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1 Effects of blood viscosity on renal function during cardiopulmonary bypass — investigations in infants and experimental setting in pig kidneys

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Objectives: Acute renal failure (ARF) is a common complication following open heart surgery especially in infants. Effects of blood viscosity on renal function are well known, but have not been investigated in cardiopulmonary bypass (CPS) as yet.

Material and methods: We investigated blood viscosity and different markers of glomerular and tubular renal function in a group of 37 infants below 18 month of age, receiving CPS surgery for different diagnoses.

In an experimental setting, we investigated 28 isolated pig-kidneys with different hematocrits in an autologous blood perfused model.

Results: In infants, creatinine clearance decreased and urinary excretion of albumin and β-NAG increased during the aortic cross clamp time (AT) and during the first hours following operation, indicating moderate glomerular and tubular damage. During AT, blood was hemodiluted to a hemoglobin of 8.4 ± 0.4 g/dl. Thus, blood viscosity during AT and hypothermia was slightly below pre-CPB values. Lower blood viscosity was related to less renal damage ($P < 0.01$).

In isolated pig-kidneys, group I ($n = 14$) was perfused with a hemoglobin of 10.2 ± 0.3 g/dl and group II ($n = 14$) was hemodiluted to 6.5 ± 0.9 g/dl. Group II kidneys showed lower vascular resistance, elevated creatinine clearance, elevated oxygen consumption and elevated sodium reabsorption ($P < 0.05$).

Conclusions: Reducing blood viscosity below physiological values improves tubular as well as glomerular function under CPB conditions. Thus we hold hemodilution to be an appropriate method for optimizing CPB procedures.

2 Uncoated and coated blood contact surfaces of a hollow-fiber oxygenator: an in-vitro comparison

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Objective: The hemocompatibility of oxygenators (OX) can be improved by coating of blood contact surfaces with biopolymers. In the new *Trillium* (TR) coating of the *Affinity* hollow-fiber OX, the blood–OX interaction was attempted to reduce by using two structurally different polymer layers. The aim of this in-vitro experiment was the comparison of both physical properties and hemocompatibility of TR-coated OX with the uncoated (UC) and *AOThel*-coated (AO) versions.

Method: For the experiment, three standardized circuits used, each with a roller-pump (flow rate:5 l/min) and a separate reservoir. The priming volume was a mixture of fresh, heparinized (100 IE/ml) human blood and Ringer's lactate solution (Hb: 8.0 g/dl). During a 180-min total circulation time, the blood temperature was reduced from 37°C to 20°C for 30 min after 120 min of per fusion. At the beginning and every 30 min of the circulation, blood count, free Hb, thrombocytic hemostasis (tPA, d-dimer, prothrombin fragments F1+2, TAT), PMN-elastase and complements C3c + C5a determined. In addition, the pressure drop was obtained. Scanning electron microscopic images of fibers, heat exchangers and OX-housing were performed after completing the experiment.

Results: The biggest pressure drop was in TR and lowest in UC. The latter showed the lowest hemolysis ratio; however, the thrombocyte consumption in UC was higher than in AO and TR. A significant difference between AO and TR was not found. Scanning electron microscopy showed clearly more accumulations of cellular blood elements and an increased aggregation of leukocytes on the UC-surface, compared to AO and TR, which in between displayed no remarkable differences.

Conclusions: 1. The pressure drop in coated systems is higher in the UC. 2. UC shows clear disadvantages in thrombocyte consumption and cellular adhesion compared with AO and TR, while significant differences could not be verified between AO and TR. 3. UC has a lower hemolysis tendency in comparison to coated systems, which is subject of a further investigation.

3 High-dose aprotinin reduces systemic inflammatory response syndrome during CABG

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Objectives: During pediatric cardiopulmonary bypass (CPB), low-dose aprotinin has been shown not to influence the systemic inflammatory response syndrome (SIRS). It is well established that aprotinin has beneficial influence on postoperative blood loss

during cardiac surgery. Thus, the aim of this study was to rule out the effect of high-dose aprotinin in respect to SIRS and clinical parameters in adult patients.

Methods: In this prospective, randomized, double-blind, placebo-controlled study, twenty patients were enrolled. In Group A patients ($n = 10$), high-dose aprotinin was administered (2 Mio KIU pre-bypass, 2 Mio KIU in prime, 0.5 Mio KIU/h during CPB). In Group C patients ($n = 10$) no aprotinin was used. Pro-inflammatory interleukin-6, anti-inflammatory interleukin-10, and clinical parameters were measured six times perioperatively. The values are presented as mean ± SEM.

Results: Four hours after CPB interleukin-6 concentration reached the maximum value being significantly lower in Group A patients as compared to Group C patients (615 ± 62 *vs* 1409 ± 252 pg/ml, respectively; $P = 0.019$). At the first postoperative day the concentration of interleukin-6 in Group A patients remained lower (218 ± 23 *vs* 526 ± 123 pg/ml, respectively; $P = 0.015$). In contrast interleukin-10 concentration was higher in Group A patients as compared to Group C patients after CPB (265 ± 91 *vs* 59 ± 13 pg/ml, respectively; $P = 0.03$). Postoperative blood loss was lower in Group A patients as compared to the Group C patients (648 ± 64 *vs* 1284 ± 183 ml, respectively; $P = 0.002$).

Conclusions: High-dose aprotinin treatment caused significantly less SIRS and reduced postoperative blood loss after CPB. Anti-inflammatory reaction was significantly enhanced in these patients, which suggests that the physiological reaction of the organism to reduce deleterious effects to CPB is strengthened by using high-dose aprotinin.

4 *In vivo* leucocyte–endothelial cell interaction induced by extracorporeal circulation: reduction by a coated tube system

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Objectives: The clinical complications of extracorporeal blood circulation (EBC) have been linked to disturbances in the microcirculation. In previous experiments we found *in vivo* an increased L/E cell interaction following EBC. As a therapeutical approach to prevent these deleterious effects a new agent to coat the tubing system, was used.

Methods: Intravital fluorescence microscopy was used on the dorsal skinfold chamber preparation in syrian golden hamsters. EBC was introduced via a micro-roller pump (1 ml/min) and a 60 cm silicon tube (1 mm inner diameter) shunted between the carotid artery and the jugular vein. Experiments were performed in chronically instrumented, awake animals (age: 10–14 weeks, weight: 65–75 g). Control tubes were uncoated, for the experiment a PEG-Hirudin-Iloprost® coating was used.

Results: Isovolemic EBC for 20 min resulted in an increase in rolling and adherent leukocytes in postcapillary venules. Micro- and macrohemodynamic parameters and functional capillary density were not affected. The use of the coated tube system resulted in a less pronounced induction of leucocyte/endothelial cell interaction.

Conclusions: L/E interaction in the microcirculation has been established as an indicator of the systemic activation induced by blood contact to synthetic surfaces during EBC. Coating the extracorporeal circuit reduced the increase in L/E interaction probably as a result of a attenuated activation of the coagulation-fibrinolytic system including a reduced platelet activation.

Experiment		Baseline	30 min	4 h	24 h
EBC 20 min	Roller (%)	9 ± 2	19 ± 4*	36 ± 5*	15 ± 3*
Control	Sticker (mm²]	24 ± 26	125 ± 46*	260 ± 51*	330 ± 130*
EBC 20 min	Roller (%)	9 ± 3	13 ± 8	24 ± 12*#	11 ± 3
Coated tube	Sticker (mm²)	28 ± 25	42 ± 42	139 ± 11	194 ± 152*#

Data are means ± SD; $n = 7$ in each group; *$P < 0.05$ BL *vs* TP; †$P < 0.05$ Control *vs* Exp.

5 Cerebral hemodynamics and oxygenation before and after modified ultrafiltration following corrective cardiac surgery in infants and children

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Introduction: Modified ultrafiltration (MUF) at the termination of cardiopulmonary bypass (CPB) has been considered to remove accumulated fluid and inflammatory mediators and thereby to improve cerebral metabolic rate in infants after cardiac surgery. The aim of this study was to investigate change in cerebral hemodynamics and oxygenation before and after MUF following corrective cardiac surgery of congenital heart defects.

