

## Meeting abstracts

**Myocardial cell damage and myocardial protection**Abstracts of the 3<sup>rd</sup> International Symposium on the Pathophysiology of Cardiopulmonary Bypass, 16<sup>th</sup> December 2000, Aachen, Germany

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(Print ISSN 1364-8535; Online ISSN 1466-609X)**P1 The use of adenosine as a trigger for pharmacological preconditioning to protect human myocardium during coronary bypass surgery****KK Klein, B Korbmayer, U Sunderdiek, E Mohan, E Gams and JD Schipke\****Department of Thoracic and Cardiovascular Surgery, and \*Research Group Experimental Surgery, Heinrich-Heine University Düsseldorf, Düsseldorf, Germany*

**Introduction:** In former studies on ischaemic preconditioning, adenosine was found to trigger this cardioprotective process. After promising experiments in rabbit hearts and the first clinical use during emergency percutaneous transluminal coronary angioplasty in patients, we started to investigate the ability of adenosine to protect the myocardium during standard cross-clamping bypass surgery. Because adenosine is metabolized within a few seconds, no systemic effects occur.

**Method:** Two groups of patients (placebo:  $n=4$ , age  $69.5 \pm 5.2$  years; adenosine:  $n=4$ ,  $59.2 \pm 10.3$  years) were

studied. All patients of both groups were male, had an ejection fraction greater than 50%, and underwent three-vessel bypass during elective cardiac surgery. On first aortic cross-clamping, 5 mg/min adenosine was infused simultaneously with a sufficient blood perfusion via the aortic root over 10 min. The patients in the placebo group received the same dose of physiological saline solution. Blood samples were collected before onset of anaesthesia, before the onset of extracorporeal circulation (ECC), 1 h after the end of surgery, and on the first and second days after surgery in order to assess the following parameters: CK, CK-MB, LDH, GOT,

**Table 1****Blood parameters and haemodynamic data**

Parameters	Placebo	Adenosine	Parameters	Placebo	Adenosine
CK (U/l)			LVP (mmHg)		
Before ECC	10 ± 8	6 ± 7	Before ECC	Syst	100 ± 24
1 h after surgery	252 ± 85	203 ± 63	Diast	7 ± 3	109 ± 12
1 day after surgery	314 ± 131	385 ± 138	End-diast	14 ± 5	8 ± 2
2 days after surgery	247 ± 161	189 ± 138	dP/dt <sub>max</sub>	892 ± 145	14 ± 3
CK-MB (U/l)			dP/dt <sub>min</sub>	-858 ± 191	850 ± 88
Before ECC	1.0 ± 0.5	2 ± 3	After ECC	Syst	-700 ± 96
1 h after surgery	26 ± 7	13 ± 8	Diast	109 ± 18	115 ± 20
1 day after surgery	26 ± 13	13 ± 19	End-diast	5 ± 2	8 ± 5
2 days after surgery	16 ± 17	5 ± 4	dP/dt <sub>max</sub>	16 ± 3	23 ± 3
Troponin I (ng/ml)			dP/dt <sub>min</sub>	1345 ± 357	1039 ± 189
Before ECC	0.5 ± 0.4	0.4 ± 0.1	ECC time (min)	-924 ± 174	-872 ± 58
1 h after surgery	56.0 ± 29.0	22.0 ± 6.0	Assisted ventilation (h)	117 ± 12	130 ± 18
1 day after surgery	97.0 ± 75.0	47.0 ± 40.0	Grafts	9.0 ± 6.4	7.3 ± 6.6
				3.5 ± 0.5	3.5 ± 0.5

GPT, troponin I, potassium, sodium, Hb, Hct and leukocytes. The following haemodynamic parameters were assessed: heart rate, central venous pressure, left ventricular pressure (LVP), and the maximal and minimal pressure rises ( $dP/dt_{max}$  and  $dP/dt_{min}$ ). For electrophysiological analyses, various ECG leads were assessed.

**Results:** The blood parameters and haemodynamic data are presented in Table 1. One placebo patient and two adenosine patients needed mild intraoperative epinephrine treatment.

Whereas in the placebo group one patient developed first-degree atrioventricular block, one patient receiving adenosine showed absolute arrhythmia after surgery.

**Conclusion:** According to these preliminary results, there was no significant difference between the two groups. This is probably explained by the small number of patients studied, or the low temperature used during the ECC, which might have obscured the expected beneficial effect of pharmacological preconditioning.

## P2 Induction of myocardial heat shock protein-60 after cardioplegic arrest and reperfusion

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**Introduction:** Cardiomyocytes respond to stress with the expression of various heat shock proteins (HSPs). Expression of mitochondrial HSP60 is known to be induced by various stress factors, including ischaemia and reperfusion. The aim of the study was to investigate the induction of HSP60 in human myocardium during cardiac surgery.

**Method:** From eight patients undergoing elective coronary artery bypass grafting or valve replacement, samples of right atrium were harvested before and after extracorporeal circulation (ECC). Two patients had atrial fibrillation and six were in sinus rhythm. The myocardial samples were excised and immediately immersed in liquid nitrogen. The HSP60 protein level was determined using sodium dodecyl sulphate-polyacryl-

amide gel electrophoresis, Western blot, and subsequent ECL technique. The amount of HSP60 protein was quantified by optical densitometry, according to the immunoreactive bands of actin.

