Dexamethasone decreases the pro- to anti-inflammatory cytokine ratio during cardiac surgery

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Background. Cytokines regulate inflammation associated with cardiopulmonary bypass (CPB). Pro-inflammatory cytokines may cause myocardial dysfunction and haemodynamic instability after CPB, but the release of anti-inflammatory cytokines is potentially protective. We studied the effects of dexamethasone on pro- and anti-inflammatory cytokine responses during coronary artery bypass grafting surgery.

Methods. Seventeen patients were studied: nine patients received dexamethasone 100 mg before induction of anaesthesia (group 1) and eight patients acted as controls (group 2). Plasma levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10 and IL-4 were measured perioperatively.

Results. TNF-α and IL-8 did not increase significantly in group 1 whereas they increased in group 2 to greater than preoperative values (P<0.05). IL-6 increased in both groups, with lower values in group 1 than in group 2 (P<0.05). IL-10 increased in both groups, with higher values in group 1 (P<0.05). IL-4 did not change in group 1 but decreased in group 2 compared with preinduction values (P<0.05). After surgery, patients in group 2 had tachycardia, hyperthermia, a greater respiratory rate and higher pulmonary artery pressure, and a longer stay in the intensive care unit.

Conclusion. Dexamethasone given before cardiac surgery changes circulating cytokines in an anti-inflammatory direction. Postoperative outcome may be improved by inhibition of the systemic inflammatory response.

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Cardiac surgery and cardiopulmonary bypass (CPB) activate a systemic inflammatory response characterized clinically by changes in cardiovascular and pulmonary function. Significant morbidity is rare, but most patients undergoing CPB show some degree of organ dysfunction from activation of the inflammatory response. This systemic inflammatory response after CPB is thought to result from contact of cellular and humoral blood components with the synthetic material of the extracorporeal circulation, leucocyte and endothelial activation, caused by ischaemia and reperfusion or endotoxins, and finally by operative trauma.1,2 Once started, the systemic inflammatory response is maintained by several factors, including cytokine production. The overproduction of the pro-inflammatory cytokines during CPB can harm the heart and other organs. For instance, they can significantly alter myocardial contractility,3,4 and may contribute to the development of multi-organ failure.5 The release of the anti-inflammatory cytokines during CPB may be protective by suppressing the production of pro-inflammatory cytokines.6,7 The bal-
challenge of these pro-inflammatory and anti-inflammatory reactions may affect the extent of the inflammatory response and the clinical outcome in certain diseases.

Corticosteroids have been recommended during cardiac surgery to prevent haemodynamic instability after CPB and to inhibit the leucocyte and tissue plasminogen activator activity generated after the release of the aortic cross clamp, and thus improve the postoperative course.10-11 However, the evidence of steroid effect on the balance between pro-inflammatory and anti-inflammatory cytokines during cardiac surgery is still very limited. We studied the effect of a single dose of dexamethasone given before anaesthesia on the balance between pro-inflammatory and anti-inflammatory cytokines during coronary artery bypass graft (CABG) surgery. We measured circulating concentrations of the pro-inflammatory cytokines tumour necrosis factor (TNF-α), interleukin (IL)-6 and IL-8 and the anti-inflammatory cytokines IL-10 and IL-4 in patients undergoing CABG with CPB, with and without dexamethasone pretreatment.

Patients and methods

Because of the cost of the assays, only 18 patients undergoing elective CABG surgery with CPB were randomized for this study. One patient in the control group was excluded from analysis because blood samples were incomplete. The study was approved by the hospital ethics committee and all patients gave their informed consent. We excluded patients with severely impaired left ventricular function (ejection fraction <40%), pulmonary disease, severe systemic non-cardiac disease, renal or liver impairment, insulin-dependent diabetes, recent myocardial infarction (<6 weeks), infectious disease before operation, and those receiving corticosteroid or other immunosuppressive treatment.