Methods: In 55 neonates and infants below the age of 9 month's (weight 7.5 ± 4 kg) undergoing surgical correction of congenital

heart disease by means of full flow CPB (120–150 ml/kg body weight) with moderate hypothermia (24 ± 6°C) and alpha-stat strategy were prospectively studied either to MUF ($n = 25$) or no MUF (n=20). Continuous determinations of regional cerebral hemoglobin saturation (rSO_2) by near infrared spectroscopy (NIRS) and mean flow velocity (MFV) in the middle cerebral artery (MCA) by transcranial Doppler (TCD) provided qualitative on-line information of cerebral perfusion and oxygenation, The pulsatility index (PI) was calculated according to the formula (PI = maximal flow velocity – end-diastolic flow velocity/mean flow velocity). Other hemodynamic parameters such as mean arterial blood pressure (MAP), hemoglobin (Hb) and arterial oxygen saturation (SO_2) were simultaneously documented.

Results: There was no significant difference in bypass time and minimal rectal temperature in infants with and without MUF. An initially decreased diastolic flow velocity pattern — resulting in higher calculated PI — decreased significantly at the end of operation in infants with more than those without MUF (Table). The change in systemic and regional cerebral hemoglobin saturation was not significantly different in both groups.

Table. Parameters pre- and after ultrafiltration in infants with and without MUF

	SO_2 (%)	MAP (mmHg)	Hb (mg/dl)	PI	Vm (cm/s)	rSO_2 (%)
MUF ($n = 25$)	96/96*	44/57**	8.7/11**	1.9/1.1**	43/39*	51/53*
No MUF ($n = 20$)	89/92*	56/65**	8.6/10**	1.5/1.3**	58/53*	54/58*

*Not significant *vs* pre MUF; **$P < 0.001$ *vs* pre MUF.

Conclusion: The magnitude of lowering the cerebrovascular resistance and possible improvements of cerebral perfusion after CPB was more observed in the MUF group. However, the beneficial effect to immediate postoperative hemodynamics and regional oxygenations seem to be not significant.

6 Is the precise control of circulating heparin levels during cardiopulmonary bypass beneficial in paediatric open-heart surgery?

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Objectives: Despite careful monitoring of anticoagulation during cardiopulmonary bypass (CPB) by means of activated coagulation time (ACT), thrombin generation does occur at variable rates, initiating several pro-inflammatory reactions. The mechanisms responsible for this activation of the coagulation cascade include inadequate heparinisation, often masked by hypothermia and haemodilution. The objective of this study was to compare the effects of two methods of managing anticoagulation during CPB in infants and children.

Methods: Twenty patients, aged 4 months to 17 years, undergoing elective cardiac surgery were prospectively randomized to receive either a standard dose of heparin (300 IU/kg) (Group A, $n = 10$) or a dose sufficient to achieve a whole blood heparin concentration [Hep] = 4.8 IU/ml (Group B, $n = 10$). ACT was maintained >480 s in both groups. [Hep] was measured by on-site testing with a heparin-protamine titration method (HMS, Medtronic, Inc.). The following variables were studied: prothrombin fragments (PF1+2), D-dimers (D-d), β-thromboglobulin (β-TG), platelet count, postoperative blood losses, standardized blood and blood products administration, intensive care and hospital stay.

Results: The groups were comparable with regards to age, weight, disease complexity, duration of CPB and a number of other variables. The results are summarized in the Table.

Blood losses during the first 24 h (26.4 ± 4.7 *vs* 15.2 ± 3.7 ml/kg/24 h, $P = 0.05$) and requirement for transfusion of blood (11.4 ± 3.6 *vs* 3.1 ± 1.3 ml/kg, $P = 0.05$) and fresh frozen plasma (6.1 ± 2.2 *vs* 0.9 ± 0.3 ml/kg, $P = 0.09$) were lower in Group B, when compared to Group A.

Conclusions: Management of anticoagulation during CPB aiming to achieve and maintain an [Hep] significantly higher than 'normal' results in less activation of the coagulation cascade, lower fibrinolysis, and lower blood losses and need for tranfusions. Further studies, on a larger number of children, are warranted to better define the clinical impact of these findings.

	[Hep] IU/ml	PF 1+2 (nmol/l)		Fibrinogen		β-TG (ng/ml)		D-dimers (ng/ml)	
		Pre-CPB	Post-CPB	Pre-CPB	Post-CPB	Pre-CPB	Post-CPB	Pre-CPB	Post-CPB
Group A	1.7 ± 0.4	1.09 ± 0.16	3.5 ± 0.68*	2.95 ± 0.20	1.0 ± 0.16*	160 ± 13	1207 ± 223*	282 ± 66	2249 ± 557*
Group B	4.8 ± 0.4	1.21 ± 0.11	1.4 ± 0.34*	2.33 ± 0.20	1.13 ± 0.13	134 ± 20	818 ± 118*	218 ± 67	857 ± 220*
P (A *vs* B)	≤ 0.001	0.58	0.02	0.03	0.05	0.28	0.40	0.50	0.09

Data are expressed as mean ± standard error of mean. *P* values calculated for % changes from baseline by Student *t* test or single factor analysis of variance (ANOVA), as appropriate, accepting as significant a $P \leq 0.05$. *$P \leq$] 0.01 Post-CPB *vs* Pre-CPB.

7 Is gastric malperfusion and endotoxemia one motor of the systemic inflammatory response syndrome following cardiac surgery?

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Introduction: Gastric mucosal acidosis and endotoxemia seems to be responsible for cytokine activation and development of the systemic inflammatory response syndrome (SIRS) in patients with congestive heart failure. In a retrospective study we previously concluded that patients with congestive heart failure (CHF) and a low preoperative cardiac index had a higher incidence of SIRS following cardiopulmonary bypass (CPB) than patients without CHF. In a prospective study we tried to prove our hypothesis that CHF leads to malperfusion of the gut and subsequently to endotoxin release with cytokine activation.

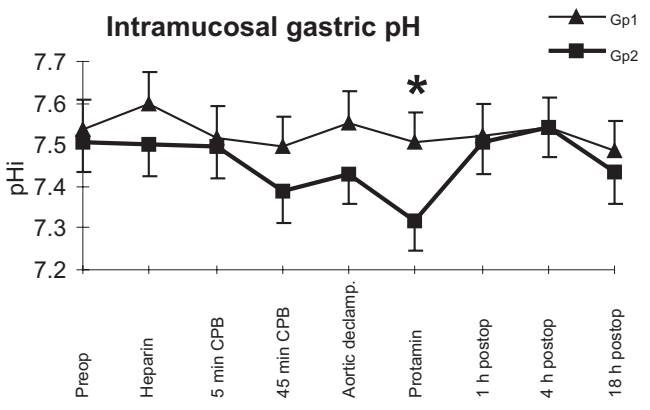
Methods: We evaluated one group with low risk for developing SIRS (Group1: coronary artery bypass grafting without CHF) and a high risk group (Group 2: mitral valve surgery with CHF) with 10 patients each for clinical and laboratory signs of SIRS as defined by BONE. Intramucosal gastric pH, endotoxin was detected using a tonometric gastric tube (Baxter Inc.), TNFα and interleukin 6 (IL6) were measured with an ELISA at nine different times pre-, intra- and postoperatively.

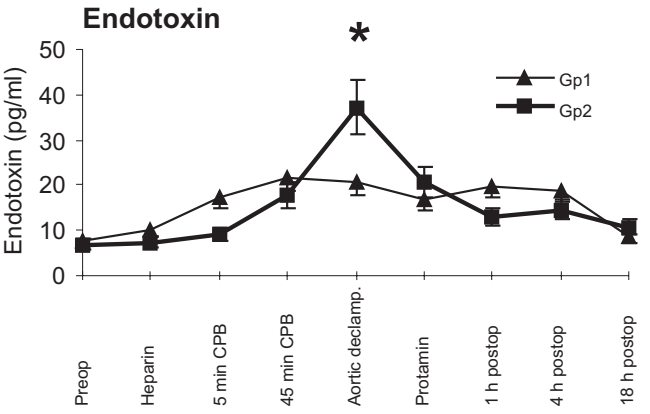
Results: Groups were similar with regards to age and sex. Cardiac Index was lower in Group 2 (1.7 ± 0.3 l/min/cm^3) than in Group 1 (2.8 ± 0.5 l/min/cm^3; $P < 0.05$). In Group 2 the aortic cross clamping time was longer (Group 1: 59.6 ± 15.2 min, Group 2: 42.7 ± 19.4 min) and norepinephrine requirements for maintenance of vascular resistance were higher (8.2 ± 12.6 mg) than in Group 1 (1.7 ± 2 mg; $P < 0.05$).