**Results:** In all samples HSP60 was detected before and after ECC. We could not find any difference in HSP60 expression before and during cardiac surgery. There was no correlation with duration of cardiopulmonary bypass or reperfusion time.

**Conclusion:** We could not demonstrate a cytoprotective upregulation of HSP60 after an obligatory period of ischaemia, cardioplegic arrest and reperfusion. This might reflect effective cardioprotection during ECC.

## P3 Enhancement of neonatal myocardial function and cardiac energy metabolism following heat stress pretreatment

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**Introduction:** We investigated the capacity of heat stress to improve myocardial tolerance and cardiac energy metabolism in the isolated perfused neonatal rabbit heart subjected to prolonged cold cardioplegic ischemia.

**Method:** Hearts from anaesthetized male neonatal New Zealand White rabbits (aged 8–10 days) were excised, isolated, perfused with modified Krebs–Henseleit buffer, and arrested for 2 h of cold cardioplegic ischaemia. In order to induce the expression of heat shock proteins (HSPs; HSP72<sup>+</sup>/73<sup>+</sup>) the rectal temperature of five neonatal rabbits was raised to 42.0–42.5°C (in a whole-body water bath) for 15 min before the onset of global, hypothermic cardioplegic arrest. Another set of five hearts without hyperthermia pretreatment served as controls. The recovery of left ventricular (LV) function was assessed by LV developed pressure, max  $+dP/dt$  and LV pressure. The status of phosphorylated energy metabo-

lites ( $\beta$ -adenosine triphosphate [ $\beta$ -ATP], phosphocreatine [PCr] and inorganic phosphate) was measured by <sup>31</sup>phosphorus nuclear magnetic resonance spectroscopy. HSPs were also detected by immunoblot analysis.

**Results:** Heat stress pretreatment resulted in significantly better recovery of LV function, as indicated by LV developed pressure ( $74.6 \pm 10$  versus  $52.1 \pm 8.5\%$ ;  $P < 0.05$ ), max  $dP/dt$  ( $910 \pm 170$  versus  $530 \pm 58$  mmHg/s;  $P < 0.01$ ), LV end-diastolic pressure ( $8 \pm 2$  versus  $18.4 \pm 5$  mmHg;  $P < 0.05$ ) and coronary blood flow ( $P < 0.05$ ), than occurred in the control group 60 min after reperfusion. During reperfusion, myocardial energy metabolism was also better preserved in the HSP-group hearts as a result of significantly ( $P < 0.05$ ) increased  $\beta$ -ATP and PCr values as compared with control animals. Immunoblot analysis showed that the brief period of systemic hyperthermia induced HSP (HSP 72<sup>+</sup>/73<sup>+</sup>) expression.

**Conclusion:** These data contribute to the evidence that heat stress mediates a beneficial effect on recovery of the neonatal

left ventricle and cardiac energy metabolism after prolonged cold cardioplegic ischaemia in rabbits.

#### P4 Transmembraneous dislocation of myocardial S100A1 calcium-binding protein during ischaemia and reperfusion: a new marker of myocardial damage during cardiac surgery

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**Introduction:** Despite myocardial protection, ischaemia during cardiopulmonary bypass induces greater or lesser degrees of damage to cardiomyocytes as a result of transient cytosolic calcium overload. Recently, increasing attention has been paid to the role of heart-specific calcium-binding proteins in the pathogenesis of myocardial ischaemia-reperfusion injury. S100A1 is a heart-specific EF-hand calcium-binding protein, which is directly involved in a variety of calcium-mediated processes in human myocytes.

**Method:** In order to elucidate the feasibility of using S100A1 calcium-binding protein for monitoring extended periods of ischaemia, we attempted to characterize the ultrastructural localization of S100A1 in the human heart under normal conditions (baseline), after prolonged ischaemia and after reperfusion. Confocal laser scanning microscopy was used to study cardiac biopsies taken at these three time points, during car-

diopulmonary bypass in patients undergoing elective cardiac surgery.

**Results:** Tissue samples obtained before initiation of extracorporeal circulation showed that S100A1 localized in the cytoplasm, which was strictly associated with actin contractile filaments. Ischaemia of the heart ( $\geq 30$  min) induced specific dislocation of S100A1 to the cell membrane and the interstitial space. However, this dislocation was reversible after reperfusion ( $\geq 30$  min).

**Conclusion:** These data suggest that S100A1 may be associated with transient perioperative myocardial damage despite cardioplegia in the human heart. This protein, which is involved in the regulation of contractile function of muscle cells, may be an important intracellular marker for ischaemia-reperfusion injury of the heart.

#### P5 Effects of high-dose methylprednisolone on neonatal pulmonary function after cardiopulmonary bypass and deep hypothermic circulatory arrest

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**Introduction:** Methylprednisolone has been widely used during neonatal cardiac surgery with cardiopulmonary bypass (CPB), in order to limit the inflammatory response and postperfusion syndrome. However, the influence of high-dose methylprednisolone pretreatment on postoperative respiratory function and pulmonary haemodynamics in the neonate is controversial. The aim of this investigation was to determine whether methylprednisolone improves preperfusion and postperfusion pulmonary function and haemodynamics.

