Background. Cardiopulmonary bypass (CPB)-related inflammatory response can be attenuated by glucocorticoid treatment, but its impact on postoperative cardiopulmonary function remains controversial. It was investigated whether the systemic and myocardial anti-inflammatory effects of glucocorticoids are associated with improved cardiopulmonary function in cardiac surgery patients.

Methods. Eighty patients undergoing elective coronary artery bypass grafting were randomly assigned to receive a single shot of methylprednisolone (15 mg/kg) or placebo before CPB. Variables of myocardial and pulmonary function and systemic hemodynamics were measured before and 1, 4, 10, and 24 hours after CPB. Blood was sampled for measurement of proinflammatory (tumor necrosis factor-α, interleukin 6, interleukin 8) and antiinflammatory (interleukin 10) cytokines (by enzyme-linked immunoassay), troponin T, and C-reactive protein. Phosphorylation of inhibitory kappa-B alpha and p38 mitogen-activated protein kinase was determined in right atrial biopsies before and after CPB (phosphoprotein assay).

Results. Preoperative and intraoperative characteristics of patients were not different between groups. Methylprednisolone attenuated postoperative tumor necrosis factor-α, interleukin 6, interleukin 8, and C-reactive protein levels while increasing interleukin 10 release. Myocardial inhibitory kappa-B alpha was preserved with methylprednisolone (p < 0.05 versus placebo), but p38 mitogen-activated protein kinase activation occurred in both groups after CPB (p < 0.05 versus before CPB). Methylprednisolone improved postoperative cardiac index and was associated with decreased troponin T when compared with placebo (p < 0.05). Postoperative blood glucose, oxygen delivery index, and pulmonary shunt flow were increased in the methylprednisolone group (p < 0.05). There was no difference in postoperative oxygenation index, ventilation time, and clinical outcome between treatment groups.

Conclusions. Glucocorticoid treatment before CPB attenuates perioperative release of systemic and myocardial inflammatory mediators and improves myocardial function, suggesting potential cardioprotective effects in patients undergoing cardiac surgery.
and proinflammatory cytokines themselves, phosphor-
ylation of the inhibitory protein of NFκB (inhibitory
kappa-B alpha [IkBα]), and p38 MAPK promotes gene
expression of potential myocardial damaging media-
tors such as TNFα, IL-1β, and IL-6 [7–9].

Although various pharmacologic, mechanistic and op-
erative strategies to attenuate CPB-induced systemic
inflammatory response have been investigated [1], ran-
domized trials have consistently demonstrated that peri-
operative administration of corticosteroids in patients
undergoing cardiac surgery with CPB inhibits the sys-
temic release of proinflammatory cytokines and de-
creases the ratio between proinflammatory and anti-
inflammatory interleukins [11–15]. Resulting clinical
benefits include improvement of postoperative hemody-
namics [14], myocardial function and protection
[11, 13, 15], and pulmonary function [11, 14], and reduced
length of stay in the intensive care unit (ICU). However,
studies addressing the role of local, antiinflammatory
myocardial actions of glucocorticoids in patients under-
going cardiac surgery are still lacking. Proposed mecha-
nisms for the local antiinflammatory glucocorticoid’s
actions are inhibition of IkBα degradation resulting in
decreased NFκB activation [16] and inhibition of p38
MAPK through induction of the mitogen-activated pro-
tein kinase phosphatase-1 [17].

In the present study the effect of a single-dose cortico-
steroid application before CPB on (1) activation of myo-
cardial transcriptional proteins of inflammation (IkBα,
p38 MAPK) and (2) systemic cytokine response (TNFα,
IL-6, IL-8, and IL-10) was investigated in patients under-
going cardiac surgery and linked to variables of postop-
erative hemodynamic, myocardial, and pulmonary
function.

Patients and Methods
Study Design
After approval by the university ethics committee and
written informed consent, 80 patients undergoing elec-
tive coronary artery bypass surgery (CABG) with CPB in
our institution between November 2003 and July 2004
were enrolled in a prospective, placebo-controlled study.
Preoperative exclusion criteria were previous emergency
or concomitant cardiac surgical procedures, age older
than 80 years, compromised left ventricular ejection
fraction (<0.30), acute myocardial infarction (<4 weeks),
acute and chronic infections, known neoplasm, renal or
hepatic dysfunction, autoimmune disease, or preceding
antiinflammatory treatment. Patients who routinely re-
ceived intraoperative aprotinin because of surgeons’
preferences were not enrolled for this study to exclude
known confounding antiinflammatory actions [14].

Following a computer-generated sequence, patients
were randomly assigned to receive either a single intra-
venous bolus of 15 mg/kg methylprednisolone (Urbason,
Sanofi-Aventis, Frankfurt, Germany; MP group) or pla-
cebo (NaCl 0.9%; PLA group) 30 minutes before CPB was
instituted.