On the morning of the operation, patients were randomized to receive either dexamethasone 100 mg (group 1, n=9) or a placebo (group 2, n=9). This dosage was masked. Cardiac medication, including beta-adrenergic blocking agents, calcium-channel blocking agents and nitrates, was continued until the morning of surgery. All patients received lorazepam 40 μg kg⁻¹ orally on the night before the operation and morphine sulphate 70 μg kg⁻¹ i.m. and scopolamine 8 μg kg⁻¹ i.m. 1 h before operation. Anaesthesia was induced with sufentanil 2 μg kg⁻¹ and midazolam 0.15 mg kg⁻¹ and maintained with sufentanil 1.0 μg kg⁻¹ h⁻¹ and midazolam 0.12 mg kg⁻¹ h⁻¹. Tracheal intubation was facilitated with pancuronium bromide 0.1 mg kg⁻¹. A bolus dose of sufentanil 0.5 μg kg⁻¹ was given before skin incision. Patients were ventilated with oxygen/air (inspired oxygen fraction 0.5) with a tidal volume of 5–7.5 ml kg⁻¹, aiming at normocapnia.

The surgical procedure was median sternotomy and placement of internal mammary artery or saphenous vein grafts. Cardiopulmonary bypass was with a Cobe hollow-fibre membrane oxygenator. The circuit was primed with 1100 ml (500 ml gelofusine plus 500 ml Ringer’s solution plus 100 ml mannitol). The CPB flow was maintained at 2.4 litre min⁻¹ m⁻², and mild hypothermia of 32°C was accomplished. Cold cardioplegic solution was given after cross-clamping for myocardial protection (800–1000 ml initially and 200–300 ml after every 30 min through the aortic root and 100 ml after each distal anastomosis through the vein graft). Blood was sampled for measurement of TNF-α, IL-6, IL-8, IL-10 and IL-4 at the following times: before induction of anaesthesia (T0), after induction of anaesthesia and before skin incision (T1), before starting cardiopulmonary bypass (T2), after aortic declamping (T3), at the end of CPB (T4), 2 h after skin closure (T5), and 24 h after skin closure (T6). Samples were collected in tubes containing lithium heparin (Venoject®, Terumo, Europe NV, Leuven, Belgium). The samples were immediately centrifuged at 1000 g, and the plasma was stored at −70°C until assays were performed. Enzyme-linked immunosorbent assays (ELISA; Immulite®, DPC, Los Angeles, USA) were used to measure TNF-α, IL-6, IL-8, IL-10 and IL-4. All assays were performed according to the manufacturer’s instructions.

After completion of surgery, patients were transferred to the ICU, where standard care and processes were followed until discharge. The physicians and nurses in the ICU did not know which patients had received dexamethasone. Patients were weaned from mechanical ventilation when they were haemodynamically stable, responded to verbal stimulation, were completely rewarmed and when blood loss did not exceed 100 ml h⁻¹. Postoperative pain management was with piritramide 5–10 mg i.v., given as necessary. Cardiovascular and respiratory values and temperature were recorded every 15 min before extubation and then hourly until discharge from the ICU. Length of stay in the ICU was also recorded. Patients were discharged from the ICU on the first morning that they were haemodynamically stable, had normal blood gases during spontaneous breathing and had satisfactory renal function. We reviewed each patient’s records after discharge from the ICU and noted the minimum and maximum values of mean arterial pressure, heart rate, cardiac index, mean pulmonary artery pressure, respiratory rate, and temperature.

Statistical analysis

Calculations were performed on a personal computer using SPSS version 10.0. Data are presented as mean (sd) and cytokine concentrations as median (interquartile range). The groups were tested for differences using Student’s t-test for continuous variables and Fisher’s exact test for categorical variables. The Mann–Whitney U test was used to compare cytokine levels between the two groups at each time point.
Repeated measures analysis of variance together with Bonferroni adjustment was used for multiple within-group comparisons. In all cases a \( P \) value less than 0.05 was considered to indicate statistical significance.