**Method:** Sixteen newborn piglets ( $2.5 \pm 0.5$  kg body weight) were subjected to CPB, and deep hypothermic circulatory arrest (DHCA) was induced for 2 h. Group 1 ( $n = 8$ ; control group) did not receive any drug treatment and group 2 ( $n = 8$ ) received 30 mg/kg methylprednisolone preoperatively. Before CPB and 20 min after bypass, blood samples and haemodynamic data (cardiac output, mean arterial blood pressure, left and right atrial pressure, pulmonary artery pressure [PAP]) were measured. Pulmonary oxygenation function was assessed by calculating alveolar-arterial oxygen gradient index (Aal) and respiratory index.

**Results:** Methylprednisolone pretreatment resulted in an increase in prebypass values of PAP ( $14.0 \pm 3.2$  versus  $10.3 \pm 1.9$  mmHg;  $P < 0.05$ ), pulmonary vascular resistance index ( $308 \pm 81$  versus  $119 \pm 44$  dyns/cm<sup>5</sup> per m<sup>2</sup>;  $P < 0.05$ ), Aal ( $279.8 \pm 10$  versus  $174.5 \pm 8.5$  mmHg;  $P < 0.05$ ) and intrapulmonary shunt ( $10.12 \pm 2.4$  versus  $4.6 \pm 1.2\%$ ) as compared with control animals, with no change in cardiac output, stroke volume or systemic vascular resistance. All animals in both groups had significantly ( $P < 0.05$ ) and severely impaired haemodynamics and lung function after CPB, including elevation of pulmonary vascular resistance with decreased pulmonary oxygenation function and lower cardiac output, without any intergroup differences.

**Conclusion:** Considering the significant increase in prebypass pulmonary haemodynamic and oxygenation variables after high-dose methylprednisolone pretreatment, these data do not provide evidence that either postperfusion pulmonary haemodynamics or oxygenation function are significantly influenced by this treatment.

## P6 Inhibition of cAMP phosphodiesterase by milrinone improves cardiac recovery after deep hypothermic circulatory arrest

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**Introduction:** Perioperative cardiac dysfunction may be related to inadequate myocardial protection during cardiopulmonary bypass (CPB) and associated procedures. Many intrinsic and extrinsic factors may act directly on vessels or indirectly by release of vasoactive metabolites to alter vascular tone and myocardial function during reperfusion. Milrinone, by inhibiting cAMP-specific phosphodiesterase enzymes in both cardiac and vascular smooth muscle, is a powerful inotrope and vasodilator, but has little effect on systemic arterial blood pressure. The purpose of the study was to investigate the effect of milrinone administration on recovery of left ventricular (LV) function and systemic haemodynamics after deep hypothermia and CPB in rabbits.

**Method:** Fourteen New Zealand White rabbits ( $3.5 \pm 0.5$  kg body weight) underwent CPB and deep hypothermic cardiopulmonary arrest (DHCA) for 1 h. LV function and systemic haemodynamics were compared between a control group ( $n = 7$ ) and a treatment group of animals ( $n = 7$ ) that received a loading dose of milrinone ( $50 \mu\text{g}/\text{kg}$  body weight) before the onset of circulatory arrest, followed by slow release ( $0.5 \mu\text{g}/\text{kg}$  body weight per min) during reperfusion. LV and haemo-

dynamic measurements were taken before surgical interventions and at 2 h after reperfusion.

**Results:** There were no statistical differences in baseline values between the two groups. Perioperative treatment with milrinone resulted in better recovery of LV function ( $\text{max+dP/dt}$ :  $1206 \pm 149$  versus  $1043 \pm 134$  mmHg/s [ $P < 0.05$ ]; LV stroke work index:  $41 \pm 2$  versus  $33 \pm 2$  gxm/m<sup>2</sup> [ $P < 0.05$ ]) and significant changes in systemic haemodynamics (cardiac index:  $3.1 \pm 0.1$  versus  $2.2 \pm 0.2$  l/min per m<sup>2</sup> [ $P < 0.05$ ]; pulmonary artery pressure:  $13.2 \pm 1.6$  versus  $18.6 \pm 3.8$  mmHg [ $P < 0.05$ ]; pulmonary vascular resistance:  $550 \pm 70$  versus  $1020 \pm 110$  dyns/cm<sup>5</sup> per m<sup>2</sup> [ $P < 0.01$ ]), with no significant change in mean arterial pressure, despite higher plasma cAMP levels ( $19 \pm 2$  versus  $12 \pm 1.1$  pmol/ml).

**Conclusion:** These data indicate that milrinone administration acutely improves systemic haemodynamics and has beneficial effects on recovery of myocardial function after deep hypothermic ischaemia. Milrinone and related drugs warrant further investigation in the treatment of vascular tone and ischaemia–reperfusion deterioration after CPB and DHCA.

## P7 Effective value of myocardial tissue oxygen pressure monitoring during cold ischaemia and reperfusion

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**Introduction:** Recent studies have shown a relation between altered myocardial function and the cardiac cellular changes that are noted with hypothermic cardioplegic arrest, such as energy store depletion and intracellular acidosis. The aim of the study was to evaluate the link between myocardial energy metabolism (high-energy phosphorylated compounds and intracellular pH), as measured using <sup>31</sup>P-phosphorus nuclear magnetic resonance spectroscopy (<sup>31</sup>P-MRS) and myocardial tissue oxygen pressure (ptiO<sub>2</sub>) in isolated rabbit hearts subjected to 2 h of cold cardioplegic ischaemia and reperfusion.