Perioperative Management
After premedication with 1 to 2 mg of flunitrazepam
orally, general anesthesia was induced with sufentanil 2
μg/kg and etomidate 0.3 mg/kg, and pancuronium 0.1
mg/kg was administered to facilitate tracheal intubation.
Anesthesia was maintained by continuous intravenous
infusion of sufentanil (1 to 2 μg/kg per hour) and iso-
flurane (0.3 to 1.0 vol%). Coronary artery bypass grafting
was performed in a standardized fashion through a
median sternotomy, and moderate hypothermic CPB
(32°C) was established through cannulation of the right
atrium and ascending aorta. Cardiopulmonary bypass
equipment consisted of a nonocclusive centrifugal pump
(Sarns Delphin System, Terumo Europe, Eschborn, Ger-
many), a membrane oxygenator (Quadrax, Jostra AG,
Hirrlingen, Germany), a 40-μm arterial filter (Quart,
Jostra AG), a hard-shell cardiomyotomy reservoir (MC-4030,
Medos Medizintechnik, Stolberg, Germany), and an ex-
tracorporeal circuit (ME H2–1551, Medos Medizintechnik).
The circuit was primed with 500 mL of hydroxyethyl
starch 6%, 500 mL of Ringer’s lactate solution, 500 mL of
saline solution 0.9%, and 7500 IU of heparin. Nonpulsu-
tile flow was set between 2.2 and 2.4 L · min⁻¹ · m⁻²,
and perfusion pressure was maintained between 50 and
70 mm Hg. During aortic clamping, cardioplegic cardiac
arrest was achieved by intermittent antegrade and retro-
grade infusion of blood cardioplegia (Köhler Chemie
GmbH, Alsbach-Hähnlein, Germany), and the left ven-
tricle was decompressed using a vent. After rewarming
to greater than 36°C, patients were weaned from CPB, and
systemic anticoagulation was reversed by protamine sul-
fate administration. If required, weaning from CPB was
supported with epinephrine or norepinephrine at the
discretion of the attending surgeon and anesthesiologist.

After surgery, patients were transferred to the ICU
where postoperative therapy was performed at the dis-
cretion of the attending ICU team. Postoperative sedation
and analgesia was achieved by intravenous administra-
tion of propofol (1 to 2 mg · kg⁻¹ · h⁻¹), midazolam (0.1
to 0.2 mg · kg⁻¹ · h⁻¹), or piritramide (maximal 7 mg/h).
No glucose infusions were used perioperatively, and
insulin (bolus or continuous infusion) was given when
blood glucose levels exceeded 200 to 210 mg/dL. Inotro-
pic and vasoactive drug therapy was managed on the
basis of patients’ hemodynamics, and extubation was
accomplished after the following criteria were met: ade-
quate level of consciousness and muscle strength, stable
hemodynamics, normothermic body temperature
(>36°C), adequate oxygenation (arterial oxygen tension
>80 mm Hg at an inspired oxygen fraction <0.4 and
positive end-expiratory pressure <8 mm Hg), adequate
renal function (urine output >1 mL · kg⁻¹ · h⁻¹), and
minimal blood loss through chest tubes (<150 mL/2 h).

Data Collection
Preoperative and operative characteristics of patients
were recorded. After induction of anesthesia a pulmo-
nary artery catheter (HANDS-OFF Thermodilution Cath-
er, Arrow International, Inc, Reading, PA) was inserted.
and hemodynamic measurements were performed before CPB (pre-CPB) and at 1, 4, 10, and 24 hours after CPB. Hemodynamic monitoring comprised heart rate, mean arterial pressure, central venous pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and cardiac output. Cardiac index, systemic vascular resistance index, pulmonary vascular resistance index, and left ventricular stroke work index were calculated from standard equations. At all time points perioperative body temperature (temperature probe from pulmonary artery catheter) and catecholamine support was recorded. Oxygenation index (arterial oxygen tension divided by fraction of inspired oxygen), pulmonary shunt, oxygen delivery index, and extraction rate index were calculated after analysis of arterial and mixed venous blood gas samples using standard formulas [14].

Corresponding to the above-mentioned time points, arterial blood samples were obtained for measurement of pH and glucose and lactate concentrations, and venous blood was sampled for measurement of troponin T, white blood cell count, C-reactive protein, and cytokine levels (IL-6, IL-8, IL-10, and TNF-α).

For cytokine determination, blood samples were immediately centrifuged (3,000 rpm for 10 minutes at 4°C), plasma was separated, and samples were stored at −80°C until assay. Cytokine concentration was determined by a human multiplex bead enzyme-linked immunosorbent assay using the BioPlex suspension array systems (Bio-Rad Laboratories Inc, Munich, Germany) with less than 10% interassay and intraassay coefficients of variation. For measurement of total and phosphorylated IκB-α and p38 MAPK, right atrial biopsies were taken before cannulation of the right atrium and after CPB was discontinued. Sterile biopsies were snap-frozen in liquid nitrogen and stored at −80°C. Total and phosphorylated IκB-α and p38 MAPK were determined in 40 patients (20 per group) using a human single-plex total target and phosphoprotein assay (Bio-Rad Laboratories Inc) according to the manufacturer’s recommendations.

Postoperative data recording included variables of renal function (maximal creatinine), renal failure (creatinine > 2.0 mg/dL; need for hemofiltration), and average insulin dose (international units per hour) during the first 24 hours in the ICU. Additionally time on mechanical ventilation, need for reintubation, in-hospital mortality, and length of stay in the ICU and at hospital were recorded. Fluid balance was calculated from total intravenous fluid input (crystalloid, colloid, and blood products) and total fluid output (urine output and blood loss through chest tubes) as documented at the operating room and the first 24 hours in the ICU. Postoperative infections were recorded if patients met one of the following criteria: any signs of wound infection, superficial and deep mediastinitis, and receiving antibiotic therapy after the second postoperative day (fever > 38.5°C, bacteremia, persistent leukocytosis > 15 × 10⁹/μL). Additionally, pneumonia was diagnosed when two of the following criteria were present: fever, chest radiography with infiltrates, tracheal secretion with cultured pathogenic bacteria, abnormal lung auscultation, and leukocytosis or leukopenia (<4 × 10⁹/μL).