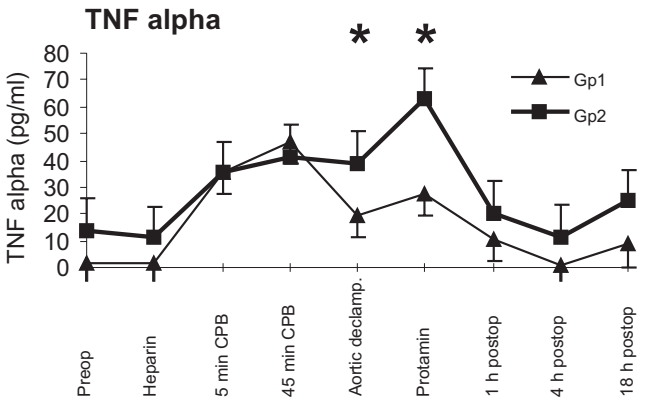
At the end of CPB gastric pH dropped to 7.33 ± 0.34 in Group 2 whereas the other group remained stable between 7.47 and 7.5 ($P < 0.05$). Endotoxin levels were significantly elevated and significantly higher in Group 2 (37.2 ± 3.2 pg/ml) than in Group 1 (20.6 ± 3.7 pg/ml; $P < 0.05$) after aortic cross clamp was opened. In Group 1 only in 1 of 3 patients (33%) with gastric acidosis endotoxin was detected, whereas in Group 2 8/9 patients (88%) endotoxemia occurred.

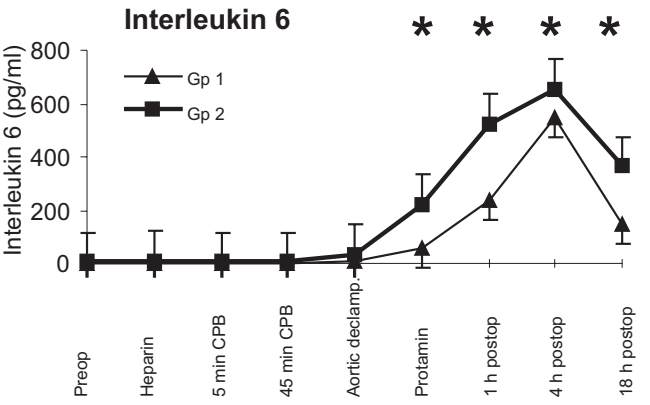
TNFα was elevated in both groups during CPB and significantly higher in Group 2 at aortic declamping (Group 1: 19.6 ± 2.9 pg/ml; Group 2: 39 ± 4.8 pg/ml; $P < 0.05$) and after protamin application (Group 1: 27.3 ± 4.2 pg/ml; Group 2: 62.8 ± 8.1 pg/ml; $P < 0.05$). After protamin application IL6 raised postoperatively and was significantly higher in Group 2 (653 ± 75 pg/ml) than in Group 1 (547 ± 439 pg/ml). SIRS occurred more often in Group 2 (9/10) than in Group 1 (6/10) postoperatively. All patients with detected endotoxemia developed SIRS (13/13).

Conclusion: SIRS is more common in patients with CHF undergoing CPB than in others. This seems to be related to a drop of gastric pH as a sign of malperfusion. Consecutively endotoxemia occurs more often and seems to be a trigger of cytokine activation (TNFα, IL6) making higher norepinephrine application necessary. Our study emphasize the role of splanchnic malperfusion and endotoxemia as one mechanism responsible for the development of SIRS.









8 Inflammatory response to cardiopulmonary bypass in neonates and young children: endotoxin release, cytokine production, and gastrointestinal permeability

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Objectives: Neonates and young children are considered as high-risk patients in developing postoperative complication following open-heart surgery. This usually results from an over-stimulated inflammatory response to cardiopulmonary bypass (CPB), which is thought to be initiated by a number of processes, including blood contact with the artificial surface and reperfusion injury. We performed a study to examine whether there is an increase in gastrointestinal permeability during and after CPB in these young patients, and whether the increase in gastrointestinal permeability will lead to release of endotoxin and further production of tumor necrosis factor α (TNFα).

Methods: Eleven pediatric patients whose body weight was less than 10 kg were prospectively included in this study. Blood samples were taken before, during, and at the end of CPB, and at 1 h, 3 h, 12 h, 24 h and 48 h postoperatively. Endotoxin was measured from platelet rich plasma by the limulus amebocyte lysate assay. TNFα production was measured by enzyme-immunoassay. At postoperative 0 h, 12 h, 24 h, and 48 h, gastrointestinal permeability was determined by the sugar absorption test that measures the ratio of urinary excretion of lactulose/L-rhamnose (non-mediated diffusion), D-xylose (passive) and 3-O-methyl-D-glucose (active carrier mediated transport) after oral administration.

Results: Endotoxin concentrations were found very low (<3 pg/ml) in most of the samples during and after CPB. Only in one patient high levels of endotoxin were observed at 20 min CPB (16 pg/ml) and 12 h post CPB (17 pg/ml). TNFα increased progressively during the postoperative period (from 1.5 ± 0.5 pg/ml at baseline to 4.2 ± 0.8 pg/ml 48 h postoperatively). An increase in gastrointestinal permeability was found in most of patients (10 of 11) up to 48 h postoperatively, as indicated by increased lactulose/L-rhamnose ratio and decreased D-xylose and 3-O-methyl-D-glucose excretion percentage. No correlation was found between increased gastrointestinal permeability and plasma concentration of endotoxin, nor between endotoxin and TNFα production.

Conclusions: These results suggest that gastrointestinal permeability increases in neonates and young children undergoing CPB. However, this increase does not lead to clinical significant endotoxemia. TNFα production during and after CPB is likely due to other mechanisms than endotoxin only.

9 Regulation of platelet–leukocyte interaction in simulated ECC: attenuation with heparin surface modification

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Background: Blood exposure to artificial surfaces results in blood cell activation. The present study analyses the impact of heparin immobilisation in a model of simulated extracorporeal circulation SECC on leukocyte and platelet activation, expression of surface markers and adhesion receptors, as well as on leukocyte-platelet interaction.

Methods: Fresh heparinized human blood was recirculated in *in vitro* cardiopulmonary bypass circuits (untreated: $n = 10$; coated $n = 10$; randomized, blinded for group affiliation). Samples were taken before and 15, 30, 60, 120, and 180 min after commencement of circulation. By means of flow cytometry neutrophil activation (respiratory burst; expression of CD11b), platelet activation (GpIb and GMP140 expression), as well as numbers of monocytes/PMNs binding platelets were assessed.

Results: Blood cell activation and interaction demonstrated ECC-dependent dynamics. SECC produced significant PMN activation and platelet GMP140 expression. Monocytes bound more platelets and at an faster rate than PMNs. In the group with heparin-coated surfaces PMN activation was significantly reduced, GMP140 expression less upregulated and leukocyte–platelet adhesion diminished.

Conclusions: Heparin coating in SECC reduces neutrophil and platelet activation and attenuates leukocyte–platelet adhesion. These studies indicate that there are cross-links between hemostatic and inflammatory disorders associated with ECC.

10 Aprotinin does not influence the inflammatory reaction to cardiopulmonary bypass in humans

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Cardiopulmonary bypass (CPB) is associated with a significant inflammatory reaction which has been related to complement activation, and release of various inflammatory mediators and proteolytic enzymes [1]. Aprotinin, a low molecular-weight peptide inhibitor of trypsin, kallikrein and plasmin has been proposed to influence whole body inflammatory response inhibiting kallikrein formation, complement activation and neutrophil activation [2,3]. The present study was designed to determine whether aprotinin is able to reduce the inflammatory reaction to CPB in humans.