**Method:** Ten New Zealand White rabbits (male,  $2.5 \pm 0.5$  kg body weight) were anaesthetized with sodium pentobarbital ( $45 \text{ mg}/\text{kg}$  intravenous) and heparinized ( $700 \text{ IU}/\text{kg}$  intravenous). The heart was rapidly excised, immersed in physiological salt solution, cannulated and perfused in the Langendorff mode at 37°C. After placing a minimally invasive, flexible catheter partial oxygen tension microprobe (polarographic Clark-type cell O<sub>2</sub>-sensor; Licox<sup>®</sup> system, GMS, Kiel, Germany) into the left ventricular anterior wall, baseline data were obtained after an equilibration period of 40 min. Hearts were

then subjected to 2 h at 10°C of cardioplegic ischaemia and reperfused. The status of phosphorylated cardiac energy metabolites (measured using a 4.7-T high-field <sup>31</sup>P-MR spectrometer) was assessed, and myocardial tissue oximetry, including temperature compensation, was measured using a microsensor catheter probe (Licox<sup>®</sup>). Linear correlation was performed between <sup>31</sup>P-MRS data and ptiO<sub>2</sub> readings.

**Results:** Intracellular pH ( $r = 0.58$ ;  $P < 0.05$ ), phosphocreatine ( $r = 0.71$ ;  $P < 0.01$ ) and inorganic phosphates ( $r = 0.62$ ;  $P < 0.05$ ) measured after cardioplegic infusion and onset of ischaemia correlated significantly with the decline in ptiO<sub>2</sub>. During reperfusion, only intracellular pH ( $r = 0.76$ ;  $P < 0.005$ ) and phosphocreatine ( $r = 0.84$ ;  $P < 0.005$ ) values correlated significantly with ptiO<sub>2</sub>.

**Conclusion:** On the basis of these findings, we conclude that ptiO<sub>2</sub> monitoring during surgically induced cold cardioplegic ischaemia and reperfusion appears to provide a real-time minimally invasive estimate of cardiac oxidative metabolism and cellular energy consumption.

**P8 The effect of temperature during extracorporeal circulation on ultrastructure of cardiomyocytes****R Chakupurakal, B Hermanns\*, JF Vazquez-Jiminez†, Ma Qing, S Lücking, BJ Messmer†, G von Bernuth and M-C Seghaye***Department of Pediatric Cardiology, \*Institute of Pathology, and †Department of Cardiovascular Surgery, Aachen University of Technology, Aachen, Germany*

**Introduction:** Previous studies have suggested that mild hypothermia (28°C) during extracorporeal circulation (ECC) confers organ protection. The study was conducted to examine whether temperature during ECC influences cardiomyocyte ultrastructure.

**Method:** Fifteen pigs were randomly assigned to one of three temperature groups (37, 28 and 20°C) during ECC ( $n = 5$  each). ECC time was 120 min and myocardial ischaemia time was 60 min. Cardioplegia was achieved by injecting a crystalloid solution (4°C cold Bretschneider solution, 30 ml/kg) into the aortic root. Flow index was set at 2.7 l/m<sup>2</sup> per min. Six hours after ECC, myocardial samples were taken from the left ventricle for ultrastructural examination by electron microscopy.

**Results:** All animals showed intact contractile apparatus, with normal texture of the myofibrils and normal configuration of the Z-bands. Quantitative and structural changes of mitochondria were frequent. Animals from the 37°C group showed marked interstitial oedema and dehiscence of the cytoplasmic membrane with ruptures, whereas lesser damage to the membrane was observed in the other two groups. The 28°C group showed the least pronounced ultrastructural changes.

**Conclusion:** These results show that cardiac operations with ECC are associated with ultrastructural lesions of the cardiomyocytes. In this experimental setup, these lesions were most pronounced under normothermic and least pronounced under moderate hypothermic ECC.

**P9 Heart failure impairs vasomotor functions of the mesenteric bed after cardiopulmonary bypass****G Szabó, TB András\*, E Zima\*, P Soós\*, F-U Sack, A Tanzeem, S Hagl and S Juhász-Nagy\****Department of Cardiac Surgery, University of Heidelberg, Heidelberg, Germany, and \*Department of Cardiovascular Surgery, Semmelweis University, Budapest, Hungary*

**Introduction:** Mesenteric dysfunction is a rare but severe complication after open heart surgery, which may be aggravated by coexistent heart failure. The aim of the study was to investigate the effects of cardiopulmonary bypass (CPB) on intestinal vascular endothelial and smooth muscle function in a canine model of heart failure.

**Method:** Volume overload heart failure was induced by arteriovenous shunt in six dogs; five healthy animals served as controls. Heart rate, mean arterial pressure (MAP), mesenteric blood flow and mesenteric vascular resistance (MVR) were measured before and after 90 min of CPB. Reactive hyperaemic response and the response to acetylcholine and sodium nitroprusside are expressed as percentage change in MVR.

**Results:** Before CPB, baseline haemodynamics (MAP: 125 ± 5 versus 117 ± 10 mmHg; MVR: 0.96 ± 0.03 versus 0.99 ± 0.17 mmHg × min/ml), reactive hyperemia (−53 ± 5

versus −53 ± 2%), and response to acetylcholine (−41 ± 3 versus −55 ± 6%) and sodium nitroprusside (−68 ± 4 versus −56 ± 4%) did not differ significantly. Ninety minutes after CPB, there was a similar significant drop in MAP in both groups (60 ± 17 and 51 ± 6 mmHg, respectively;  $P < 0.05$  versus baseline). After CPB, reactive hyperaemia (−16 ± 5 versus −36 ± 15%;  $P < 0.05$ ) and response to acetylcholine (−22 ± 9 versus −42 ± 9%;  $P < 0.05$ ) and to sodium nitroprusside (−14 ± 4 versus −50 ± 7%;  $P < 0.002$ ) exhibited a more pronounced decrease in the heart failure than in the control group.

