Critical Care Volume 7 Supplement 1, 2003

Abstracts of the 4th International Symposium on the Pathophysiology of Cardiopulmonary Bypass: Endothelial Damage
Munich, Germany, 29 November 2002

Received: 15 January 2003    Published online: 18 February 2003
This article is online at http://ccforum.com/supplements/7/S1
© 2003 BioMed Central Ltd (Print ISSN 1364-8535; Online ISSN 1466-609X)

1 Antithrombin substitution before extracorporeal circulation attenuates perioperative coagulation activation and might decrease postoperative troponin elevation: a report of preliminary data

R Busley1, W Dietrich1, S Braun2, J Weipert3, JA Richter1
Departments of 1Anesthesiology, 2Laboratory Medicine and 3Cardiac Surgery, German Heart Center Munich, Germany
(e-mail: r.busley@lrz.tum.de)

Objectives Antithrombin (AT) has been proven to have major impact on perioperative activation of the coagulation system. The aim of this prospective, controlled, single-blind clinical trial was to determine the impact of AT substitution on perioperative thrombin formation.

Methods Forty male coronary artery bypass graft patients participated in the trial. Prior to skin incision, 30 patients received AT according to a formula targeted at 120% AT activity before extracorporeal circulation (ECC), plus an additional 1000 U (group A, n = 10), 2000 U (group B, n = 10) or 3000 U (group C, n = 10) of AT in order to compensate for increased consumption during ECC. Control patients did not receive any AT substitution (group D, n = 10). The following parameters were determined perioperatively and until the fifth postoperative day: AT levels, parameters of coagulation activation (prothrombin fragment F$_{1+2}$, thrombin–antithrombin complex, D-dimer), inflammation (IL-6) and myocardial perfusion (troponin). Statistical comparison between groups was performed using analysis of variance, followed by Fisher’s PLSD ($P<0.05$) after ECC.

Results AT substitution resulted in a significant increase in AT during ECC and until the first postoperative day (POD1), followed by a steep decrease at days 2–5. AT substitution attenuated thrombin generation significantly, as indicated by decreased concentrations of prothrombin fragments F$_{1+2}$, thrombin–antithrombin complex, D-dimer, inflammation (IL-6) and myocardial perfusion (troponin). Statistical comparison between groups was performed using analysis of variance, followed by Fisher’s PLSD ($P<0.05$) after ECC.

Conclusions A substantial decrease in AT must be taken into account not only during ECC but also in the early postoperative period, indicating major enhancement of coagulation activation. High-dose AT substitution attenuates coagulation activation significantly. Attenuation of hemostatic activation may reduce postoperative complications, as lower postoperative troponin levels may indicate in AT substituted patients.

Figure 1

Perioperative course of troponin. *$P<0.05$, versus groups A, B and C.

2 Phosphorycholine or heparin coating for pediatric extracorporeal circulation causes similar biological effects in neonates and infants

A Böning1, J Scheewe1, C Friedrich2, U Bläse1, J Stieh3, P Dütschke3, JT Cremer1
Departments of 1Cardiovascular Surgery, 2Pediatric Cardiology and 3Anaesthesiology, University Hospital Kiel, Germany
(e-mail: aboening@kielheart.uni-kiel.de)

Objectives Cardiac surgery for complex congenital malformations with use of extracorporeal circulation (ECC) predisposes the patient to an excessive systemic inflammatory response and a consecutive capillary leak syndrome. In a prospective, randomized study, the...
influence of two oxygenators especially designed for pediatric use on inflammatory markers and clinical outcome was investigated.

**Methods:** Forty neonates and infants (body surface area <0.36 m²) undergoing cardiac surgery using ECC were randomised into three groups: in the first group (n = 14) the Medtronic Minimax® Oxygenator was used, and in the second group (n = 12) the Dideco Liliput 1® Oxygenator was used, both with 750 ml priming volume. In the third group the Dideco Liliput 1® Oxygenator was filled with a reduced priming volume of 450 ml.