**Statistical Analysis**

Data are expressed as mean ± standard deviation. Preoperative, intraoperative, and postoperative characteristics of groups were compared by unpaired Student’s t test for continuous data or Fisher’s exact test for categorical data. Intergroup and intragroup differences for hemodynamic and pulmonary data, catecholamine support, body temperature, and biochemical variables were assessed by two-way analysis of variance with the Fisher’s least significant difference procedure for post hoc repeated measurements. Correlation analysis between cytokines and perioperative variables was performed using Spear-

### Table 1. Preoperative and Intraoperative Characteristics of Patients (n = 78)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 38)</th>
<th>MP (n = 40)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.6 ± 7.2</td>
<td>66.8 ± 8.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Males</td>
<td>25 (66%)</td>
<td>30 (75%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.1 ± 4.4</td>
<td>28.5 ± 4.3</td>
<td>0.65</td>
</tr>
<tr>
<td>Smoking history</td>
<td>10 (26%)</td>
<td>14 (35%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (87%)</td>
<td>36 (90%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>19 (50%)</td>
<td>26 (65%)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (37%)</td>
<td>11 (28%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Preoperative medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td>30 (79%)</td>
<td>29 (73%)</td>
<td>0.60</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>25 (66%)</td>
<td>30 (75%)</td>
<td>0.46</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>4 (11%)</td>
<td>4 (10%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Nitrates</td>
<td>13 (34%)</td>
<td>13 (33%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretics</td>
<td>15 (39%)</td>
<td>21 (53%)</td>
<td>0.27</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (8%)</td>
<td>2 (5%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0 ± 0.2</td>
<td>1.1 ± 0.2</td>
<td>0.17</td>
</tr>
<tr>
<td>MI history</td>
<td>13 (34%)</td>
<td>13 (33%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.61 ± 0.16</td>
<td>0.61 ± 0.15</td>
<td>0.84</td>
</tr>
<tr>
<td>Diseased coronaries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30 (79%)</td>
<td>35 (88%)</td>
<td>0.37</td>
</tr>
<tr>
<td>≥2</td>
<td>8 (21%)</td>
<td>5 (12%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Euroscore additive</td>
<td>3.5 ± 1.9</td>
<td>3.4 ± 2.1</td>
<td>0.70</td>
</tr>
<tr>
<td>Number of grafts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVG</td>
<td>3.1 ± 0.9</td>
<td>3.1 ± 0.9</td>
<td>0.88</td>
</tr>
<tr>
<td>LIMA-LAD</td>
<td>37 (97%)</td>
<td>39 (98%)</td>
<td>1.0</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>141 ± 38</td>
<td>138 ± 43</td>
<td>0.69</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>88 ± 24</td>
<td>89 ± 32</td>
<td>0.94</td>
</tr>
<tr>
<td>Lowest CPB temperature (°C)</td>
<td>31.5 ± 1.3</td>
<td>31.2 ± 2.3</td>
<td>0.49</td>
</tr>
</tbody>
</table>

*Preoperative and intraoperative characteristics were not different in patients with (MP group) or without (placebo group) methylprednisolone treatment. Data are mean ± standard deviation or n (%). ACE = angiotensin-converting enzyme; CPB = cardiopulmonary bypass; LIMA-LAD = left internal mammary artery to left descending artery bypass; LVEF = left ventricular ejection fraction; MI = myocardial infarction; SVG = saphenous vein grafts.
man correlation test. All data were analyzed with Statistica 6.1 (Statsoft GmbH, Hamburg, Germany), and p values of 0.05 or less were considered statistically significant.

Results

Two patients in the PLA group were excluded from the study after receiving aprotinin treatment for postoperative bleeding in the ICU. Demographic data and preoperative and intraoperative characteristics were not different between groups (Table 1).

Postoperative Hemodynamics

Hemodynamic variables were not different between both groups before CPB. Heart rate, mean arterial pressure, mean pulmonary arterial pressure, and central venous pressure increased during the postoperative period in both groups but did not reach significant intergroup differences (Table 2). Pulmonary capillary wedge pressure and pulmonary vascular resistance index remained unchanged compared with before CPB in both groups. In contrast, MP treatment increased cardiac index at 1 and 4 hours after CPB when compared with PLA (Fig 1A), and decreased systemic vascular resistance index at 1 and 4 hours after CPB compared with before CPB and PLA (p < 0.05). Whereas left ventricular stroke work index was decreased at 1 and 4 hours after CPB in PLA (p < 0.05 versus before CPB), it remained unchanged in MP and was increased at 1 and 4 hours after CPB compared with PLA. Improvement of cardiac index and decrease in systemic vascular resistance index in the MP group was independent of postoperative inotropic and vasopressor drug support. Catecholamine concentrations, number of patients treated, and duration of treatment with inotropic or vasopressor agents were not different between treatment groups.

Pulmonary Function and Biochemical Markers

Baseline pulmonary function indices, pulmonary shunt flow, oxygen delivery and extraction were similar in both groups (Table 3). Oxygenation index decreased in both groups in the first 4 hours after CPB, returning to pre-CPB values thereafter. A higher pulmonary shunt was observed at 1 hour and 4 hours in MP compared with PLA, suggesting less myocardial injury.