After institutional approval and written informed consent, 60 male patients, scheduled for primary coronary artery bypass grafting, were enrolled in this prospective double-blinded study. The patients were randomized into three groups: Group high dose aprotinin (HD) received 2×10^6 KIU followed by 0.5×10^6 KIU/h and 2×10^6 KIU added to the pump prime; group low dose (LD) received half that dose and the control group (CTRL) received no aprotinin. No corticosteroids were given. Anesthesia consisted of a high dose sufentanil infusion. The CPB circuit was primed with

gelatin and the flow rate was maintained at 2.4 l/min/m^2 using a non-pulsatile flow. An anterograde, cold, crystalloid cardioplegic solution was used and mild hypothermia (30°C) was maintained during CPB. We measured tumor necrosis factor (TNF), interleukin 6, 8, 10 (IL6, IL8, IL10), endotoxin, prekallikrein, and prostaglandin D2 (PGD2) at the following time points: 30 min after study drug loading, 10 min after beginning of CPB, before end of CPB, 4 h after CPB, 1st postoperative day (POD1) and 2nd postoperative day (POD2). Data were analyzed using an analysis of variance for repeated measurements after logarithmic transformation to achieve normalization. There was no significant difference between groups in number of anastomosis, duration of CPB and aortic clamping. All three groups showed a significant inflammatory reaction characterized by an increase of TNF up to 46 pg/ml, IL6 up to 600 pg/ml, IL8 up to 27 pg/ml with no difference between the treatment and the placebo groups. This inflammatory reaction started at the beginning of CPB, was maximal 4 h post-CPB and resolved on POD1 and POD2. Endotoxin levels at end of CPB as well as the maximum increase were slightly lower in the treated than in the CTRL group. However, this difference was essentially due to one CTRL patient with very high endotoxin levels. The proinflammatory reaction was accompanied by a significant increase in the anti-inflammatory cytokine IL10. No group has a significant activation of the complement system. Prekallikrein decreased all groups and PGD2 increased in all groups up to 100 pg/ml. Prekallikrein was significantly lower and PGD2 was significantly higher in the CTRL group only 10 min after beginning of CPB.

Our data show that aprotinin has no significant influence on the inflammatory reaction to CPB in men.

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11 Free radicals induced lipid peroxidation following reperfusion in infants cardiac surgery: relationship to the release of the brain marker protein S-100 into the serum

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Introduction: Measurement of malondialdehyde (MDA) in the serum, as a marker of free radical induced lipid peroxidation may provide possible information on radicals accentuated structural membrane injury. The detection of protein S-100 in serum, which is exclusively specific for cytoplasma of astroglial and Schwann cells in association with extracorporeal perfusion, may quite possibly indicate either an increased cell membrane permeability or cell injury. The aim of this study therefore was to evaluate the serum kinetics of protein S-100 in relationship to possible free radicals mediated cerebral membrane injury in infants undergoing cardiac surgery by means of cardiopulmonary bypass (CPB).

Methods: 56 patients (neonate $n = 7$, infants $n = 16$, children $n = 23$) were enrolled in this study. Cardiac surgery was performed using full-flow CPB (120–150 ml/kg/min), minimal rectal temperature (26 ± 7.5°C), and minimal hemoglobin concentration (7.4 ± 1.1 mg/dl). Total circulatory arrest was not used. Blood samples were collected from the same venous line at the following intervals: before CPB, 10 min. after CPB start, 10 min after aortic cross clamping, during CPB, 5 min following declamping of the aorta. The blood samples were treated separately immediately after collection. The S-100 protein serum concentrations were analyzed using a commercially available LIA kit (Sangtec® Medical AB, Bromma, Sweden). MDA was measured (MDA-thiobarbituric acid adduct) using HPLC.

Results: In comparison to the pre-bypass values, a significant increase in the concentration of protein S-100 was found immediately after the start of CPB ($P = 0.01$). There was a continuous elevation of the concentration of protein S-100 in the following phases of CPB. However, the main release of protein S-100 was found in the reperfusion phase after the declamping of the aorta and the end of CPB ($P = 0.0001$). In comparison to the pre-bypass values the serum concentrations of malondialdehyde were decreased 5 minutes after cross clamping of the aorta ($P = 0.001$). Parallel to the increase of protein S-100 concomitant elevation of serum MD were also found following the declamping of the aorta and after the end of CPB ($P = 0.0003$).

The maximal serum concentrations of protein S-100 correlated significantly to bypass time ($r = 0.7$, $P = 0.0007$), cross-clamping time ($r = 0.57$, $P = 0.001$) and minimal rectal temperature during CPB (–0.57, $P = 0.001$). The maximal MDA values correlated significantly to cross-clamping time ($r = 0.46$, $P = 0.004$) and minimal rectal temperature ($r = 0.40$, $P = 0.007$).

Conclusion: The concomitant elevation of the concentration of MDA and the astroglial cell marker S-100 could support the view of the role of free-radicals mediated transient ischemia reperfusion membrane injury in the cerebral endothelial microvascular. These observations may have potential therapeutic applications to preserve and protect cellular and tissue function in clinical conditions

12 Nerve growth factor levels rise following cardiopulmonary bypass in children: a novel mediator in the systemic inflammatory response syndrome?

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Objectives: Nerve growth factor (NGF) plays a crucial role in the differentiation and survival of sympathetic neurones, including the ones represented in the cardiovascular system. NGF has also been reported to be an intermediary product in various inflammatory reactions. The aim of this study was to investigate whether cardiopulmonary bypass (CPB) has any effects on NGF release and to determine the time course of any changes in its release.

Methods: Twelve consecutive children undergoing elective cardiac surgery were recruited for the purposes of this study. The

plasma levels of NGF, interleukin 6 (IL-6) and interleukin-8 (IL-8) were measured by enzyme-linked immunosorbent assay (ELISA). Samples were obtained from the patients at the following time points: induction of anaesthesia, end of CPB, and at 1, 2 and 24 h following CPB.

Results: There was a highly significant increase in the release of NGF following CPB, reaching its highest concentration at 2 h following CPB. The pattern of release was very similar to that observed for IL-6 and IL-8. The results are summarised in the Table.

Conclusions: NGF is released following CPB in paediatric patients, with a similar pattern to the one observed for known mediators of the systemic inflammatory response to CPB. Further studies, both in paediatric and adult patients, are needed to elucidate the role of NGF in the pathophysiology of the body response to CPB and to evaluate its clinical impact.

	Pre-op	End-CPB	1 h post-CPB	2 h post-CPB	24 h post-CPB
NGF (pg/ml)	199.5	1023.3	3198.9	3382.2	1398.6
CI	(64.7–615.2)	(429.6–2437.2)	(1692.8–6045.0)	(1838.6–6221.6)	(504.5–3827.4)
P value		≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
IL-6 (pg/ml)	4.1	40.4	167.5	252.4	66.1
CI	(1.4–12.2)	(17.0–96.3)	(101.6–276.0)	(152.1–418.8)	(39.9–109.6)
P value		≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05
IL-8 (pg/ml)	5.5	36.0	111.1	97.2	20.3
CI	(2.0–15.2)	(20.6–62.7)	(74.9–165.0)	(57.0–165.6)	(8.1–50.9)
P value		≤ 0.05	≤ 0.05	≤ 0.05	≤ 0.05

Data are expressed as geometric means of log-transformed values with 95% confidence interval (CI). Single factor analysis of variance (ANOVA) and Student *t* test were used, as appropriate, to determine differences in NGF and cytokine levels at different time points. A *P* value ≤ 0.05 was accepted as significant.

13 Induction of interleukin-10 during extracorporeal circulation

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Problem: The extracorporeal circulation (ECC) causes changes in cellular and cytokine pattern in addition to activation of complement system. These alterations result in a temporary depression of immunity and a perioperative susceptibility to infections. T lymphocytes required for both cell-mediated immune response and the production of antibody by B lymphocytes, are composed of two distinct subsets: Th1 and Th2 cells. Th1 cells produce IL-2 and interferon-γ and execute cell-mediated immune response; whereas Th2 cells produce IL-4, IL-5 and IL-10 and assist in antibody production for humoral immunity. While the influence of ECC in production and changes of several interleukins are known, it is still unclear if ECC induces IL-10 production and contribute to depression of immunity.

Material and methods: Twenty patients undergoing open heart operations without evidence of a concomitant malignant or immunologic disease; HIV and HBV seronegative were studied. EDTA-blood samples were drawn on six occasions. WBC was performed and FACS analysis enrolled. IL-10 was measured after cryopreservation of plasma by quantitative "sandwich" enzyme immunoassay technique (sensitivity 1 pg/ml).