**Conclusion:** The development of heart failure *per se* does not attenuate mesenteric vasomotor function. However, CPB induces a more pronounced impairment of mesenteric endothelium-dependent and -independent vasodilatory response in animals with heart failure. This phenomenon may have an impact on the higher incidence of mesenteric complications in cardiac patients with manifest heart failure.

**P10 Noncardioplegic myocardial protection in high-risk coronary artery bypass grafting****G Kleikamp, N Reiß, N Mirow, B Hansky, A El-Banayosy, K Minami and R Körfer***Department of Thoracic and Cardiovascular Surgery, Heart Center NRW, Ruhr University of Bochum, Bad Oeynhausen, Germany*

**Introduction:** This study was undertaken to determine whether intermittent aortic cross-clamping in the fibrillating heart can be used successfully in high-risk coronary artery bypass grafting.

**Method:** From 1 January 1988 to 30 April 2000, 25,887 patients underwent isolated coronary bypass grafting for coronary artery disease at our institution. In all cases, myocardial pro-

tection consisted of intermittent aortic cross-clamping in the fibrillating heart under mild hypothermia. A total of 908 patients (797 male [88%]; mean age 60.1 ± 9.5 years, range 29–78 years) were suffering from ischaemic cardiomyopathy defined as global (left ventricular ejection fraction <30%) and regional wall motion abnormalities. The pre-, peri- and postoperative data for this subgroup were entered prospectively into a database.

**Results:** Mean aortic cross-clamp time was  $25.01 \pm 8.2$  min (range 0–46 min), mean perfusion time was  $60.8 \pm 26.3$  min (range 19–336 min), and the number of bypass grafts per patient was  $3.11 \pm 0.927$ . Weaning from extracorporeal circulation was possible without catecholamines in 348 patients (38%); 560 (62%) received dopamine intravenously. Intra-aortic balloon counterpulsation was used in 85 patients (9%) and assist devices were used in nine patients. Twenty-eight patients (3.1%) suffered from perioperative myocardial infarction, 96 patients developed ventricular arrhythmia and 191

atrial fibrillation. Ventilatory support for longer than 24 h was required by 118 patients. Eighteen patients (2.0%) died within 30 days of the operation.

**Conclusion:** Intermittent aortic cross-clamping in the fibrillating heart can be used safely for myocardial protection in all patients undergoing surgical revascularization. The results even in this high-risk group of patients compare favourably with all published series utilizing other forms of myocardial protection. Furthermore, this method is easy to use and cost neutral.

**P11 Low-molecular-weight heparin-coated cardiopulmonary bypass: coagulatory and clinical findings**

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**Introduction:** The aim of the study was to evaluate clinical and coagulatory effects of low-molecular-weight heparin-coated extracorporeal circulation (ECC) in coronary artery bypass grafting (CABG).

**Method:** CABG was performed in 287 patients, who were included in a prospective, randomized study. In patients treated using heparin coated technology (AOTHEL®; AOT, Bad Oeynhausen, Germany), low-molecular-weight heparin coating was employed. Conventional roller pumps and coronary suction were used, and operations were performed in conditions of moderate hypothermia, with application of intermittent aortic cross-clamping. Patients were divided into three groups. Group A ( $n = 97$ ) had a standard uncoated ECC set

and intravenous heparin was administered at an initial dose of 400 IE/kg body weight; during ECC activated clotting time (ACT) was kept at 480 s or greater. Group B ( $n = 94$ ) had the same ECC set but completely coated with low-molecular-weight heparin, and intravenous heparin was administered at the same dose as that employed in group A; ACT was kept at the same level. Group C ( $n = 96$ ) had the same coated ECC set as group B, but intravenous heparin was reduced to 150 IE/kg, and during ECC ACT was set to be 240 s or greater. Coagulatory effects were measured in a consecutive subset of 119 patients.

**Results:** The coagulatory and clinical findings are presented in Tables 1 and 2, respectively.

**Table 1**

**Coagulatory findings during ECC**

Group	60 min ECC			>60 and <120 min ECC		
	Group A ( $n = 39$ )	Group B ( $n = 42$ )	Group C ( $n = 38$ )	Group A ( $n = 39$ )	Group B ( $n = 42$ )	Group C ( $n = 38$ )
β-thromb (U/ml)	$456.3 \pm 210.6^{\ddagger}$	$377.7 \pm 338.7$	$298.9 \pm 194.7^*$	$425.3 \pm 192.5$	$394.7 \pm 158.6$	$348.8 \pm 192.5$
TAT (μg/l)	$24.5 \pm 19.0$	$25.1 \pm 35.3$	$22.2 \pm 14.9$	$28.3 \pm 14.8^{\ddagger}$	$34.6 \pm 45.9$	$45.4 \pm 34.3^*$
F1/2 (nmol/l)	$2.5 \pm 1.3$	$2.5 \pm 1.6$	$2.7 \pm 1.3$	$3.6 \pm 2.7^{\ddagger}$	$2.7 \pm 1.6^{\ddagger}$	$5.5 \pm 4.2^{**}$
D-dimers (mg/l)	$0.3 \pm 0.4$	$0.3 \pm 0.3$	$0.3 \pm 0.3$	$0.4 \pm 0.5$	$0.4 \pm 0.4$	$0.4 \pm 0.3$

\* $P < 0.05$  versus group A;  $^{\ddagger}P < 0.05$  versus group B; and  $^{**}P < 0.05$  versus group C.