Parameters of interest for evaluation of a systemic inflammatory response after ECC were IL-6, tumor necrosis factor (TNF)-α, neutrophil elastase, complement C3 and free hemoglobin (Hb). In addition, erythrocyte, leukocyte and thrombocyte counts, hemoglobin and C-reactive protein (CRP) values were determined at different measurement points before, during and after surgery.

**Results** In all three groups, peak values for TNF-α were observed during surgery, whereas IL-6, elastase and free Hb peaked in the first 4 hours. Highest values for leucocytes and CRP were obtained between 24 and 72 hours after surgery. Erythrocyte and thrombocyte counts as well as Hb values were lowest at ECC onset, normalizing under substitution in the first 4 hours after surgery. Using the Liliput/750, higher IL-6 values 1 hour and 4 hours after surgery, and higher TNF-α values during and 1 hour after surgery could be observed, as compared with Minimax and Liliput/450. In spite of our randomization protocol, patients in the Liliput/750 group were significantly smaller and younger than those in the Minimax group. Accordingly, the number of children with a clinically complicated course (cicallep, and longer duration of catecholamine therapy and ventilation) was higher in the Liliput/750 group.

**Conclusions** Using an adequate priming volume, the systemic inflammatory response is similar after employment of the Dideco Liliput 1® Oxygenator and the Medtronic Minimax® Oxygenator. Tip-to-tip surface coating of the ECC with either heparin or phosphocholine appears to have similar biological effects in neonates and infants undergoing cardiac surgery.
injury. Recently, we demonstrated lung ischemia during cardiopulmonary bypass (CPB). We therefore hypothesize that (1) lung ischemia induces an inflammatory reaction in the lung parenchyma and (2) that pulmonary perfusion during CPB reduces the inflammatory reaction of the lung.

**Methods** Eighteen piglets (5.0 ± 0.5 kg) underwent 120 min of normothermic, total CPB without aortic cross-clamping, followed by 60 min of postbypass perfusion. Nine of them received continuous pulmonary perfusion with autologous, oxygenated blood during CPB while the pulmonary artery was clamped. Six additional piglets served as control and were ventilated after sternotomy for 180 min only.

**Results** With the beginning of CPB, bronchial arterial blood flow decreased to 13% of the baseline value (42.1 ± 10.4 to 5.6 ± 1.0 ml/min), remained decreased until the end of CPB, and returned to starting levels 60 min after CPB. The decrease in bronchial blood flow was associated with a threefold increase in tissue lactate content. At the end of reperfusion there was a twofold increase in alveolar septal thickness and a significant accumulation of albumin, lactate dehydrogenase, neutrophils and elastase in the bronchoalveolar fluid as compared with control. Controlled pulmonary perfusion significantly ameliorated all of the observed changes.

**Conclusions** (1) CPB causes a reduction in bronchial arterial blood flow, which is associated with injury to the lung. (2) Controlled pulmonary perfusion reduces injury to the lung during CPB. (3) The inflammatory response, as evidenced by the analysis of bronchoalveolar lavage fluid, may be caused by ischemia.

### 5 Influence of stress doses of hydrocortisone on levels of cytokines and nuclear transcription factor kappa B in patients after cardiac surgery

**F Wels**, J Briegel, AE Goetz, D Reuter, P Fraunberger, A Walli, E Kilger

Departments of 1Anaesthesiology and 2Clinical Chemistry, Klinikum Großhadern, Ludwig Maximilian University Munich, Germany (e-mail: Erich.Kilger@ana.med.uni-muenchen.de)


**Objectives** Severe systemic inflammation (SIRS) is a serious complication in patients after cardiac surgery. Hydrocortisone has been successfully used to treat this complication (Kilger et al., *Crit Care Med*, in press), potentially by lowering levels of proinflammatory cytokines. The purpose of this prospective, randomized, double-blind, placebo-controlled trial was to evaluate the influence of stress doses of hydrocortisone on levels of cytokines and nuclear factor-κB (NF-κB) in a group of high-risk patients after cardiac surgery.