Results: The total leukocyte count decreases at the institution of ECC (3521 ± 871) and remains nearly unchanged through the aortic clamping time (3503 ± 1370). After removal of aortic clamp a significant leucocytosis occurs (8085 ± 3571), through 3.POD (10708 ± 3606). The phasic changes of leukocytes is mainly caused by identical course of neutrophils. IL-10 shows a monophasic course with a peak concomitant to removal of aortic clamp (45.5 ± 49.6 pg/ml) and falls to preoperative levels at 3.POD (3.2 ± 4.5 pg/ml).

Conclusion: The increased level of IL-10 during the ECC indicates an activation of Th2 cells. IL-10 inhibits the production of IFN-γ, induces the differentiation of Th2 cells from uncommitted T cells. The inhibitory effect of IL-10 on Th1 cell differentiation causes a further depression of cell-mediated immunity during the early postoperative phase.

14 L-arginine and substance P reverse the pulmonary endothelial dysfunction caused by congenital heart surgery

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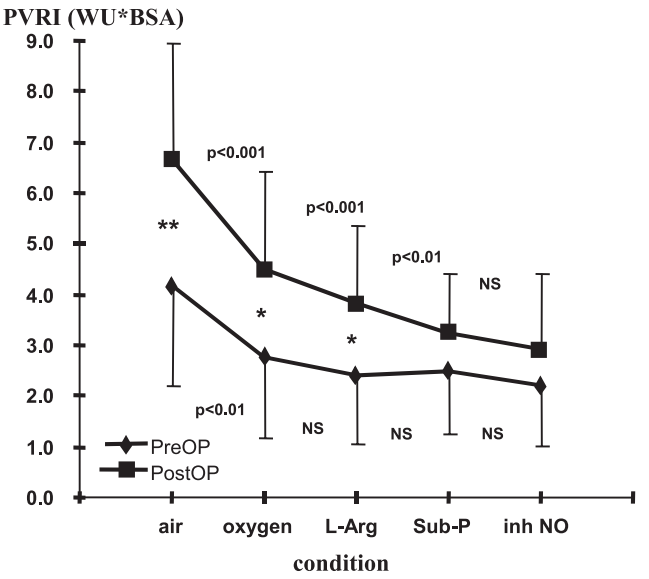
Objectives: The increase in pulmonary vascular resistance (PVR) seen in children after cardiopulmonary bypass has been attributed to transient pulmonary endothelial dysfunction (PED). We therefore examined PED in children with congenital heart disease by assessing the L-arginine-nitric-oxide (NO) pathway in terms of substrate supplementation (L-arginine [L-Arg]), stimulation of endogenous nitric oxide release (substance P[Sub-P]), and end-

product provision (inhaled NO) before and after open heart surgery.

Methods: Ten unoperated patients (0.62 ± 0.27 years) with pulmonary hypertension undergoing cardiac catheterisation, and 10 patients (0.64 ± 0.73 years) early after cardiopulmonary bypass were examined. All were sedated, paralysed and received positive pressure ventilation. Blood samples and pressure measurements were taken from catheters in the pulmonary artery and the pulmonary vein or left atrium. Respiratory mass spectrometry was used to measure oxygen uptake, and cardiac output was determined by the direct Fick method. PVR was calculated during steady state at ventilation with room air, during $FiO_2 = 0.65$, and then during additional intravenous infusion of L-Arg (15 mg/kg/min), Sub-P (1 pmol/kg/min), and finally inhalation of NO (20 parts per million).

Results: In both patient groups, oxygen supplementation was the most potent pulmonary vasodilator. In preoperative patients, the lack of a further significant change with L-Arg, Sub-P and inhaled NO suggests little pre-existing PED. Postoperative PVR was higher with an additional endothelial contribution that was restorable with L-Arg and Sub-P.



Conclusion: Postoperatively, the rise in PVR suggested pulmonary endothelial dysfunction restorable by L-Arg and Sub-P with no additional effect of inhaled NO. These results may indicate important new treatment strategies for these patients.

15 Is there a capillary leak after cardiopulmonary bypass in pigs?

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Objectives: Systemic inflammatory response to cardiopulmonary bypass (CPB) is claimed to cause capillary leakage, which has not yet been demonstrated in a standardized animal model.

Methods: Twenty-six pigs were subjected to 120 min CPB (90 min cardioplegic cardiac arrest, 30 min reperfusion). Left ventricular (LV) power during ejection (= CO × AoP/ejection time) was calculated. Blood samples (before CPB, at 90 min, 120 min CPB and every 30 min until 5 h after CPB) were analyzed for the receptor antagonist IL-1ra, leukocytes, the leukocyte neutral proteinase inhibitor (LNPI to assess leukocyte activation), and plasma protein concentration (PP). Half-life of intravenously injected Evans Blue and intravascular protein content (IVP) were measured before and 3.5 h after CPB. Histologic samples of the LV-wall and septum were assessed for leukocyte infiltration.

Results: LV-power was markedly reduced after CPB. Leukocytes, LNPI and IL-1ra were significantly upregulated following CPB and a marked leukocyte infiltration to the subendocardium of the LV was present 5 h after CPB. PP was reduced by the crystalloid primed CPB, it increased after CPB, but did not reach the pre-CPB level. IVP was reduced after CPB. Half-life of intravenously injected Evans Blue was not affected by CPB.

Conclusion: In the present model CPB was followed by depression of left ventricular function and a systemic inflammatory response. An increase in microvascular permeability to plasma proteins, however, was absent after 120 min of CPB including 90 min of myocardial ischemia. Fluid shift from the intra- to extravascular compartment occurred due to an increased microvascular effective filtration pressure. This is a result of reduced plasma colloid osmotic pressure due to hemodilution and, in part, to protein loss to the foreign surfaces of the CPB-system.

16 Progesterone and interleukin-8 during and after cardiopulmonary bypass in infants and children

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Objectives: It has been shown that proinflammatory cytokines are suppressed by progesterone (P). cardiopulmonary bypass (CPB) leads to the release of pro- and anti-inflammatory cytokines. Because sex steroids have the ability to adsorb extensively to synthetic surfaces a decrease of P during the contact with the CPB circuit is conceivable. If P concentrations would decrease the inflammatory response to CPB could be effected. The purpose of the study was to look for the course of P in relation to the proinflammatory cytokine interleukin-8 (IL-8) during and after CPB.

Methods: Twelve infants and children (age 2 months to 15 years, median 2.4 years, four females) were operated on CPB for congen-

ital heart disease (2 ASD, 5 VSD, 3 Fallot, subaortic stenosis, aortopulmonary window). Blood samples were taken before, during (10 min after onset) and after (disconnection, 6 and 24 h, 3 and 7 days) CPB. Plasma concentrations of P and IL-8 were determined using a RIA- and an ELISA-kit, respectively.

Results: P concentrations before CPB were 0,21 ng/ml (median, 0.012–0.72). They increased to a maximum of 5.59 ng/ml (0.13–35.4) at 6 h after CPB. The pre-CPB concentrations were reached on the 7th day post-CPB. This course of P concentrations was similar in female and male infants of every age. The maximum IL-8 concentrations were found at 6 h after CPB. The decline of IL-8 from 6 to 24 h after CPB was correlated to the P concentration at 6 h ($r = 0.77$).

Conclusion: The results were in contrast to our expectation because P increased with CPB. However, the significant increase with a maximum at 6 h after CPB needs further explanation. The maximal P concentrations coincided with the peak of the IL-8 response and correlated to the following decrease of IL-8. We speculate that the release of P during and after CPB could be of benefit in terminating the associated proinflammatory response. Further studies are needed to clarify the physiology and role of the P increase in the setting of CPB.

17 Leukocyte interactions with surface modified biomaterials on *in vitro* flow conditions

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It is well known that blood contact to foreign surfaces is leading to an inflammatory response including stimulation of complement system and leukocytes.

Investigating the influence of modified biomaterials on leukocyte activation we used a dynamic model approaching flow conditions of extracorporeal circulation. Four different surface modifications (three heparin and one non-heparin coatings) were compared to each other and native control material, which is routinely used in cardiopulmonary bypass and extracorporeal circulation. Fresh human donor blood was heparinized and recirculated for 180 min in a tubing circuit with an integrated blood filter and a roller pump.