**Table 2**

**Clinical findings**

Group	Neurologically deficient ( $n$ )	Mechanically ventilation (h)	Renal insufficiency ( $n$ )	Blood loss (ml/12 h)	Blood units/patient	ICU stay (h)	Hospital stay (days)
A ( $n = 97$ )	2	$6.0 \pm 5.2$	0	$453 \pm 190$	$1.2 \pm 1.6$	$22 \pm 16$	$7.1 \pm 1.5$
B ( $n = 94$ )	1	$5.2 \pm 2.7$	3	$455 \pm 190$	$1.1 \pm 1.8$	$23 \pm 16$	$7.3 \pm 1.8$
C ( $n = 96$ )	3	$5.6 \pm 2.9$	2	$361 \pm 190^*$	$0.7 \pm 1.4^{\ddagger}$	$25 \pm 18$	$7.0 \pm 1.5$

ICU, intensive care unit. \* $P < 0.002$  versus groups A and B;  $^{\ddagger}P < 0.04$  versus group A.

**Conclusion:** CABG can be performed effectively employing heparin-coated ECC. Thrombin generation is significantly elevated by low intravenous heparinization at ECC durations greater than 60 min, but fibrinolysis is not increased. Platelet activation is

less and there are few clinical complications, even if intravenous heparin is greatly reduced. Significantly less postoperative bleeding and need for blood replacement occurs only if coated ECC technology is combined with low-dose systemic heparin.

## P12 Implantation of HIA-Medos system in children with and without cardiopulmonary bypass

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**Introduction:** Mechanical circulatory assistance is a routine procedure in severe heart failure. The goal of the HIA-Medos system is to develop two miniaturized ventricles for cardiovascular support in children. We report our experiences with implantation of the HIA-Medos system in children with and without cardiopulmonary bypass.

**Method:** A HIA-Medos system was implanted by cannulation in the right atrium and the pulmonary artery for right heart support. In bridge-to-transplant patients, the left ventricle and the ascending aorta were cannulated for left heart support. In those patients who were expected to recover, the left atrium was cannulated. Cardiopulmonary bypass was instituted using standard techniques.

**Results:** Five patients (ages 5 days, 5 months, and 1, 5 and 8 years) were supported. Body weights ranged from 3.5 to 20 kg, and body surface area from 0.19 to 0.83 m<sup>2</sup>. The underlying disease was myocarditis in two patients, dilatative cardiomyopathy in one patient, d-transposition of the great arteries in one patient, and undetected Bland-White-Garland syndrome in one patient. Four patients underwent biventricular

support, and one had left heart support. One patient had postoperative low-output syndrome, who could be weaned after a support time of 5 days. The HIA-Medos system was implanted in three out of the four bridge-to-transplant patients, with cardiopulmonary bypass. In these three patients re-exploration was necessary because of bleeding complications due to disturbed coagulation cascade. They received a mean of 2.9 erythrocyte concentrates per support day. The patients died because of multiple organ failure, among other complications. In the fourth child the HIA-Medos system was implanted without cardiopulmonary bypass. No bleeding complication occurred. Pre-existent organ dysfunction recovered. Disturbances of coagulation system were not apparent.

**Conclusion:** Postoperative bleeding is the most frequent complication in children supported by the HIA-Medos system with cardiopulmonary bypass. Multiple transfusions were necessary, and the patients treated died because of multiple organ failure. Implantation without cardiopulmonary bypass appears to prevent bleeding complications, with nearly normal coagulation conditions. Recovery of all pre-existent major organ dysfunctions occurred.

## P13 The clinical relevance of an elevated lactate level after surgery for congenital heart disease

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**Introduction:** Lactate is a product of anaerobic glycolysis, and may be increased due to inadequate oxygen supply, excessive oxygen demand, liver failure or exogenous supply with blood products. Children after cardiothoracic operations may therefore be at risk for elevated lactate concentrations. We examined the impact of elevated lactate levels on postoperative outcome.

**Method:** The records of 253 children, aged 1 day to 17 years, who underwent open or closed cardiac surgery in our institution between March 1997 and May 1998, were examined retrospectively. Twenty children were excluded because of incomplete data sets. The postoperative concentration of lactate was measured at the time of admission to our intensive care unit and was related to intraoperative and postoperative data.