**Methods** Twenty-two cardiac surgical patients were randomly assigned to receive stress doses of hydrocortisone or placebo from the time point of induction of anesthesia until discharge from the intensive care unit. Levels of NF-κB, IL-6, tumor necrosis factor (TNF)-α and IL-10 were measured preoperatively, and 4 and 24 hours after the operation. Activation of NF-κB was assayed in nuclear extracts from monocytes.

**Results** Patients demographic data were similar in both groups.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 11)</th>
<th>Hydrocortisone (n = 11)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF-κB (1 hour; %)</td>
<td>66 (27/125)</td>
<td>75 (50/98)</td>
<td>NS</td>
</tr>
<tr>
<td>NF-κB (24 hours; %)</td>
<td>86 (61/116)</td>
<td>59 (34/105)</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-α (4 hours)</td>
<td>45 (31/66)</td>
<td>31 (28/40)</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-α (24 hours)</td>
<td>41 (17/45)</td>
<td>27 (16/40)</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6 (pg/ml; 4 hours)</td>
<td>438 (396/931)</td>
<td>178 (93/375)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-6 (pg/ml; 24 hours)</td>
<td>281(245/454)</td>
<td>139 (104/231)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IL-10 (pg/ml; 4 hours)</td>
<td>16 (9/42)</td>
<td>137 (79/215)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-10 (pg/ml; 24 hours)</td>
<td>3.5 (2/10)</td>
<td>3.5 (1/12)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Conclusions** In our study, hydrocortisone reduced the postoperative serum levels of IL-6 and increased the levels of IL-10. The levels of TNF-α and NF-κB remained unaffected. Increased levels of IL-6 may be independent of TNF-α. Further studies are needed to clarify this point.

### 6 Cardiopulmonary bypass and pulmonary surfactant: influence on composition and function?

**J Thul**, B Friedrich, R Günther, I Reiss, D Schranz, L Gortner

1Zentrum für Kinderheilkunde and 2Medizinische Klinik, JL-Universität Giessen, Germany (e-mail: josefthul@hotmail.com)


**Objectives** To characterize early pulmonary surfactant features in children undergoing cardiovascular surgery with cardiopulmonary bypass (CPB).

**Methods** Fifty children were undergoing cardiac surgery for congenital heart disease: 35 procedures with CPB and 15 without (control group). Tracheal aspirates (TA) were obtained by saline lavage before and after CPB, and 4, 8 and 24 hours after pediatric intensive care unit admission. Total protein and phospholipid (PL) contents were assessed in native TA, in functional active large surfactant aggregates (LA), and in degraded small aggregates (SA). PL profiles, surfactant apoproteins SP-A, SP-B and SP-C (enzymelinked immunosorbent assay), and surface activity (bubble surfacometer) were analyzed in LA only.
Results Surfactant properties did not change in the control group. In the CPB group, PL content increased in TA 24 hours after CPB. LA concentration dropped 4 hours after CPB ($P<0.01$) but recovered within 24 hours. The PL : protein ratio of LA was decreased at 24 hours as compared with baseline ($P<0.01$). The relative amount of phosphatidylglycerol in LA-PL content dropped linearly over time. The relative content of the hydrophobic SP-B and SP-C in LA increased almost threefold as compared with baseline. There were no significant changes in biophysical function of LA.

Conclusions CPB in children induces profound changes in the surfactant system, involving both PL and protein components. Biophysical function may be maintained by compensatory increases in SP-B and SP-C of LA.