Blood glucose (Fig 1C) and lactate concentrations were elevated in both groups after surgery, but MP resulted in higher blood glucose concentrations at 1 and 4 hours, and increased lactate levels at 4 hours when compared with PLA. Consistent to this, MP-treated patients received

Table 2. Perioperative Hemodynamics and Catecholamine Support of Patients (n = 78) a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pre-CPB</th>
<th>1 h</th>
<th>4 h</th>
<th>10 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>PLA</td>
<td>69 ± 14</td>
<td>94 ± 15b</td>
<td>94 ± 17b</td>
<td>89 ± 14b</td>
<td>84 ± 16b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>65 ± 15</td>
<td>91 ± 14b</td>
<td>87 ± 12b</td>
<td>83 ± 11b</td>
<td>83 ± 13b</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>PLA</td>
<td>69 ± 9</td>
<td>71 ± 11</td>
<td>77 ± 11b</td>
<td>72 ± 11</td>
<td>77 ± 13b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>68 ± 10</td>
<td>71 ± 12</td>
<td>77 ± 13b</td>
<td>75 ± 12b</td>
<td>78 ± 11b</td>
</tr>
<tr>
<td>MPAP (mm Hg)</td>
<td>PLA</td>
<td>19 ± 6</td>
<td>20 ± 5</td>
<td>23 ± 6b</td>
<td>21 ± 5b</td>
<td>19 ± 6</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>20 ± 8</td>
<td>23 ± 9b</td>
<td>22 ± 7b</td>
<td>23 ± 6b</td>
<td>19 ± 5</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>PLA</td>
<td>9 ± 3</td>
<td>11 ± 4</td>
<td>11 ± 3b</td>
<td>10 ± 3</td>
<td>10 ± 4</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>9 ± 4</td>
<td>12 ± 3b</td>
<td>11 ± 3b</td>
<td>11 ± 4b</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>PLA</td>
<td>11 ± 3</td>
<td>12 ± 4</td>
<td>12 ± 3</td>
<td>11 ± 4</td>
<td>10 ± 3</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>12 ± 4</td>
<td>12 ± 4</td>
<td>11 ± 4</td>
<td>11 ± 4</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>SVRI (dyne · s · cm⁻³/m²)</td>
<td>PLA</td>
<td>1991 ± 514</td>
<td>1866 ± 614</td>
<td>2159 ± 644b</td>
<td>1881 ± 480</td>
<td>1996 ± 545</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>1867 ± 567</td>
<td>1511 ± 517bc</td>
<td>1716 ± 632c</td>
<td>1789 ± 495</td>
<td>1848 ± 450</td>
</tr>
<tr>
<td>PVRI (dyne · s · cm⁻³/m²)</td>
<td>PLA</td>
<td>312 ± 206</td>
<td>318 ± 187</td>
<td>366 ± 176</td>
<td>276 ± 115</td>
<td>304 ± 195</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>320 ± 186</td>
<td>297 ± 149</td>
<td>275 ± 138</td>
<td>306 ± 129</td>
<td>259 ± 142</td>
</tr>
<tr>
<td>LVSWI (g · m/m²)</td>
<td>PLA</td>
<td>32 ± 11</td>
<td>24 ± 6b</td>
<td>25 ± 7b</td>
<td>29 ± 7</td>
<td>32 ± 9</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>31 ± 8</td>
<td>29 ± 8</td>
<td>33 ± 9b</td>
<td>33 ± 8</td>
<td>33 ± 10</td>
</tr>
<tr>
<td>Epinephrine (µg/min)</td>
<td>PLA</td>
<td>0 ± 0</td>
<td>2.0 ± 1.8b</td>
<td>1.2 ± 1.7b</td>
<td>0.7 ± 1.4b</td>
<td>0.1 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>0 ± 0</td>
<td>2.2 ± 2.1b</td>
<td>1.3 ± 1.5b</td>
<td>0.9 ± 1.5b</td>
<td>0.5 ± 1.2</td>
</tr>
<tr>
<td>Norepinephrine (µg/min)</td>
<td>PLA</td>
<td>0 ± 0</td>
<td>0.7 ± 1.5b</td>
<td>1.3 ± 1.7b</td>
<td>1.2 ± 1.3b</td>
<td>0.5 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>0 ± 0</td>
<td>0.9 ± 1.1b</td>
<td>1.2 ± 1.9b</td>
<td>0.5 ± 1.3</td>
<td>0.6 ± 1.0</td>
</tr>
</tbody>
</table>

a Hemodynamic data and catecholamine support during the postoperative period of patients with (methylprednisolone [MP] group) or without (placebo [PLA] group) methylprednisolone treatment. Data are mean ± standard deviation. b p < 0.05 compared with pre-CPB. c p < 0.05 compared with PLA group.

CVP = central venous pressure; HR = heart rate; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; Pre-CPB = before cardiopulmonary bypass; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.
more insulin during the postoperative period than the PLA group \( (p < 0.05; \text{Table } 4) \). Acidity was present at 1 hour after CPB in both groups, with lower pH values in MP \( (p < 0.05) \).

**Inflammatory Markers**

Body temperature increased postoperatively in both groups and was higher after 4 hours after CPB in PLA compared with MP \( (\text{Fig } 1D) \). Furthermore, MP increased white blood cell counts and decreased C-reactive protein levels at 24 hours and 3 days after CPB compared with PLA \( (\text{Table } 3) \).

Baseline cytokine concentrations were similar in both groups. Postoperative TNFα concentrations remained unchanged in MP, but increased at 1 and 4 hours after CPB in PLA \( (\text{Fig } 2A) \) and were higher at 4 hours compared with MP. Postoperative IL-8 levels increased in both groups after CPB \( (\text{Fig } 2B) \). Compared with PLA, MP treatment attenuated IL-8 release at 1 and 4 hours.