**Results:** Lactate concentrations for various durations of cardiopulmonary bypass (CPB) are shown in Table 1. The mean lactate was 3.37 mmol/l on postoperative admission. In the 215 patients who survived, mean lactate was 2.8 (0.6–19.6) mmol/l,

**Table 1**

### Lactate concentrations

	Duration of CPB in minutes (n)				
	0 (37)	1–60 (21)	61–120 (91)	121–180 (67)	>181 (17)
Lactate (mmol/l)	1.3	1.8	2.64	4.6	9.14

versus 10.6 (2.1–22.4) mmol/l in the 18 children who died during the postoperative period. In 10 children with multiple organ failure lactate was 9.8 (2.1–19.6) mmol/l, versus 3.1 (0.6–22.4) mmol/l in children without. In 23 children who suffered from neurological complications we found higher lactate (9.0 [1.0–22.4] mmol/l) than in 210 children without (2.8 [0.6–21.3] mmol/l). In the group of children with a lactate level

greater than 6 mmol/l ( $n=34$ ) mortality was 41.1%, incidence of multiple organ failure was 14.7% and incidence of neurological complications was 44.1%. In contrast, in the group with lactate levels below 6 mmol/l ( $n=199$ ) mortality rate was 2.0%, incidence of multiple organ failure was 5% and incidence of neurological complications was 4.5%.

**Conclusion:** The concentration of lactate in the blood is higher after operations with CPB than after those without, and the level of lactate increases with the duration of CPB. The risk for postoperative morbidity and mortality is increased with higher lactate concentrations. Therefore, lactate concentration might be a valuable parameter during CPB and during the postoperative period.

#### **P14 Phosphorylcholine-coated cardiopulmonary bypass in paediatric cardiac surgery improves biocompatibility: reduced contact activation and endothelin-1 release**

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**Introduction:** Modification of cardiopulmonary bypass (CPB) circuits by using a phospholipid coating is a promising option for improving biocompatibility of CPB and thus reducing CPB-associated organ dysfunction. Endothelin-1 is a potent vasoconstrictor peptide that is synthesized and secreted by vascular endothelial cells. Its biological functions are widespread, acting as a mitogen and stimulant of collagen synthesis. It has been reported to be positively inotropic, to increase after vascular injury, and to induce pulmonary vasoconstriction, cardiac hypertrophy and heart failure. The aim of this study was to analyze the impact of a new phospholipid coating with respect to contact activation and endothelin-1 release in paediatric cardiac surgery patients.

**Method:** We randomly assigned 20 neonates and young children to two groups, using a completely phospholipid-coated CPB circuit in group A ( $n=10$ ) and an equivalent but uncoated set in group B ( $n=10$ ). The children were scheduled for elective congenital heart surgery. Their parents gave informed consent, and the study was approved by the local ethics committee. Arterial blood samples were drawn at times 0, 30 min and 48 h, and analyzed using enzyme-linked immunosorbent assay. The intensive care unit (ICU) course and further recovery was studied with regard to the alveolar-arterial oxygen gradient, the respiratory index, and duration of intubation and ICU stay.

**Results:** In group A mean age was  $11.3 \pm 4$  days (range 6–24 days), with a mean body weight of  $3.8 \pm 0.2$  kg (range 3.5–4.0 kg). In group B mean age was  $172 \pm 148$  days (range 7–528 days, median 154 days), with a mean body weight of

$4.8 \pm 1.1$  kg (range 3.0–5.9 kg). The average perfusion time in group A was  $125.8 \pm 25.6$  min, and in group B it was  $78.5 \pm 33.8$  min; the mean cross-clamp time in group A was  $44.3 \pm 17.9$  min, and in group in B it was  $31 \pm 16.8$  min. In both groups a significant loss of complement factors was observed: in group A C3c 0.45 mg/ml versus 0.71 mg/ml, C4 0.08 versus 0.14 mg/ml; and in group B C3c 0.28 mg/ml versus 0.68 mg/ml, C4 0.05 versus 0.13 mg/ml. The difference between the groups (0.45 versus 0.28, and 0.08 versus 0.05) is significant for C3, but not for C4. In both groups, complement factors normalized after 48 h. Endothelin-1 release was significantly reduced in the phospholipid group, whereas in group B elevated levels could be observed even after 48 h. The respiration parameters, such as alveolar-arterial oxygen gradient and respiratory index, revealed advantages for group A ( $240 \pm 101$  versus  $375 \pm 105$ , and 0.70 versus 1.60, respectively). Parameters such as duration of intubation and ICU stay should be considered with caution, because of the interindividual range of postoperative courses.

**Conclusion:** Phospholipid-coating of CPB circuit elements in paediatric cardiac surgery leads to a lower C3 consumption, which can also be observed with regard to C4. Improvement in biocompatibility is evident by reduced endothelin-1 release, which may lead to decreased vasoconstriction and thus to a decrease in cardiac afterload in postischaemic myocardium. The reduction in oxygen consumption is likely to improve clinical outcome. Clinical parameters such as respiration and duration of ICU stay indicate beneficial effects for phospholipid-treated patients; this needs confirmation in further studies including many more patients, as have already been initiated.