**Results**

The two groups appeared similar in physical and preoperative clinical characteristics (Table 1). The intraoperative course was uneventful and intraoperative characteristics were comparable (Table 2). At all measurement times, serum TNF-\( \alpha \) (Fig. 1) and IL-8 (Fig. 2) concentrations did not increase significantly above the pre-induction value in group 1 but in group 2 both cytokines increased at T3, T4 and T5 compared with pre-induction concentrations (\( P < 0.05 \)). TNF-\( \alpha \) was significantly lower in group 1 than in group 2 at T4 (median [interquartile range] 8 [0–9] vs 80 (11–335) pg ml\(^{-1} \); \( P < 0.05 \)) and T5 (9 [6–13] vs 57 [27–209] pg ml\(^{-1} \); \( P < 0.05 \)). Concentrations of IL-8 were lower in group 1 than in group 2 at T3 (0.5 [1.5] vs 1.5 [3.0]) and T4 (58 [6] vs 61 [15]). Concentrations of IL-6 (Fig. 3) increased in both groups above the pre-induction values starting from T3 and peaked at T5 (\( P < 0.05 \)) but the concentrations were significantly lower in group 1 than in group 2 at T4 (14 [10–33] vs 99 [35–229] pg ml\(^{-1} \); \( P < 0.05 \)) and T5 (108 [60–209] vs 1000 [354–1000] pg ml\(^{-1} \); \( P < 0.05 \)) and T6 (31 [19–45] vs 90 [48–147] pg ml\(^{-1} \); \( P < 0.05 \)). Serum concentrations of IL-4 (Fig. 5) did not change significantly in group 1 whereas they decreased in group 2 compared with the pre-induction concentrations from T1 to
T5 ($P<0.05$). The ratio of IL-10 to TNF-$\alpha$ was greater in group 1 than in group 2 at T2 ($3 \pm 1$ vs $1 \pm 1$; $P<0.05$), T3 ($28 \pm 21$ vs $4 \pm 4$; $P<0.01$), T4 ($33 \pm 15$ vs $3 \pm 5$; $P<0.01$) and T5 ($2 \pm 2$ vs $12 \pm 5$; $P<0.01$). The follow-up of patients is shown in Table 3. The maximum heart rate and respiratory rate and the maximum and minimum temperatures were significantly greater in group 2 than in group 1. The length of stay in the ICU was significantly shorter in group 1 than in group 2 (Fig. 6). The maximum arterial pressure and cardiac index seemed less in group 2. There were no major complications or mortality.

**Discussion**

Our data show that dexamethasone shifts the circulating cytokine balance towards the anti-inflammatory direction. Dexamethasone abolished the TNF-$\alpha$ and IL-8 responses, reduced the IL-6 response, and exaggerated the IL-10 response. TNF-$\alpha$ is an important mediator involved in the pathogenesis of myocardial ischaemia-reperfusion injury.\(^{12}\) TNF-$\alpha$ reduces myocardial contractility and ejection fraction, and causes hypotension, decreased systemic vascular resistance and biventricular dilatation.\(^{13, 14}\) These effects can explain the lower cardiac index in the control group in our study, although this was not statistically significant.

IL-8 affects ischaemia-reperfusion injury through an effect on neutrophil activation and adherence to the vascular endothelium.\(^{15}\) Treatment with anti-IL-8 antibodies prevents lung ischaemia-reperfusion injury in rabbits.\(^{16}\) This could explain the higher mean pulmonary artery pressure we noticed in the control group, who had high IL-6 concentrations.

Our results confirm those of others\(^{10, 11}\) that corticosteroid administration inhibits but does not abolish the IL-6 response. This is because the production of IL-6 is affected by the degree of surgical trauma and tissue damage, as well as the effect of CPB.\(^{15}\) Hennein and colleagues suggested that IL-6 may be a sensitive indicator of myocardial damage, and reported an association between the IL-6 response and cardiac morbidity.\(^{3}\) Cruickshanks and colleagues reported that high concentrations of IL-6 had a negative inotropic effect, possibly by impairing entry of calcium into myocardial cells.\(^{16}\)

IL-10 has been described as a cytokine synthesis inhibitory factor, and the most potent inhibitor of IL-8.\(^{17}\) This may explain the abolished TNF-$\alpha$ and IL-8 response and the weak IL-6 response in the dexamethasone-treated group, in whom the IL-10 response was greater.

IL-4 inhibits the differentiation and action of Th 1 cytokines. It can antagonize these inflammatory responses,
which can cause excessive tissue destruction.\textsuperscript{18} In our study IL-4 decreased in the control group before skin incision. Thereafter, the pro-inflammatory cytokines increased after aortic declamping. Thus, low concentrations of IL-4 may be another reason for the greater pro-inflammatory cytokine response in this group.

