

Effect of Dexamethasone on Atrial Fibrillation After Cardiac Surgery: Prospective, Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: The purpose of this study was to assess the effect of preoperative dexamethasone (DEX) on the occurrence of postoperative atrial fibrillation (AF).

Design: Prospective, randomized, double-blind, placebo-controlled clinical trial.

Setting: Tertiary referral center.

Participants: Seventy-eight adult patients undergoing combined valve and coronary artery bypass graft (CABG) surgery were randomized to receive either DEX or placebo.

Interventions: The DEX group received dexamethasone, 0.6 mg/kg, after induction of anesthesia, and the placebo group received an equal volume of normal saline. Interleukin (IL)-6, -8, and -10; tumor necrosis factor α ; and endothelin (ET)-1 were measured preoperatively and on postoperative days (POD) 1, 2, and 3. Complement (C-4) and C-reactive protein (CRP) were measured preoperatively and on POD 2. Exhaled nitric oxide (NO) was measured preoperatively, 15 minutes after aortic unclamping, and 1 hour after intensive care unit admission.

Measurements and Main Results: No significant difference

in the incidence of AF was found between the placebo (41%) and DEX groups (30%) (95% confidence interval [-11%, 34%]; $p = 0.31$). DEX significantly reduced at least 1 postoperative level of IL-6, IL-8, IL-10, CRP, and exhaled NO. DEX did not affect ET-1 or C-4 levels. IL-10 on POD 3 was positively correlated with postoperative hospital length of stay ($r = 0.30$, $p = 0.01$). Increased levels of IL-8 and IL-10 on POD 1 were positively correlated with the intubation time ($r = 0.31$, $p = 0.01$; $r = 0.30$, $p = 0.01$, respectively). Conversely, C-4 on POD 2 was negatively correlated with the intubation time and intensive care unit length of stay ($r = -0.32$, $p = 0.006$; $r = -0.30$, $p = 0.01$, respectively).

Conclusions: DEX did not affect the incidence of AF in patients undergoing combined CABG and valve surgery. However, it did modulate the release of several inflammatory and acute-phase response mediators that are associated with adverse outcomes.

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KEY WORDS: dexamethasone, atrial fibrillation, cardiopulmonary bypass, cytokines

AN ESTIMATED 400,000 adults in the United States undergo coronary artery bypass graft (CABG) surgery annually.¹ Atrial fibrillation (AF) develops in up to 41.6% of patients after CABG surgery² and in over 60% of patients after combined CABG and valve surgery.³ AF after CABG remains a major problem that is likely to increase in frequency because the typical patient undergoing CABG surgery today is older and has more left ventricular dysfunction than the typical patient decades ago.⁴

With physicians and hospitals facing increasing pressure to control costs, the future of therapy for this condition lies in prophylaxis. The cumulative cost of AF care will exceed that of any other complication. Any reduction in its occurrence may result in enormous savings. Hravnak and colleagues⁵ found that the economic impact of AF after CABG surgery was underestimated in most previous reports. However, a recent report by Connolly et al⁶ found that AF did not increase total costs. Further understanding of the pathophysiology of AF at the

cellular and the molecular levels may provide more specific targets for prevention and treatment.⁷

Cardiopulmonary bypass (CPB) triggers an inflammatory response and release of several mediators that may affect outcome after cardiac surgery.⁸ Inflammatory markers including C-reactive protein (CRP), endothelin-1 (ET-1), complement, and interleukin (IL)-6 have been associated with an increased incidence of AF.⁹⁻¹² The effect of CPB on the inflammatory system may stem from circulatory and metabolic derangement and myocardial injury,¹³⁻¹⁵ and this derangement may play a role in the pathogenesis of postoperative AF.¹¹ IL-6 and tumor necrosis factor α (TNF- α) may contribute to myocardial dysfunction and hemodynamic instability after CPB.^{16,17} Indeed, the myocardium is the major source of IL-8 during reperfusion after an extended period of ischemia or after acute myocardial infarction.¹⁸ Anti-inflammatory cytokines such as IL-10 are released during CPB and may play a protective role by suppressing the production of proinflammatory cytokines.^{18,19} Cytokines and chemokines as well as exhaled nitric oxide (NO) have been used as markers of inflammation and may indicate the effectiveness of anti-inflammatory therapy.²⁰⁻²²