7 Evaluation of a mathematical model for blood gases and acid-base status during extracorporeal circulation

TM Schmidt, E Naujokat, J Barrho, J Albers, U Kiencke, CF Vahl
1Chirurgische Universitätsklinik Heidelberg, Abt. Herzchirurgie, Heidelberg, and 2Institut für Industrielle Informationstechnik, Universität Karlsruhe (TH), Germany (e-mail: Tanja.Schmidt@urz.uni-heidelberg.de)

Objectives Blood gases and acid–base status are important parameters during extracorporeal circulation. They are controlled by the perfusionist, by varying arterial pump flow, gas flow over the oxygenator, inspiratory oxygen fraction, and carbon dioxide content in the inspiratory gas mix. To support the perfusionist with suggestions based on a control algorithm, a reliable system description is needed. Reliability of a complex model of human acid–base and blood gas status under extracorporeal circulation was evaluated using clinical documentation data.

Methods A mathematical model for blood gas and acid–base status under extracorporeal circulation was developed. This model consists of a multiple compartment model for the oxygenator, and models for arterial and venous PCO$_2$, Po$_2$, (including temperature- and pH-dependent shift in oxygen-binding capacity of haemoglobin), So$_2$, bicarbonate, base excess and pH. It was implemented in a Matlab/Simulink environment. Input parameters were oxygenator type, gas flow, FiO$_2$, arterial pump flow, temperature, haemoglobin concentration and haematocrit. As output parameters, venous and arterial So$_2$, Po$_2$, PCO$_2$, and pH were analyzed. The model was tested by using clinical monitoring data during extracorporeal circulation.

Results Estimations of arterial Po$_2$, PCO$_2$, and So$_2$ were adequate. They followed the time course appropriately and remained within a narrow error band (Max. dev.: Po$_2$ <17 mmHg, PCO$_2$ <7 mmHg, So$_2$ <0.01%). Venous Po$_2$ followed appropriately (Max. dev.: <4 mmHg), whereas PCO$_2$ (Max. dev.: <8 mmHg) did not reproduce the time course. Simulations for arterial and venous pH over-estimated continuously and were not acceptable (Max. dev.: arterial pH +0.14, venous pH +0.07). The best results were achieved for estimation of So$_2$.

Conclusions Modelling the patients’ acid–base status and blood gases will be important for further development of control algorithms used in extracorporeal circulation. The presented model shows good concordance with clinical data for blood gas estimation, but needs to be reviewed concerning acid–base status. Further validation and in controlled experimental setups will be required.

8 Transpulmonary vascular gradients of nitric oxide pathway metabolites and asymmetrical dimethyl-L-arginine in the flow - or pressure-overloaded pulmonary vasculature

J Kreuder, R Zimmermann, D Tsikas, I Michel-Behnke, D Schranz
1Department of Paediatric Cardiology, Justus-Liebig-University, and 2Department of Clinical Pharmacology, Medical School, Hannover, Germany

Objectives Alterations in pulmonary vascular nitric oxide (NO) production have been implicated in the regulation of pulmonary vascular tone and the development of pulmonary hypertension (PH). Asymmetrical dimethyl-L-arginine (ADMA), an endogenous inhibitor of NO synthesis, has been suggested to counteract endothelial NO production.

Methods Transpulmonary gradients of nitrite (NO$_2$), nitrate (NO$_3$) and ADMA were determined in patients with increased pulmonary flow (Qp) before (1) and after (2) intervention. In patients with increased pulmonary vascular resistance (Rp) (3). Twenty patients with ASD: median age 6.1 years (range 3.5–17.1 years), median Qp/Qs 2.1, Rp/Rs <0.12. Twenty patients with PH: median age 8.1 years (range 1.2–13.5 years), median Rp/Rs 1.1 (range 0.36–1.79). NO$_2$, NO$_3$ (chromatography mass spectrometry) and ADMA (high-performance liquid chromatography) were measured in plasma samples from the main pulmonary artery (PA) and femoral artery (SA).