Leukocyte number, differential blood analyses, elastase and anaphylatoxin C5a were determined to investigate the effects of blood/surface contact on leukocytes.

Leukocyte stimulation was reduced in different amount compared to the control depending on the coating method. Heparin coatings showed a slight drop of monocyte and granulocyte percentage after 180 min of perfusion, whereas the control and the non-heparin modification induced a larger decrease. Elastase and C5a concentrations detected differences between the modifications themselves. C5a and elastase increased in each case in the course of the perfusion time.

We conclude that heparin coatings induce less leukocyte activation than the native control material. The effect of biomaterials on leukocyte activation depends on the type of the coating method. It is shown that the flow model is suitable for investigations on leukocytes under hemodynamic flow conditions similar to those usual in clinical application.

18 Mechanical and pharmacological strategies to reduce the systemic inflammatory response during CABG

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Objectives: Zero-balanced and modified ultrafiltration are known to reduce the systemic inflammatory response syndrome (SIRS) during pediatric cardiopulmonary bypass (CPB), while corticosteroids have been used successfully in adult patients. Thus, the aim of this study was to compare the effect of mechanical to pharmacological strategies in respect to SIRS in adult patients.

Methods: In a prospective, randomized, controlled study, 73 patients were enrolled. In Group UF patients ($n = 21$), zero-balanced ultrafiltration was performed during re-warming and modified ultrafiltration immediately after CPB. In Group MP patients ($n = 26$), 1 g methylprednisolone was given 30 min before CPB. The Group C patients ($n = 26$), received placebo instead.

Results: After CPB the concentration of interleukin(IL)-6 was significantly lower in Group UF and in Group MP compared with Group C (105 ± 20 and 124 ± 29 *vs* 203 ± 46 pg/ml, respectively; $P < 0.05$, mean ± SEM). Anti-inflammatory IL-10 showed a significant ($P < 0.01$) peak after CPB in Group MP as compared to Group UF and also to Group C. In Group UF, intrapulmonary shunt fraction decreased during modified ultrafiltration from 31 ± 1.2 to $25 \pm 1.3\%$ while PaO_2 and mean arterial pressure increased ($P < 0.01$). After CPB the PaO_2 and also oxygen distribution in Group MP were higher ($P < 0.05$) as compared with Group C patients. Extubation-time was shorter in the UF-group compared to the Group C patients (6.1 ± 0.5 *vs* 8.6 ± 0.7 h, respectively; $P < 0.05$).

Conclusions: The combination of zero-balanced and modified ultrafiltration reduces SIRS immediately after CPB, resulting in higher arterial pressure, improved pulmonary gas exchange, and shorter need of respiratory support. Methylprednisolone led to a marked reduction of the pro-inflammatory and an increase of anti-inflammatory response. Both strategies to reduce SIRS had positive influence on clinical parameters.

19 Neurodevelopmental outcome related to cerebral risk factors in children after neonatal arterial switch operation

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Objectives: Prospective study to evaluate midterm neurodevelopmental status in childhood and to correlate it to pre-/perinatal asphyxia, intraventricular cerebral haemorrhage, seizures and neuronal cell damage after neonatal arterial switch operation for transposition of the great arteries with combined cardiopulmonary bypass (CPB) and deep hypothermic cardiocirculatory arrest.

Methods: Protracted birth (PB), perinatal asphyxia (PA), intraventricular cerebral haemorrhage (IVH) evaluated by pre/peri/postoperative cranial ultrasound, clinical seizures (CS) and high levels of the neuron-specific enolase (NSE) prior to as well as immediately after and 4 and 24 h after CPB in 25 neonates (mean age 7 days) were defined as cerebral risk factors. Correlation analyses (Fisher's Exact Test, Pearson Coefficient) were performed to the results of formalized clinical neurological (CNS) and complete developmental score (CDS) including 7 subtests (Vienna developmental test, standard values defined normal 100 ± 10, mean ± SD) at mean age 3.7 ± 0.5 years.

Results: PB was found in 16%, PA 0%, IVH 48%, residual IVH at discharge 24%, CS prior to surgery 16%, CS >24 h after CPB 12%. NSE, elevated prior to surgery (11.3 ± 4.5 ng/ml, mean ± SD), increased to peak values 4 h after CPB (17.3 ± 6.0) and individual peak values within 24h after CPB (19.9–7.0). CNS was normal in 84%, 16% had strabism. CDS was normal in 88% (100 ± 8), motor score 96% (99 ± 6), visual perception 88% (100 ± 9), learning and memory 96% (102 ± 7), cognitive score 100% (101 ± 8), language 100% (99 ± 5), socio-emotional score 100% (103 ± 7). Developmental scores did not differ significantly from normal children. None of the considered risk factors had significant influence on any outcome parameter ($P > 0.1$ in all).

Conclusions: In our study, neurodevelopmental outcome was not found dependent on cerebral risk factors as elevated NSE indicative of neuronal cell damage, intraventricular haemorrhage, seizures or pre-/perinatal asphyxia. Rare incidence of reduced test results might have masked significant correlations.

20 Effect of temperature on leukocyte activation during cardiopulmonary bypass (CPB) and postoperative organ damage

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Aim: To investigate the effect of core temperature (T°) during CPB on leukocyte activation and cytokine production and to correlate those findings to postoperative organ damage in an animal experimental model.

Methods: 18 young pigs were randomly assigned to a T°- group during CPB: normothermia (T° 37°C; $n = 6$), mild hypothermia (T° 28°C; $n = 6$) and deep hypothermia (T° 20°C; $n = 6$). Leukocyte count and plasma levels of tumor necrosis factor (TNFα) were measured before, during and after CPB. At the end of the experimentation (6 h post-CPB), probes of heart, lungs, liver, kidney, and intestine were taken for histological examination.

Results: There was a significant fall of leukocyte count at induction of CPB, without any intergroup difference. During and at the end of CPB, leukocyte count was significantly higher in group 37°C as compared with the other groups. At a later stage after CPB, group 20°C showed significantly higher leukocyte count than group 28°C and group 37°C, respectively. The course of neutrophils was similar.

TNF-α was not released in group 28°C neither during nor after CPB. By contrast, there was a significant production of TNF-α in groups 37°C and 20°C, the circulating levels being significantly higher in group 37°C. Histological examination showed that the most important tissue damage in terms of interstitial edema and leukostasis in heart, lung, liver, kidney, and small intestine was seen in group 37°C followed by group 20°C while the least important damage was present in group 28°C.

Conclusion: CPB-induced postoperative organ damage, probably related to leukocyte activation and TNF-α production, is highest in pigs operated on in normothermia and lowest in those operated on in mild hypothermia.

21 Impact of cardiopulmonary bypass and cardioplegic arrest on myocardial efficiency

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Objective: Mechanical efficiency of the heart, defined as cardiac work over myocardial oxygen consumption, is an important parameter of cardiac function. This study investigated the impact of cardiopulmonary bypass (CPB) and cardioplegic arrest (CPA) on myocardial efficiency (ME).

Methods: After initiation of CPB 10 dogs were submitted to 60 min of CPA with continuous, normothermic blood cardioplegia. 30 min after CPA all animals were weaned from CBP. Stroke work (micromanometry and sonomicrometry), contractility (preload recruitable stroke work and dP/dt_{max}), cardiac output (thermodilu-

tion), coronary blood flow (Doppler flow), and myocardial oxygen extraction (O_2-Sat difference aorta–coronary sinus) were determined at baseline and at 1 and 2 h after CPB. ME was calculated as the relation of stroke work over myocardial oxygen consumption. Two dogs with identical instrumentation and experimental time, but without CPB and CPA served as controls.

Results: Contractility, cardiac output, and myocardial oxygen extraction after CPB and CPA showed no significant difference to baseline. However, myocardial oxygen consumption, determined 1 and 2 h after CPB increased to 151, and 167% of baseline, respectively ($P < 0.05$). At the same time points ME decreased to 58, and 49% of baseline, respectively ($P < 0.05$). In controls all measurements were within 15% of baseline values.

Conclusions: Although contractility and cardiac output remained at baseline level after CPB and CPA, ME decreased significantly after CPB and CPA. The systemic inflammatory response to CPB, myocardial edema formation during CPB, or the Gregg phenomenon may be considered as possible mechanisms for this finding. ME indicated a significant change in cardiac function when hemodynamic parameters such as contractility and cardiac output were still unchanged. ME may be a valuable parameter for the assessment of post CPB cardiac function.