Similarly, IL-6 concentrations were increased during the entire postoperative period in PLA and at 1 and 4 hours in MP compared with baseline \( (\text{Fig } 2C) \). Compared with PLA, IL-6 increase was attenuated in MP at 4 and 10 hours after surgery. In contrast, MP treatment accentuated the release of antiinflammatory IL-10, which was significantly higher in MP at 1 and 4 hours compared with PLA \( (\text{Fig } 2D) \). Ratio of phosphorylated IκB-α to total IκB-α in atrial biopsies was not different between groups before CPB \( (\text{Fig } 3A) \) and increased after CPB only in PLA. In MP, IκB-α ratio remained unchanged after CPB and was decreased compared with PLA. In contrast to this, MP had no effect on observed activation of p38 MAPK after CPB, resulting in similar increases of the phosphorylated p38 MAPK to total p38 MAPK ratio in both groups \( (\text{Fig } 3B) \).

In addition, comparable amounts of propofol \( (\text{MP, } 780 \pm 135 \text{ vs. PLA, } 551 \pm 82 \text{ mg}; p = 0.33) \), midazolam \( (\text{MP, } 0.9 \pm 0.4 \text{ vs. PLA, } 1.2 \pm 0.6 \text{ mg}; p = 0.85) \), and piritramide \( (\text{MP, } 5.5 \pm 0.8 \text{ vs. PLA, } 7.4 \pm 1.2 \text{ mg}; p = 0.28) \) for postoperative analgesia and sedation were given in the two groups. Total 24-hour fluid balance, variables of renal function, and new onset of atrial fibrillation were similar in both groups \( (\text{Table } 4) \). Furthermore, infections \( (\text{PLA, } 1 \text{ sternal wound, } 1 \text{ pneumonia}; \text{MP, } 1 \text{ sternal wound, } 2 \text{ pneumonia}) \), mechanical ventilation time, necessity for reintubation, and total length of stay in ICU and at hospital were not different between groups. One patient of the MP group died of multiorgan failure 3 days after CPB.

**Correlations**

Peak cytokine (IL-6 and IL-8) concentrations correlated positively to maximal postoperative body temperature \( (r = 0.45, 0.44, \text{respectively}; p < 0.001) \), troponin T \( (r = 0.39, 0.42, \text{respectively}; p < 0.001) \), and C-reactive protein \( (r = 0.32, 0.034, \text{respectively}; p < 0.01) \), and negatively with cardiac index \( (r = -0.26, -0.39, \text{respectively}; p < 0.05) \). In contrast to that, peak IL-10 correlated positively to cardiac index \( (r = 0.34; p = 0.002) \) and inversely to maximal postoperative body temperature \( (r = -0.38; p < 0.001) \), troponin T \( (r = -0.27; p < 0.015) \) and C-reactive protein \( (r = -0.43; p < 0.001) \) concentrations. No correlations were found between cytokines and postoperative clinical outcome of patients.

**Comment**

The present clinical study demonstrates that a single shot of methylprednisolone before CPB \( (1) \) attenuates release of systemic proinflammatory cytokines (TNFα, IL-6, and IL-8) and induces antiinflammatory cytokine release \( (IL-10) \), \( (2) \) inhibits myocardial inflammation by stabilization of NFκB inhibitory protein IκB-α, \( (3) \) reduces markers of myocardial injury and general inflammation, and \( (4) \) is associated with improved cardiac index, oxygen delivery, and oxygen extraction rate in the postoperative period after cardiac surgery. Adverse effects of glucocorticoid treatment included increases in pulmonary shunt flow and alterations in glucose metabolism with postoperative hyperglycemia, acidosis, and hyperlactatemia.
Table 3. Perioperative Variables and General Inflammation Markers of Patients (n = 78)∗

