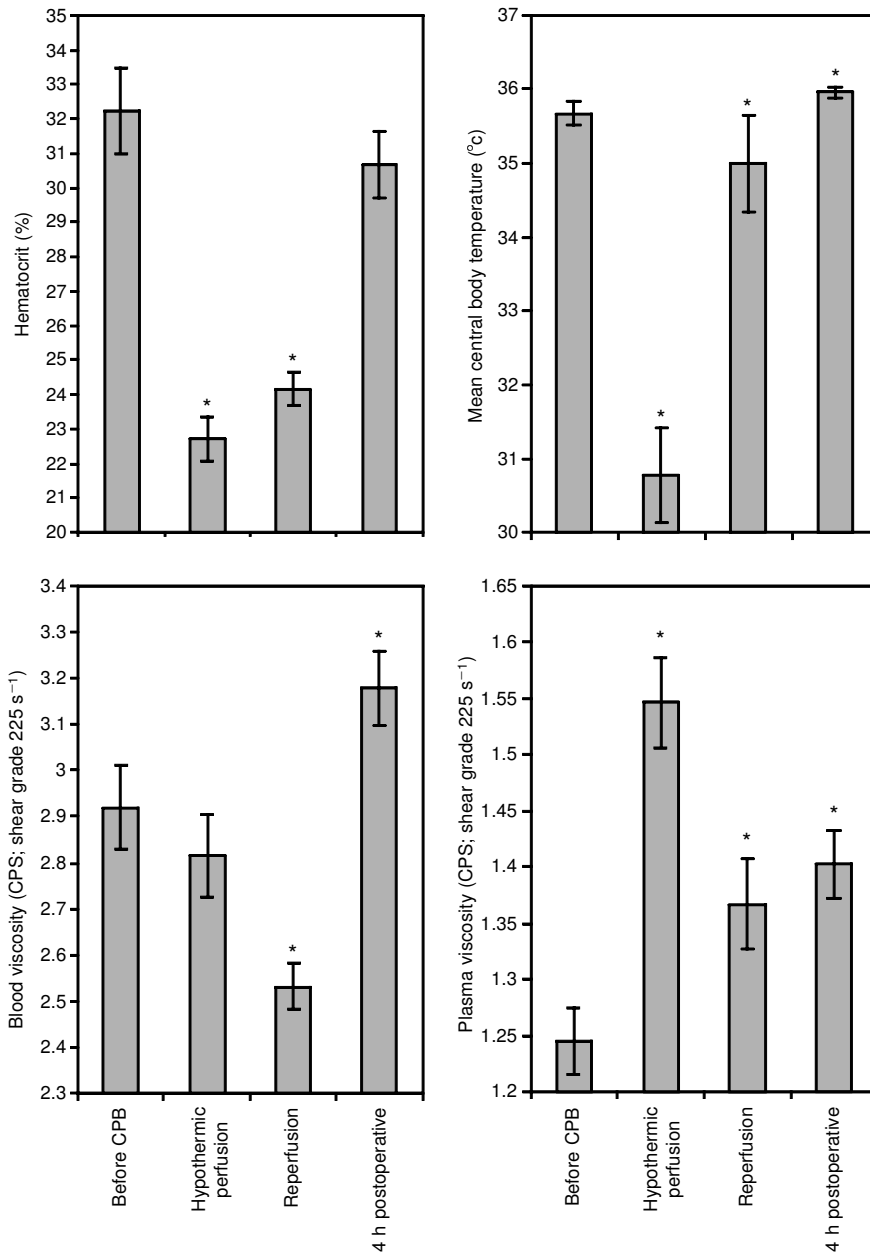
Figure 2.
*Data are given as mean ± SEM. *p < 0.05 compared to first column. The bars represent the analyses at the intra- and postoperative sample periods during cardiopulmonary bypass. During hypothermic perfusion (second bar in each diagram), plasma viscosity was elevated (lower right diagram), while blood viscosity (lower left diagram) was less elevated due to hemodilution (upper left diagram).*

Table 2. Cardiopulmonary bypass conditions.

	Before CPB	Aortic cross-clamping	Reperfusion	4 h postoperatively
Colloid oncotic pressure (mmHg)	16.0 (9.8–20.1)	15.8 (11.6–24.6)	16.6 (13.1–22.4)	19.7 (13.3–39.1)
Mean CPB flow (ml/min/kg)		184 (107–263)	201 (87–304)	
Central body temperature (°C)	35.8 (33.5–37.4)	30.7 (18–36.2)*†	36 (15–37)*	35.9 (35–36.9)

Data are given as median (minimum–maximum); CPB: cardiopulmonary bypass

functional renal alteration, or meaningful damage. The findings indicating decreased tubular function were only minor, and could not be interpreted as serious ischemic tubular damage. Elevated diuresis during cardiopulmonary bypass in the presence of constant colloid osmotic pressures might be interpreted as a worsened capacity for tubular concentration, or a raised gradient of glomerular filtration. Thus, the observed albuminuria, and the loss of higher molecular weight proteins into the urine,

Table 3. Correlation of main predictors to blood viscosity at normothermia and hypothermia.