22 Value of cranial ultrasound for diagnosing neuronal cell damage during arterial switch operation (ASO) in neonates with transposition of the great arteries (TGA)

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Objective: To assess the reliability of cranial ultrasound in diagnosing neuronal cell damage after the ASO in neonates.

Methods: Cranial ultrasound was prospectively performed in 35 neonates with TGA before the operation as well as 4 h, 1, 2, 3 days, 1 and 2 weeks postoperatively (po). Blood concentrations of neuron specific enolase (NSE), a marker of neuronal cell damage, were determined before, during as well as 4 and 24 h po. The ASO was performed under combined low-flow cardiopulmonary bypass and hypothermic circulatory arrest.

Results: Areas of enhanced echogenicity in the choroid plexus and the ventricular system were seen in one newborn before the ASO, whereas 17 of 35 (49%) showed po enhanced echogenicity not distinguishable from intraventricular hemorrhage (IVH) I° to III°. No other abnormalities were seen intracranially before or after the operation. In 11 neonates findings were only temporary with normal scans 2 weeks po, while in the other 6 there was evidence of resolving hemorrhage. Also retrospectively, it was not possible to distinguish the findings in neonates with and without early signs of IVH during the first week po. In all neonates there was a significant rise in NSE blood concentrations during and 4 h after extracorporal circulation when compared to preoperative values ($P < 0.005$). No significant correlation was observed between NSE levels and occurrence of intracranial enhanced echogenicity during or after the ASO. NSE blood concentrations, however, were correlated to the occurrence of po seizures ($P < 0.05$).

Conclusion: Our data show that the presence of po enhanced echogenicity in the cerebral ventricular system of neonates with TGA after ASO is not correlated with neuronal cell damage. We speculate that enhanced echogenicity seen in cranial ultrasound is caused more likely by plexus edema than by intraventricular hemorrhage.

23 Age related response of cerebral mitochondrial oxygenation in neonates and infants undergoing circulatory arrest in deep hypothermia

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Introduction: Total circulatory arrest in deep hypothermia required in corrective cardiac surgery of complex congenital heart defects such as hypoplastic left heart syndrome (HLHS) in early life has been claimed to cause brain injury and altered psychomotor development. Determination of the changes in the regional intravascular concentration of oxygenated (HbO_2) and deoxygenated hemoglobin (Hb) by near infrared spectroscopy (NIRS) may provide noninvasive information about change in cerebral intravascular blood oxygenation. Relative change in the redox state of the cytochromeoxydase (cyt.aa3), the terminal enzyme in the mitochondrial respiratory chain that accounts for 90% of oxygen utilization in aerobic metabolism, may provide information about the availability of oxygen at cellular level.

The aim of this study therefore was to evaluate the patterns of changes in intravascular and intracellular oxygenation states in neonates with HLHS and infants with other congenital heart defects, undergoing corrective cardiac surgery using TCA in deep hypothermia.

Methods: Eight neonates with HLHS , median age 10 days (3–21), weight (3.3 ± 0.25 kg), and 9 infants with other diagnosis of congenital heart defects, median age 3.6 month (1–8), weight (4.7 ± 3.6–7 kg), were included in this study. Cardiac surgery was performed using uniform perfusion and anesthesia methods: full-flow CPB (120–150 ml/kg/min), minimal rectal temperature (16 ± 1.3°C), and minimal hemoglobin concentration (7 ± 1.5 mg/dl). Management of acid-base status during CPB was performed according to the alpha-stat method. Total circulatory arrest (TCA) was induced after establishment of a hypothermic blood temp at 12–15°C. Cerebral oxygenation monitor (Criticon cerebral redox monitor 2020, Johnson&Johnson) was used to obtain the on-line measurements of regional concentrations of cyt.aa3, HbO_2, tHb and Hb.

Results: There was a significant difference in the change of intravascular and intracellular oxygenation according to the postnatal age during full flow bypass and in the circulatory arrest time. A continuous parallel decrease of rSO_2 and HbO_2 were found in

both groups during hypothermic TCA. However marked divergent change in the mitochondrial cyt.aa3 signal was noted between the neonates and the infants particularly during TCA. These discordant divergent patterns in the intracellular and intravascular NIRS signal continued also during reperfusion after TCA.

Conclusion: The main preliminary finding in this study was the paradoxical increased signal of mitochondrial cyt.aa3 during TCA in the neonates with HLHS in comparison to the infants despite the simultaneous relative decline in intravascular concentration of HbO_2 in both groups. The observed age dependent change in the cyt.aa3 patterns may indicate an alteration of oxygen metabolism at mitochondrial level and possible disturbance of electron transport of the oxidative pathway in deep hypothermic TCA.

24 Acute phase response following cardiopulmonary bypass: impact of corticoid therapy

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Cardiac surgery with cardiopulmonary bypass (CPB) leads to an acute phase response characterized by the synthesis of proinflammatory cytokines and activation of the complement system. The following study was performed to analyse the influence of corticoid-premedication on acute phase response and clinical course of the patients.

Twenty-one male patients with three-vessel disease and normal or moderately impaired left ventricular function undergoing elective or urgent CABG-surgery were included. 10 patients received 125 mg of dexamethasone in addition to the standard premedication regimen, while 11 patients served as controls. Blood samples were drawn preoperatively, 10 min after termination of CPB and 4 h after CPB to determine the levels of interleukin-6 (IL-6), interleukin-8, tumor-necrosis-factor (TNF) and the anaphylatoxin C3a.

There was a marked increase of cytokines and activation of the complement system in all patients following the surgical intervention. Corticoid treatment resulted in a significant reduction of IL-6, IL-8 and TNF 10 min and 4 h following CPB. The activation of complement did not differ in both patients groups.

Pretreatment with corticosteroids results in a significant suppression of the cytokine response following CPB, which, however, does not have a major impact on the clinical course. Further studies have to analyse, whether inhibition of the acute phase response may lead to clinical improvements in selected high-risk patients.

25 Evaluation of myocardial cell damage in cardiac lymph during cardiopulmonary bypass

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Introduction: Cardiac lymph is a medium which reflects the myocardial interstitial space. The purpose of our study was to evaluate the inflammatory response marker TNFα (tumor necrosis factor-α) and myocardial injury marker Troponin I during cardiopulmonary bypass (CPB) in cardiac lymph and to compare them with blood values taken from the coronary sinus (SC).

Methods: In 14 young pigs the efferent cardiac lymph trunk and the SC was cannulated before starting CPB. Concentration of TNFα and Troponin I were measured pre, during and post CPB.

Results: A significant release of TNFα in SC and cardiac lymph was not observed.

Troponin I values in SC-blood rose from 2 ± 1.1 ng/ml (mean ± SEM) before aortic cross-clamping (AoX) to 9.1 ± 3.2 ng/ml at the end of CPB and peaked 2 hours post CBP at 28.1 ± 10.9 ng/ml ($P < 0.03$). Troponin I concentration in cardiac lymph rose from 352 ± 64 ng/ml before AoX and became significantly higher in the following hours with a maximum value at 6 hours post CPB ($12\,638 \pm 5321$ ng/ml; $P < 0.01$). A significant correlation between the lymphatic and SC-blood concentrations was noted.

Conclusion: (1) a significant release of TNFα was not observed in our study. (2) The high concentrations of Troponin I in cardiac lymph indicate a myocardial cell damage during CPB which is strongly underestimate by Sinus Coronarius blood samples.

26 Prediction of outcome in patients undergoing cardiac surgery on cardiopulmonary bypass using procalcitonin

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The prognostic value of elevated serum levels of procalcitonin (PCT) in patients early after cardiac operation on cardiopulmonary bypass (CPB) remains unclear and was therefore investigated in a prospective study.

Using a modified APACHE-II-score 39 patients (group I) at high risk and 20 patients (group II) at low risk were identified on the first postoperative day after cardiac surgery on CPB and hypothermic (26°C) cardioplegic (HTK-solution, 4°C, 15 ml/kg body weight) cardiac arrest. There were no differences regarding length of operation, CPB and aortic clamping time. While preoperative mortality reached 23%, infection rate 41% and complication rate 59% in group I, the postoperative course was uneventful in all but 2 patients (10%) in group II suffering from infections. PCT serum levels were measured (LUMItest®, Fa. Brahms) preoperatively (PCT0), at the 1. (PCT1), 2. (PCT2) and 5. (PCT5) postoperative

day in all patients and analyzed with respect to infections, complications and perioperative mortality.