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pre-CPB</th>
<th>1 h</th>
<th>4 h</th>
<th>10 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao2/Fio2 (mm Hg)</td>
<td>PLA</td>
<td>391 ± 171</td>
<td>275 ± 114b</td>
<td>307 ± 114b</td>
<td>324 ± 146</td>
<td>415 ± 132</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>378 ± 172</td>
<td>305 ± 87b</td>
<td>306 ± 125b</td>
<td>368 ± 163</td>
<td>391 ± 158</td>
</tr>
<tr>
<td>AaDO2 (mm Hg)</td>
<td>PLA</td>
<td>368 ± 106</td>
<td>398 ± 94</td>
<td>475 ± 35b</td>
<td>523 ± 25b</td>
<td>532 ± 33b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>363 ± 112</td>
<td>368 ± 93</td>
<td>486 ± 42b</td>
<td>516 ± 30b</td>
<td>533 ± 31b</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>PLA</td>
<td>28 ± 9</td>
<td>33 ± 9a</td>
<td>27 ± 5</td>
<td>34 ± 7b</td>
<td>33 ± 6b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>30 ± 11</td>
<td>38 ± 10b</td>
<td>34 ± 8b</td>
<td>32 ± 5</td>
<td>34 ± 8b</td>
</tr>
<tr>
<td>ODI (mL·min⁻¹·m⁻²)</td>
<td>PLA</td>
<td>43 ± 8</td>
<td>33 ± 9a</td>
<td>35 ± 8a</td>
<td>38 ± 7b</td>
<td>38 ± 8b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>48 ± 13</td>
<td>42 ± 13c</td>
<td>44 ± 12a</td>
<td>40 ± 9b</td>
<td>41 ± 9b</td>
</tr>
<tr>
<td>OER (%)</td>
<td>PLA</td>
<td>20 ± 8</td>
<td>23 ± 7</td>
<td>34 ± 9b</td>
<td>31 ± 7b</td>
<td>34 ± 7b</td>
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<tr>
<td></td>
<td>MP</td>
<td>19 ± 7</td>
<td>18 ± 7b</td>
<td>28 ± 12bc</td>
<td>32 ± 6b</td>
<td>34 ± 10b</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>PLA</td>
<td>0.8 ± 0.3</td>
<td>1.9 ± 0.8b</td>
<td>2.5 ± 1.8b</td>
<td>3.1 ± 2.5b</td>
<td>1.9 ± 0.8b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>0.8 ± 0.3</td>
<td>3.0 ± 2.2b</td>
<td>5.6 ± 3.2bc</td>
<td>3.8 ± 2.2b</td>
<td>2.2 ± 1.1b</td>
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<tr>
<td>pH</td>
<td>PLA</td>
<td>7.39 ± 0.06</td>
<td>7.36 ± 0.05b</td>
<td>7.37 ± 0.06</td>
<td>7.40 ± 0.07</td>
<td>7.43 ± 0.04b</td>
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<tr>
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<td>MP</td>
<td>7.40 ± 0.04</td>
<td>7.32 ± 0.06bc</td>
<td>7.36 ± 0.07b</td>
<td>7.41 ± 0.05</td>
<td>7.44 ± 0.04b</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Pre-CPB</th>
<th>1 h</th>
<th>24 h</th>
<th>3 d</th>
<th>7 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (10³/μL)</td>
<td>PLA</td>
<td>7.6 ± 1.8</td>
<td>10.6 ± 3.7b</td>
<td>9.9 ± 2.2b</td>
<td>10.9 ± 2.7b</td>
<td>11.4 ± 3.4b</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>7.1 ± 1.6</td>
<td>10.8 ± 3.4b</td>
<td>13.4 ± 3.2bc</td>
<td>13.3 ± 3.0bc</td>
<td>12.2 ± 3.1b</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>PLA</td>
<td>9 ± 14</td>
<td>95 ± 30b</td>
<td>167 ± 70b</td>
<td>59 ± 40</td>
<td></td>
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<tr>
<td></td>
<td>MP</td>
<td>8 ± 15</td>
<td>62 ± 23bc</td>
<td>127 ± 47bc</td>
<td>54 ± 34</td>
<td></td>
</tr>
</tbody>
</table>

∗Perioperative pulmonary function variables, oxygen delivery index, oxygen extraction rate, general inflammation markers, pH and lactate levels of patients with (methylprednisolone [MP] group) or without (placebo [PLA] group) methylprednisolone treatment. Data are mean ± standard deviation. ∗∗p < 0.05 compared with pre-CPB. ∗∗∗p < 0.05 compared with PLA group.

AaDO2 = alveolar–arterial oxygen difference; CRP = C-reactive protein; Fio2 = fraction of inspired oxygen; ODI = oxygen delivery index; OER = oxygen extraction rate; PaO2 = arterial oxygen tension; Pre-CPB = before cardiopulmonary bypass; Qs/Qt = pulmonary shunt fraction; WBC = white blood cell count.

Comparable inhibition of the systemic release of proinflammatory cytokines such as TNFα, IL-6, and IL-8, augmentation of antiinflammatory IL-10 release, and decrease of C-reactive protein levels by glucocorticoid treatment after cardiac surgery has been reported in numerous studies [11–15]. Although this report did not investigate the exact inhibitory mechanisms of methylprednisolone on the CPB-related systemic cytokine generation, our results demonstrate a sustained systemic antiinflammatory effect of the 15-mg/kg dose used in this study. Elevated blood levels of TNFα, IL-6, and IL-8 are associated with postoperative hemodynamic instability, myocardial and pulmonary dysfunction, and major perioperative complications [2]. In agreement with other studies [14, 18], we report a catecholamine-independent improvement in postoperative systemic vascular resistance index and cardiac index, inversely related to proinflammatory and directly related to antiinflammatory cytokine levels. The favorable effect of glucocorticoid treatment on cardiac index is also mirrored by increased oxygen delivery and lower oxygen extraction rate, a finding that has also been confirmed by other clinical studies [14]. Moreover, the lower body temperature in the MP group during the postoperative course might have contributed to reduced oxygen consumption and has been related to decreased generation of proinflammatory cytokines [6].

Intraoperative myocardial damage is a major determinant of postoperative cardiac dysfunction, and troponin T is well documented to reflect myocardial damage and clinical outcome after adult and pediatric cardiac surgery [19, 20]. In the present study, methylprednisolone treatment was linked to decreased levels of troponin T,
suggesting reduced myocardial injury when compared with nontreated patients. The potential cardioprotective effects might be explained by the improved balance of systemic proinflammatory and antiinflammatory cytokine release, which is known to directly correlate with perioperative myocardial markers of injury [13, 15]. These findings are consistent with recent reports [13, 15] that documented a decreased cytokine-related postoperative myocardial injury in glucocorticoid-treated patients undergoing cardiac surgery, but in contrast to our results failed to show beneficial effects on postoperative myocardial performance.