#### **P15 High oxygen treatment during preparation of children for open-heart surgery leads to a decrease in total antioxidant capacity**

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**Introduction:** Children who undergo cardiac surgery with cardiopulmonary bypass (CPB) often suffer myocardial damage after the operation. It has been hypothesized that this damage

is enhanced by mechanisms that involve increased oxidative stress. This oxidative stress damage could be caused by ischaemia-reperfusion injury, which could be intensified by the



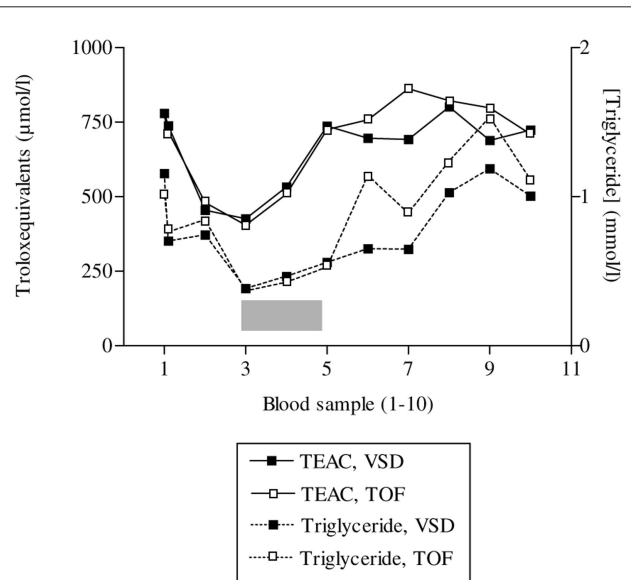
high oxygen treatment that is used during CPB and by inflammatory activity. To verify this, we assessed the antioxidant capacity in plasma samples collected at a number of time points before, during and after CPB, from children undergoing open-heart surgery.

**Method:** Total trolox equivalents in antioxidant capacity (TEAC) were calculated from the reactivity toward the artificially generated 2,2'-azinobis-(3-ethyl-benzothiazoline-6-sulfonic acid) (ABTS) radical. To exclude the possibility that TEAC values decrease as a result of haemodilution, we measured the triglyceride content using the GPO-trinder (Sigma) reagent in a microtitre-plate spectrophotometric analysis.

**Results:** Total antioxidant capacity was decreased shortly after the onset of surgery in plasma of children (aged 8–14 months) treated for ventricular septal defect (VSD;  $n = 17$ ) and tetralogy of Fallot (TOF;  $n = 15$ ). Figure 1 shows a significant (Friedman test;  $P < 0.05$ ) decrease in both VSD and TOF from time point 1.1 (induction of anaesthesia) to time point 2 (heparin administration before CPB). Decrease in TEAC values can therefore not be a result of haemodilution during CPB. This was confirmed by the fact that total plasma triglyceride values did not decrease between these time points. Shortly after CPB (time point 4) the TEAC values were already significantly ( $P < 0.05$ ) higher than at time point 3 (10 min after the onset of CPB), and they returned to normal during the 4 h after the operation and remained normal thereafter.

**Conclusion:** We showed a decrease in antioxidant capacity early during the operation, which could not have been caused by haemodilution. The most likely cause appears to be the high

**Figure 1**



Average TEAC and triglyceride values in infants with VSD or TOF. Shown are changes in TEAC and triglyceride values before, during (grey area) and after CPB.

oxygen that was given during preparation for CPB. The methodology described here will be useful for study of the influences of different approaches in, for example, oxygen treatment, clamping techniques, temperature treatment and antioxidant supply on the oxidative stress that occurs during open-heart surgery.

## P16 Myocardial cell damage related to arterial switch operation in neonates with transposition of the great arteries

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**Introduction:** It was of objective of this study to investigate clinical and laboratory risk factors for myocardial dysfunction (MD) in neonates after arterial switch operation for transposition of the great arteries.

**Method:** Sixty-three neonates (age 2–28 [ $8.1 \pm 4.6$ ] days), who were operated on under combined deep hypothermic ( $15^{\circ}\text{C}$ ) circulatory arrest and low-flow cardiopulmonary bypass (CPB), were studied. Inclusion criteria were transposition of the great arteries with or without ventricular septal defect (VSD) that was suitable for arterial switch operation (VSD<sup>-</sup>;  $n = 53$ ), and if necessary additional VSD closure (VSD<sup>+</sup>;  $n = 10$ ). Patients were differentiated clinically into two groups by presence or absence of MD within 24 h after surgery. MD was defined as myocardial ischaemia after coronary reperfusion and/or myocardial hypocontractility as assessed by echocardiography. MD was related to clinical outcome parameters and

to perioperative release of cardiac troponin-T (cTnT) and production of interleukin-6 and interleukin-8.

**Results:** MD was observed in 11 patients (17.5%). Two patients died early after surgery from myocardial infarction, and two died late after surgery (6.3%). CPB and cross-clamping, but not deep hypothermic circulatory arrest times, were correlated with MD; MD was more frequent in the VSD<sup>+</sup> than in the VSD<sup>-</sup> group because of longer support times. Coronary status and age at surgery were not related to MD. Patients with MD had more frequently impaired cardiac, respiratory and renal functions. cTnT, interleukin-6 and interleukin-8 were significantly elevated at the end of CPB, and 4 and 24 h after surgery, as compared with preoperative values in both groups. Postoperative cTnT, interleukin-6 and interleukin-8 concentrations were significantly higher in MD patients than in the others. Multivariable analysis of independent risk factors for MD

revealed interleukin-6 4 h after surgery to be significant ( $P=0.04$ ; odds ratio 1.24 [95% confidence interval 1.01–1.52] per 10 pg/ml). The cutoff point for prediction of MD was set at 500 pg/ml (specificity 95.4%, sensitivity 72.7%).

**Conclusion:** Cardiac operations in neonates induce the production of the proinflammatory cytokines interleukin-6 and interleukin-8, as well as release of cTnT. These results suggest that proinflammatory cytokines are, at least in part, responsible for myocardial cell damage and MD occurring after arterial switch operations in this age group.