Results (1) In ASD patients, NO$_2$ showed a significant gradient with a median SA:PA ratio of 1.34 ($P<0.01$), but this was not so for ADMA (1.05) or NO$_3$ (1.01). (2) After closure, SA:PA ratio of NO$_2$ decreased to 0.89 ($P<0.05$), indicating a switch from NO$_2$.
Fourteen young pigs were operated on with standard-
κ = 7). Six hours after termination of CPB, forehead brain tissue
(0.84). Median levels of ADMA in SA
n Analysis of transpulmonary metabolite gradients may
system. A
3 In our model, cardiac surgery is related to upregula-
µ
2 During our initial experience between April and October
κ
κ < 0.05) and NO
µ
2 µ
Cerebral cell damage after cardiac surgery with car-
and IL-6, as well
consumption, whereas ADMA (1.00) and NO
31x320
10 Management of extracorporeal circulation in heart surgery through a right mini-thoracotomy
MR Hoda1, E Schmitz1, H El-Achkar1, KH Krauskopf2, H Psyk1, F Lewark1, HO Vetter1
Heart Center Wuppertal, Departments of 1Cardiothoracic Surgery and 2Anaesthesiology, University of Witten-Herdecke, Wuppertal, Germany
Objectives Minimally invasive open heart surgery requires car-
diopulmonary bypass (CPB) to be initiated via peripheral access.
We report our initial experience with a modified femoro-femoral
CPB, with the superior vena cava being drained by a supple-
mentary cannula inserted via the jugular vein. However, because of
smaller diameter of the cannula, a slight modification to the CPB
was necessary to improve the impeded venous return.
Methods Cannulation of the superior vena cava was performed
through the right jugular vein during maintenance of anesthesia.
After right mini-thoracotomy and exposure of the femoral site, CPB
was initiated by cannulation of the femoral artery, and the inferior
vena cava via the femoral vein using the Heartport® system. A
modified open CPB system (Jostra®) was used. In order to improve
the venous return, the venous reservoir was completed with a
device offering undertow, which was monitored by a low pressure
valve in the venous and a vacuum controller in the arterial line.
Myocardial protection was performed using Bretschneider’s solu-
tion. A minimal (7–9 cm) right thoracotomy through the fourth inter-
costal space was used in all cases as the surgical approach. All
procedures were performed video-assisted.
Results During our initial experience between April and October
2002, seven patients were operated on using this technique (five
males/two females; age 52.6 ± 9.5 years; body weight
78.7 ± 19.4 kg; body surface area 1.94 ± 0.3 m²). Five patients
were operated on for mitral valve repair/replacement and two
patients for closure of an atrial septal defect. Cannula sizes were
18–20 Fr for the femoral artery, 25 Fr for the femoral vein and
16 Fr for the superior vena cava. Considering the theoretical perfu-
sion flow of 5.5 l/min, the venous flow through both cannulae was
4.27 ± 0.5 l/min. Mean CPB and cross-clamp times were
141.7 ± 38.6 min and 87.5 ± 24.5 min, respectively. Minimum
venous saturation was 97.4 ± 1.8 %. There were no cases of hos-
pital or late postoperative mortality. No case of postoperative
adverse events occurred. All patients were extubated within
8 hours postoperatively and were discharged from the intensive
care unit by the first postoperative day.
Conclusions Despite our limited initial experience, and considering the smaller internal diameter of percutaneous cardiopulmonary bypass cannulae as compared with the classic one, the modifications to the CPB system we used in this study improved venous drainage significantly, so that minimally invasive open heart procedures could be performed under optimal CPB conditions in our center.

11 Increased apoptosis of circulating leukocytes during cardiac surgery with cardiopulmonary bypass

J Hambsch, D Lenz, P Schneider, A Tarnok
Pediatric Cardiology, Herzzentrum Leipzig, University Hospital, Leipzig, Germany

Objectives Surgical trauma has been reported to be associated with an elevated apoptotic rate of circulating leukocytes. However, the effect of cardiac surgery on leukocyte apoptosis has not yet been investigated. Our study was therefore designed to address this question.