	Blood viscosity at normothermia (prior to cardiopulmonary bypass)	Blood viscosity at hypothermic perfusion
Hemoglobin	**r = 0.805** **p < 0.0005**	r = 0.407 p = 0.012
Hematocrit	**r = 0.803** **p < 0.0005**	r = 0.403 p = 0.025
Plasma viscosity	r = 0.19 p = 0.259	**r = 0.589** **p < 0.0005**
Mean central body temperature	r = 0.118 p = 0.494	**r = −0.749** **p < 0.0005**

Significant correlations are highlighted
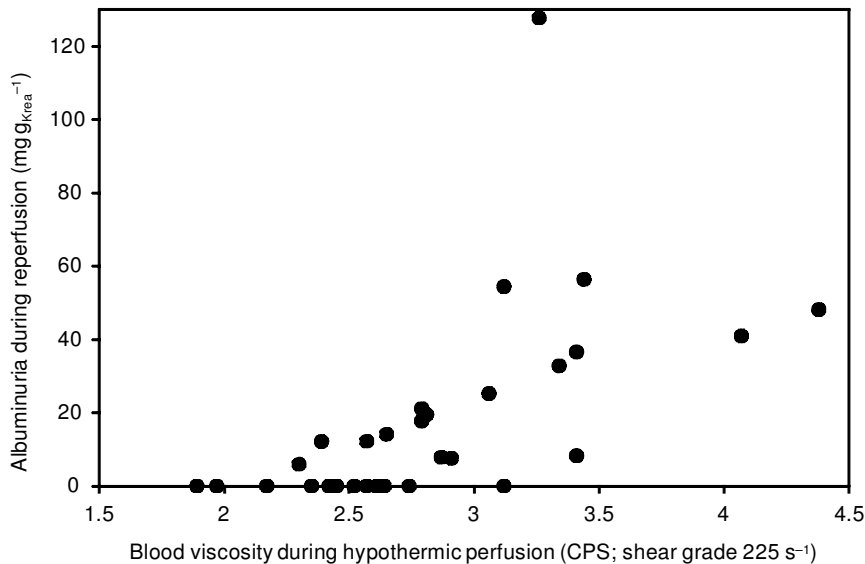
Figure 3.
Correlation of blood viscosity during hypo-sthermic perfusion and albuminuria during reperfusion: r = 0.705;   p < 0.0005; n = 34.

might be caused simply by an increased trans-glomerular filtration gradient, and not by the destruction of the glomerular membrane.[6,16,17] The quick postoperative normalization of proteinuria further supports the thesis of transitory functional disorder. The elevation of the transglomerular gradient, nonetheless, might be influenced by post-glomerular limitations in perfusion. If the capillary blood flow in the postglomerular plexus does not provide enough oxygen to the tubular cells, the kidney perpetuates the perfusion in the postglomerular capillary bed by dilation of the preglomerular capillaries at the expense of an increased filtration gradient.[17] This would explain the elevated excretion of sodium, and the elevated activity of N-acetyl-β-D-glucosaminidase, both of which are indicative of tubular alterations during cardiopulmonary bypass.

It is known that hemodilution during hypothermia improves the microcirculation,[11,12,18] while high blood viscosity can lead to capillary occlusion.[19] Besides all the factors influencing the kidneys

during cardiopulmonary bypass, our data showed a statistical correlation between blood viscosity during cardioplegia and albuminuria, as well as between blood viscosity and urinary values of N-acetyl-β-D-glucosaminidase. The descriptive design of our study does not allow to comment on the causality of this observations. The possibility that improvement of blood viscosity during hypothermic cardioplegia might improve renal function and protection now needs validation in a prospective interventional study. Moreover, the influence of plasma viscosity on blood viscosity during hypothermia should be considered as a means of elevating blood viscosity without changing the hematocrit.[20,21]

Limitations of the study

Clearly, some surgical procedures are associated with renal dysfunction more than others. It is reasonable to assume, therefore, that there is substantial heterogeneity within the population studied, and that such heterogeneity will attest to the number of factors

which may influence the kidney. For the same reason, it is difficult to comment on the potential impact of perioperative medication, or the use of nitroprusside, on renal function. As numerous postoperative conditions are associated with postoperative cardiac and renal function, it is advisable not to comment on the question whether intraoperative renal dysfunction as described is a predictor of acute renal failure or the need of dialysis.

Acknowledgements

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