The mean PCT levels were significantly elevated in both groups early after surgery, however, they reached significant higher values in group I compared to group II (see table):

µg/l	group I	group II
PCT0	0.2	0.2
PCT1	22.2*†	2.6*
PCT2	21.2*†	2.6*
PCT5	5.7*†	0.4

*$P < 0.05$ versus preoperative PCT0; †$P < 0.05$ versus group II.

In group I PCT1/2/5 were significantly increased in patients suffering from a complication, PCT2/5 in patients with an infection and PCT5 in patients who died perioperatively (see table):

group I	compl.		infection		per. mort.	
(µg/l)	yes	no	yes	no	yes	no
PCT1	33.7*	5.6	43.4	7.5	36.9	17.8
PCT2	32.6*	4.6	43.1*	5.9	44.1	14.3
PCT5	8.9*	1.6	12.1*	1.9	18.2*	2.8

*$P < 0.05$ versus no.

PCT serum levels are significantly elevated in patients early after cardiac surgery on CPB. Very high serum levels of PCT at the first postoperative day are predictors for the occurrence of complications, at the second postoperative day for a high incidence of infections and at the fifth postoperative day for a significantly worsened outcome.

27 Corticosteroids reduce early troponin-T release after cardiac surgery with cardiopulmonary bypass in men.

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Objectives: To study whether administration of corticosteroids (CS) prior to cardiac surgery for coronary artery bypass grafting (CABG), can influence early troponin-T release after cardiac surgery with cardiopulmonary bypass (CPB).

Material and methods: Fifty-eight male patients with coronary artery disease undergoing programmed CABG with CPB were divided into five groups: Group 1 (Control; $n = 10$); Group 2 (methylprednisolone, (MPS) = 10 mg/kg, 4 h before CPB; $n = 14$); Group 3 (MPS = 10 mg/kg, at induction of anesthesia (IA); $n = 10$); Group 4 (MPS = 10 mg/kg, 12 h before, as well as at IA; $n = 10$); Group 5 (MPS = 30 mg/kg 4 h before CPB; $n = 14$). CPB was conducted using a blood-free priming, a cold crystalloid cardioplegia and moderate hypothermia (29–30°C). Anesthesia consisted of continuous administration of midazolam, sufentanil and pancuronium. Aprotinin was not used. Plasmatic troponin-T levels were measured before induction of anesthesia (t0) and 4h after CPB (t1) using specific ELISA.

Results: There was no significant difference in age, weight, duration of CPB, aorta clamping time and number of grafts between groups (Table). Troponin-T values at t0 were similar in all patients. Troponin-T levels measured 4h after the end of CPB were similar in control (Group 1), Group 3, and Group 4. In contrast, troponin-T levels were significantly lower in the 2 groups receiving MPS 4h before CPB (Group 2: 10 mg/kg and Group 5: 30 mg/kg) as compared to controls (*$P = 0.001$ and **$P = 0.0004$, respectively). There was no significant difference in troponin-T levels between Group 2 and Group 5.

Conclusion: Pharmacological doses of CS significantly reduce early troponin-T release after CPB. The timing of CS administration plays an important role, as the treatment was effective when CS were given 4 h prior to CPB but not at the beginning of surgery. Doses of 10 mg/kg and 30 mg/kg are equally effective.

	Group control	Group 2: MPS 10 mg/kg (h-4)	Group 3: MPS 10 mg/kg (IA)	Group 4: MPS 2 × 10 mg/kg (h-12 + IA)	Group 5: MPS 30 mg/kg (h-4)
Tropo-T (ng/ml) (t = 0) mean ± SEM	0.07 ± 0.2	0.10 ± 0.06	0 ± 0	0.04 ± 0.04	0.07 ± 0.3
Tropo-T (ng/ml) (t = 1) mean ± SEM	6.2 ± 2.0	1.4 ± 0.5*	5.0 ± 1.5	5.8 ± 1.9	1.0 ± 0.2**
Age (years)	60 ± 3	63 ± 2	62 ± 5	64 ± 2	64 ± 2
Weight (kg)	86 ± 4	79 ± 2	79 ± 3	80 ± 3	82 ± 3
CPB (min)	95.3 ± 6.1	95.0 ± 7.5	95.0 ± 7.5	110.3 ± 4.4	104.5 ± 7.6
Ao cl (min)	65.6 ± 6.3	59.3 ± 5.9	64.6 ± 5.7	84.3 ± 4.6	59.2 ± 4.8
No. of grafts (*n*)	3.0 ± 0.2	2.6 ± 0.2	2.7 ± 0.3	3.5 ± 0.3	2.6 ± 0.2

28 Clinical validity of pre-bypass filters in standard extracorporeal circulation

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Microembolism of silicone particles from the extracorporeal circuit (ECC) may cause organ dysfunction after open heart surgery. To evaluate a possible clinical effect of reducing the number of particles by pre-bypass filtering, we performed a prospective randomized clinical study with a 0.2 µm pre-bypass filter (PBF).

336 consecutive patients undergoing all kinds of open heart operation were randomized into two groups (A and B). In group A the heart–lung machine (HLM) was prepared with a PBF, in group B it was not. The filter strains the priming volume for 10 min by flow rates of 4 l/min. Primary excluded were patients younger than 18 years and patients who needed blood priming of the HLM. In case of emergency cannulation patients were secondary excluded. The average age was 61 ± 8.5 years (mean ± SEM) in both groups. 66% of patients were male. Coronary artery bypass grafting (CABG) was performed at 229 (68%) patients, aortic valve replacements at 54 (16%) patients, mitral valve replacements at 23 (7%) patients and other including complicated operations were done in 30 (9%) of patients. Both groups were similar in distribution of the different operations and their duration, gender and average age. Preoperatively and postoperatively (1, 2, 3 and 6 days) liver enzymes (GOT, GPT, γ-GT, GLDH, Bilirubin), pancreatic enzymes (amylase, lipase), renal function (urea, creatine, urinary volume/24 h) and general inflammatory parameter (leucocytes, c-reactive protein) were measured. Also drug demand of catecholamines and furosemide and frequency of rhythm disturbances were registered. For evaluation each parameter was compared with the students *t* test for each day on statistical differences between the groups.

Results: Both groups showed no differences in any parameter. The mean demand of catecholamines (suprarenin/dopamine) has its maximum value at the first postoperative day and then fall contiguously to the sixth postoperative day in both groups. Mechanical ventilation time was 16.2 ± 1.3 h in group A and 17.8 ± 1.3 h in group B. The maximum demand of furosemide is found on the second postoperative day in both groups, on day 6 only a few patients needed furosemide. Urea and creatine remained nearly constant for both groups at each day. In group A urea levels range between 6.7 mmol/l (preoperative) and 8.8 mmol/l (third postoperative day), and group B levels were between 6.7 mmol/l (preoperative) and 8.9 mmol/l (third postoperative day) and showed no significant difference between the groups. The highest urinary flow/24 h was noticed at the first postoperative day in both groups (4676 ± 176 ml/24 h Group A/4368 ± 150 ml/24 h Group B), than it fell significantly to preoperative values at the third and sixth postoperative days. Pancreatic enzymes showed maximum values at the first postoperative day. While Amylase fall to normal lipase has a second maximum on the 6th postoperative day. Liver enzymes remain inconstant the following maximum values are reached [U/l] Group A/Group B: GOT 35 ± 4/32 ± 2; GPT 25 ± 2/31 ± 4; γ-GT 38 ± 4/45 ± 5; GLDH 8 ± 2/10 ± 2; LDH 420 ± 35/404 ± 15; Bilirubin 17 ± 1/17 ± 1. The maximum response of leucocytes and CRP appeared at the second postoperative day without reaching reference scope at the sixth postoperative day also showing no significant difference between the groups.

Conclusion: We conclude that use of 0.2 µm pre-bypass filters in ECC for removal of microparticles does not prevent organ dysfunction after open heart surgery. Possible effects seem to be of less clinical importance or appear elsewhere.