Beyond inhibition of the systemic inflammation, the impact of glucocorticoid treatment on local myocardial inflammation after cardiac surgery and its sequelae has been investigated less extensively. Recent studies have demonstrated that intramyocardial activation of NFκB by degradation of IκB-α and induction of p38 MAPK occur after cardiac surgery [8, 9, 21]. This promotes the expression of proinflammatory cytokines such as IL-1β, TNFα, and IL-6, which in turn substantially contribute to postoperative myocardial depression and injury [7, 8, 16]. An important finding of our study is that a single dose of methylprednisolone before CPB was effective in preventing myocardial degradation of NFκB inhibitory protein IκB-α. Thus, the observed attenuation of myocardial injury and the improvement of postoperative myocardial function may be related not exclusively to the systemic but also intramyocardial antiinflammatory effects of methylprednisolone. In agreement with this, methylprednisolone treatment prevented myocardial inflammation and TNFα-associated myocardial contractile dysfunction in animals subjected to CPB with 1 hour of cardioplegic cardiac arrest [22]. In a piglet model of deep hypothermic circulatory arrest, methylprednisolone preserved postoperative myocardial function and reduced cardiac NFκB protein levels, while attenuating myocardial IL-6 and increasing antiinflammatory IL-10 expression [16].

Surprisingly, however, was the finding that glucocorticoid treatment had no effect on intramyocardial activation of p38 MAPK after CPB. Although the exact crosstalk between the glucocorticoid receptor, NFκB, and MAPK signaling pathway remains to be further elucidated [17, 23], it might be speculated that methylprednisolone failed to induce mitogen-activated protein kinase phosphatase-1, an inhibitor of p38 MAPK [17, 24]. Thus, more-specific therapeutic approaches toward inhibition of the p38 MAPK signaling pathway

Fig 2. Release of systemic proinflammatory tumor necrosis factor-α (TNFα; A), interleukin 8 (IL-8; B), and interleukin 6 (IL-6; C) after surgery was attenuated in methylprednisolone-treated subjects (MP group; O) compared with placebo (PLA group; ●). In contrast, systemic antiinflammatory interleukin 10 (IL-10; D) release was significantly induced with MP treatment; data are mean ± standard deviation (*p < 0.05 compared with pre-CPB; #p < 0.05 between treatment groups). (CPB = cardiopulmonary bypass.)

Fig 3. Phosphorylated to total protein ratios of inhibitory kappa-B alpha (IκB-α; A) and p38 mitogen-activated protein kinase (p38 MAPK; B) as measured in right atrial biopsies of the placebo (PLA group; black bars) and methylprednisolone group (MP group; white bars) before and after cardiopulmonary bypass (pre-CPB, post-CPB); data are mean ± standard deviation (*p < 0.05 compared with pre-CPB; #p < 0.05 between treatment groups).
might prove beneficial to further limit postoperative myocardial and vasomotor dysfunction [10]. Consistent with this, application of the serine protease inhibitor aprotinin has been reported to inhibit p38 activity after CPB, resulting in decreased myocardial endothelial dysfunction and tissue edema [24].

Pulmonary injury and impairment of lung function in states of systemic inflammatory response is well documented [1]. Glucocorticoids are known to decrease vascular resistance and capillary permeability of the lungs, thereby improving pulmonary functional variables in adults with acute respiratory distress syndrome [25]. Numerous well-designed studies demonstrate a beneficial effect of glucocorticoids on variables of pulmonary function [11, 14, 15], fluid balance [11, 14, 15], and decreased time on mechanical ventilation [14, 26] after cardiac surgery. Conversely, others report absent [12] or even detrimental effects on pulmonary function with decreased oxygenation indices [13], increased pulmonary shunt flow [18], and increased extravascular lung water and delayed extubation [13, 18]. In agreement with observations showing that steroids inhibit hypoxia-related changes of pulmonary vascular resistance [25], we demonstrate a significant increase of pulmonary shunt flow in methylprednisolone-treated subjects. These findings might have further been promoted by increased postoperative cardiac index at comparable amount of atelectasis formation in the study groups. No other detrimental glucocorticoid effects on postoperative pulmonary function or infections related to hyperglycemia [13, 14, 18, 26] and immunosuppression [12] could be demonstrated by the current and a larger randomized study [26]. However, hyperglycemia is associated with increased morbidity and mortality in critically ill patients [27] and has been found to be a strong predictor of organ injury in patients undergoing elective coronary artery bypass grafting [13]. Thus, the authors suggest that a tighter glucose control should be used for every patient receiving glucocorticoids during cardiac surgery to avoid postoperative hyperglycemia, as also indicated by the hyperlactatemia of the methylprednisolone group in this study.

We acknowledge the limitations of a randomized and controlled but not blinded study. However, the fact that most clinical decisions in the operating room and on the ICU (CPB, anesthetic, hemodynamic and respiratory management) are guided by standard algorithms may somehow attenuate the resulting bias. Moreover, it might be speculated that measurement of inflammatory markers in atrial tissue might not reflect ventricular changes. However, beyond ethical restrictions for ventricular tissue sampling, prior data on myocardial inflammatory markers have suggested a similar protein expression in atrial and ventricular biopsies after CPB [4].

Our study demonstrates that a single-shot treatment of MP before CPB effectively attenuates the release of systemic and myocardial inflammatory mediators after cardiac surgery. Inhibition of inflammatory mediators was associated with improved postoperative myocardial function and reduced myocardial injury, suggesting potential cardioprotective effects. Adverse effects of glucocorticoid treatment are mainly attributed to alterations in glucose metabolism and should be controlled by a tight glucose control regimen. Future studies, especially addressing high-risk patients, will have to show whether the beneficial hemodynamic and myocardial effects of glucocorticoid treatment will stand a critical risk-benefit evaluation.

References


DISCUSSION

DR FRANK W. SELLEKE (Boston, MA): Are you routinely now giving steroids, methylprednisolone?

DR LIAKOPOULOS: Yes, based on the results of the study the majority of the surgeons at our department are currently giving a single methylprednisolone bolus before cardiopulmonary bypass.

DR TURKI ALBACKER (Montreal, Quebec, Canada): I congratulate you on the nice work that you guys have done.