Methods Flow-cytometric immunophenotype data from 70 children (age 3–16 years) who underwent cardiac surgery with (n = 50) or without (n = 20) cardiopulmonary bypass (CPB) were analyzed for T-cell apoptosis, based on light scatter and surface antigen (CD45/CD3) expression. Additionally, in vitro isolated leukocytes from healthy volunteers were incubated with serum obtained from cardiac surgery patients before, during and after surgery. Apoptosis was detected by flow cytometry after staining with annexin V and DNA condensation by laser scanning cytometry. Serum cytokine and troponin I levels were also determined.

Results Patients undergoing CPB had elevated lymphocyte apoptosis. In particular, T-cell apoptosis increased from 0.45% (baseline) to 1.34% (4 hours postoperative; analysis of variance \( P = 0.0034 \)). No effect was found during and after surgery without CPB. These results were in accordance with in vitro findings demonstrating elevated apoptotic activity for lymphocytes and neutrophils in the serum from patients with CPB at reperfusion and up to 3 days after surgery (\( P < 0.01 \)). No such activity was found in patients operated on without CPB. The increase in apoptosis correlated well with the increase in troponin I and IL-10 levels.

Conclusions At present, the agents that induce apoptosis during CPB surgery are not well identified. However, IL-10 might be involved in peri- and postoperative neutrophil apoptosis. Increased apoptosis of circulating lymphocytes and neutrophils further contributes to the immune suppressive response to surgery with CPB, for example by inactivating phagocytes by uptake of apoptotic cells (e.g. via CD36) or removal of activated cells. Elevated apoptotic activity in the blood of patients during CPB might also contribute to the destruction of cardiomyocytes during and after pediatric cardiac surgery.

12 In vitro bleeding time (PFA-100™) helps to identify patients with platelet dysfunction-dependent increased bleeding after coronary artery bypass grafting

F Zaccaria, W Dietrich, JA Richter
Department of Anesthesiology, German Heart Center Munich, Germany

Objectives Platelet dysfunction and surgical bleeding are the most important causes of blood loss after cardiopulmonary bypass (CPB). The aim of this study was to find out whether there is a correlation between pre- and postbypass PFA-100 (Dade Diagnostika, GmbH, Germany) in vitro bleeding time and blood loss within the first 6 postoperative hours.

Methods After local ethics committee approval, 110 consecutive patients scheduled for elective first time coronary artery bypass grafting (CABG) were enrolled. Platelet function was assessed using a PFA-100 analyzer with epinephrine-mediated platelet activation. The measurements were performed 15 min before skin incision and 15 min after protamine administration. Patients were classified as increased bleeders (blood loss >600 ml/6 hours) and normal bleeders (blood loss <600 ml/6 hours). PFA values greater than 180 s were considered abnormal.

Results See Figure 1 opposite. Increased bleeding occurred in 28 patients and 82 had normal blood loss. Prebypass PFA values showed a sensitivity of 75% and a specificity of 65% for increased bleeding, whereas postbypass PFA values showed a sensitivity of 60% and a specificity of 41%. No patient required surgical re-exploration.

Conclusion In this study, prebypass PFA values identified 75% of the patients with increased bleeding risk due to pre-existing (mainly drug-induced) platelet dysfunction. Postbypass PFA values, reflecting drug-induced and CPB-related platelet dysfunction as well as a combination of both, showed the same sensitivity and specificity problems as reported in previous studies. A differential diagnosis based exclusively on this point-of-care test appears to be, in presence of a mixed etiology, less reliable. However, our data suggest that, in addition to the classic differential diagnosis management of
postoperative bleeding, the identification of increased bleeders with normal PFA values (false negative) may facilitate the decision for early surgical re-exploration. Also, the identification of increased bleeders with abnormal PFA values (true positive) may help to select patients who can benefit from administration of desmopressin or platelets. Therefore, routine use of PFA (with epinephrine-mediated platelet activation) may provide a useful additional information for the early differential diagnosis of increased bleeding after CBP.