The effect of steroids on the cytokine balance during cardiac surgery has been previously studied by Kawamura and colleagues.\textsuperscript{19} They gave methylprednisolone 30 mg kg\textsuperscript{–1} before CPB and declamping, and investigated IL-6, IL-8, IL-10 and IL1ra, whereas we investigated TNF-\(\alpha\), IL-6, IL-8, IL-4 and IL-10. In their patients, methylprednisolone did not abolish the IL-8 response as the dexamethasone did in our patients, but the response was inhibited. They found a balanced pro-inflammatory and anti-inflammatory response. In our study, the balance was shifted towards the anti-inflammatory responses. These differences may be the result of the different times of steroid injection or the different doses of steroid. The finding that the pre-induction dose of dexamethasone in our patients was associated with unbalanced cytokine response may be relevant, because wound healing and resistance to infection may depend on this balance. A perioperative pro-inflammatory cytokine response, held in balance by a concomitant anti-inflammatory response could be important.\textsuperscript{20}

The mechanisms involved are far from clear. In non-cardiac-surgery patients, immunosupression has often been associated with exaggerated production of IL-10 and a high ratio of IL-10 to TNF-\(\alpha\).\textsuperscript{21,22} Although the dexamethasone group in our study had a high ratio of IL-10 to TNF-\(\alpha\), no patients had adverse events such as infectious complications or sepsis in the postoperative period. These patients were discharged earlier than those in the control group, which could suggest reduced morbidity in the dexamethasone group.

<table>
<thead>
<tr>
<th>Table 3 Postoperative characteristics of patient groups. Data are mean (SD); * statistically significant difference between the groups</th>
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<tbody>
<tr>
<td>Group 1</td>
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<tr>
<td>((n=9))</td>
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<tr>
<td>Minimum mean arterial pressure (mm Hg)</td>
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<tr>
<td>Maximum mean arterial pressure (mm Hg)</td>
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<tr>
<td>Minimum heart rate (beats min\textsuperscript{–1})</td>
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<tr>
<td>Maximum heart rate (beats min\textsuperscript{–1})*</td>
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<tr>
<td>Minimum cardiac index</td>
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<td>Maximum cardiac index</td>
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<tr>
<td>Minimum mean pulmonary artery pressure (mm Hg)*</td>
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<td>Maximum mean pulmonary artery pressure (mm Hg)</td>
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<td>Minimum respiratory rate (bpm)</td>
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<tr>
<td>Maximum temperature (°C)*</td>
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<tr>
<td>Time to tracheal extubation (h)</td>
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<tr>
<td>Length of stay in ICU (h)*</td>
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<td>Need for inotropic support (number of patients)</td>
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</table>

In our study the clinical effects of dexamethasone in the postoperative period were shown by normothermia, lower heart rate and lower respiratory rate, which may indicate a smaller systemic inflammatory response.

Inhibition of TNF-\(\alpha\) and IL-6 by dexamethasone might explain the greater cardiac index and arterial blood pressure in group 1. Reduced temperature in the immediate postoperative period can be advantageous in cardiac surgery patients, because oxygen consumption is directly related to temperature.\textsuperscript{23} However, Chaney and colleagues showed that methylprednisolone had no clinical benefits in patients undergoing elective CABG and possibly hindered early postoperative tracheal extubation.\textsuperscript{24} This contrasts with our finding that the dexamethasone-treated patients were extubated earlier than the control patients (albeit statistically insignificant).

The small size of our study is not sufficient to assess clinical outcomes. The main purpose of the present study was to investigate the effect of steroid on the cytokine balance. Our results can only partly confirm the improvements of clinical outcome found in previous investigations,\textsuperscript{8,19,25,26} which may explain the shorter stay in the ICU in our study and in that of Jansen and colleagues.\textsuperscript{8} We conclude that dexamethasone before cardiac surgery shifts the circulating cytokine profile towards the anti-inflammatory responses and may improve the postoperative course by inhibition of the systemic inflammatory response. Future studies should consider the correlation between circulating cytokines and clinical course.

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