We have conducted a recent study about the effect of high dose insulin on the inflammatory markers post cardiopulmonary bypass. And as you showed here in the group in which you used methylprednisone, you used higher doses of insulin. Did you study the correlation between the insulin dose and inflammatory markers?

Question No. 2, you showed that patients who received methylprednisolone had higher glucose levels? And we know that hyperglycemia is detrimental in cardiac surgery patients, so how do you defend this point?

DR LIAKOPOULOS: Thank you very much for these good questions.

Regarding the first question, no, we did not look at the correlation between postoperative blood glucose levels or insulin therapy and inflammatory markers. But, since methylprednisolone was associated with hyperglycemia resulting in higher insulin therapy, I would suspect that statistically this would lead to an inverse relation to pro-inflammatory cytokine release. Thus, this might not be the perfect setting to investigate this question.

Regarding your second question, it is well known that hyperglycemia, especially in diabetic patients, is a predictor of postoperative morbidity and mortality. When we conducted this study several years ago we did not employ a strict perioperative glucose control protocol. Now, of course, our strategy at the intensive care unit has changed and we target much lower glucose levels, than the ones we showed here. However, neither our study nor any larger randomized trials using a single shot of glucocorticoids have shown that steroid related hyperglycemia contributes to an increased morbidity or mortality. However, the number of patients investigated in our study is certainly too small to reliably detect any differences in outcome.

DR EDWARD B. SAVAGE (St. Louis, MO): Those of us who have been around long enough remember that a gram of Solu-Medrol was given to try and prevent bad things happening from the bypass machine; so it’s interesting to see it come back again but in a different format.

What’s interesting is that you did see a discrete measurable response, but your markers of outcome really were not different. Part of the problem is that like so many studies done in our field, this was done on elective CABG patients, not on the patients who might actually benefit from this therapy more. For example, can you identify in advance patients who might be at risk for lung injury and treat them? So I would encourage you to take this concept and advance this more in these types of patients.

The second question is, how does this compare to the responses related to aprotinin?

DR LIAKOPOULOS: Thank you very much for the very good questions.

Indeed, we conducted this study intentionally enrolling low-risk patients to identify any beneficial or adverse effects of anti-inflammatory steroid pretreatment on cardiopulmonary function, and I believe that the low-risk profile of patients investigated in previous randomized trials is the main reason for the failure to show any beneficial effects on clinical outcome. Encouraged by the current results, we are planning to investigate in a next step whether higher risk patients (i.e preoperative LV-dysfunction or lung disease etc.) might benefit the most, in terms of better clinical outcome, from the cardioprotective and anti-inflammatory effects of steroids.

And sorry, I missed the second question.

DR SAVAGE: How do these results compare to the results shown for anti-inflammatory effects of aprotinin?

DR LIAKOPOULOS: That is a very good question. We intentionally avoided aprotinin use in our study. The reason for this was to exclude the known anti-inflammatory actions of aprotinin, which might affect the accurate interpretation of our glucocorticoid therapy. Interestingly, Dr. Selleke’s group recently published a paper showing that aprotinin has its own anti-inflammatory effects, especially on myocardial p38-MAPK activation. Thus, a combined approach using low-dose glucocorti-
coids with aprotinin might lead to additive perioperative myocardial anti-inflammatory effects by inhibiting both the p38-MAPK and NFkB signaling pathways.

DR SAVAGE: One last thing I did remember, I would just comment, that about 20 years ago a paper was published by a surgeon named Jonathan Bromberg about renal transplant patients where they compared stress steroids to maintenance steroids (5 to 10 mg of prednisone), and the stress patients had a significantly higher incidence of infections and mortality rates.

DR LIAKOPOULOS: Of course, hyperglycemia and immunosuppression due to glucocorticoids, which potentially might contribute to a higher infection rate and mortality, is always of concern. However, as I mentioned before, no randomized trials in this field have shown these adverse effects, even when using higher steroid doses than applied in our study. Thus, the current evidence suggests that a single, preoperative low-dose methylprednisolone bolus is well tolerated by the patient and considered to be safe.

DR MARC RUEL (Ottawa, Ontario, Canada): I have 2 questions regarding your study's design. First, why did you not blind the intervention? Second, what was the primary outcome of your study and what was your sample size calculation? The relevance of this latter point is that you have showed pathophysiological differences between the two groups with, however, a lack of difference in clinical outcome.

DR LIAKOPOULOS: Thank you very much for your excellent questions.

Initially, we planned a blinded study design. Unfortunately, this was not possible due to restrictions from our local ethic committee and we acknowledge the limitation and possible bias of a non-blinded trial.

Regarding your second question, our primary endpoint was cardiac function (i.e. cardiac index). Our power analysis revealed that, to detect a minimum cardiac index difference of 0.5 L/min/m² between groups, up to 25–30 patients had to be enrolled per group. However, as aforementioned, our group size is certainly large enough to show differences in hemodynamic and biochemical parameters, but underpowered to detect any differences in clinical outcome.

Notice From the American Board of Thoracic Surgery Regarding Trainees and Candidates for Certification Who Are Called to Military Service Related to the War on Terrorism

The Board appreciates the concern of those who have received emergency calls to military service. They may be assured that the Board will exercise the same sympathetic consideration as was given to candidates in recognition of their special contributions to their country during the Vietnam conflict and the Persian Gulf conflict with regard to applications, examinations, and interruption of training.

If you have any questions about how this might affect you, please call the Board office at (312) 202-5900.

Carolyn E. Reed, MD
Chair
The American Board of Thoracic Surgery