The authors previously reported as an incidental finding that dexamethasone (DEX) reduced the incidence of new-onset AF from 52.6% to 18.2% after combined CABG and valve surgery.²³ This finding served as a hypothesis generator, and the present study was designed so that the dose and timing of DEX would be similar to the ones used in the original study. The previous study was designed to assess the effect of DEX on postoperative shivering, but AF was not looked at prospectively (post hoc analysis). The present study was designed to verify whether this incidental finding could be confirmed prospectively. The objective of this study was to evaluate the ability of

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preoperative administration of DEX to modulate perioperative cytokines (IL-6, 8, and 10, TNF- α) and acute-phase markers (CRP, C-4) in such a way that the occurrence of postoperative AF is reduced.

MATERIALS AND METHODS

The institutional review board of the Cleveland Clinic Foundation approved the study. Informed consent was obtained from all participants. Between October 2000 and July 2001, 78 patients age 20 years or older scheduled for elective, combined coronary and valvular heart surgery were randomized to receive either DEX or placebo. A computer-generated random table was used. Patients were excluded if they had a history of AF or if they were receiving amiodarone or corticosteroid therapy. Seven patients who were initially enrolled in the study were excluded from analysis because there was a change in the surgical plan (5 patients) or they received aprotinin (1 patient) or additional corticosteroids (1 patient). Of the remaining 71 patients, 37 were randomly assigned to receive DEX, 0.6 mg/kg (group DEX), and 34 to receive an equal volume of placebo (group PL). Both DEX and the placebo were administered immediately after induction of anesthesia. All patients received routine premedication, monitoring, and anesthetic management. Blood cardioplegia was used, and CPB was performed under normothermia or mild hypothermia followed by rewarming to bladder temperature of 37°C before separation from CPB.

The Cardiothoracic Anesthesia Registry provided demographic and clinical information, including the department's Preoperative Severity Score of Illness for extended CABG patients and the incidence of hospital mortality and major morbidities.²⁴ Major morbidities include pulmonary morbidity (intubation time >72 hours), renal morbidity (need for hemodialysis), cardiac morbidity (postoperative myocardial infarction, cardiac index ≤ 2.0 L/min/m², need for mechanical assist device), neurologic morbidity (focal or global neurologic deficit), and infection morbidity (sepsis, pneumonia, wound infection, or mediastinitis). AF was defined as AF requiring treatment. Brief isolated non-sustained episodes of AF were excluded. In the cardiovascular ICU (CVICU), automated detection of AF was obtained from the bedside arrhythmia monitor Solar 9500 (GE Medical Systems, Milwaukee, WI). The diagnosis was confirmed by the CVICU physician who also initiated treatment as appropriate. In the stepdown units, detection of AF was obtained by continuous electrocardiogram telemetry monitoring (Eagle 4000; GE/Marquette Medical Systems, Milwaukee, WI). The diagnosis was confirmed by a cardiologist and/or a house staff before initiation of therapy.

Because the majority of postoperative AF occurs in the first 3 days after cardiac surgery,² cytokines and acute-phase markers were measured during that time. Four blood samples were collected for every patient as follows: the first sample (7 mL) (baseline) before induction of anesthesia, the second sample (3 mL) on postoperative day 1 (POD 1), the third sample (7 mL) on POD 2, and the fourth sample (3 mL) on POD 3. The first blood sample was drawn from the arterial catheter just before induction of anesthesia. The second, third, and fourth samples were drawn from an upper extremity by direct venipuncture with the morning laboratory work at 9 AM. For the first and third samples (7 mL each), 4 mL was placed into 2 SST yellow-top siliconized vacuum tubes (2 mL in each) (Becton Dickinson, Franklin Lakes, NJ) and were sent directly for immediate analysis of CRP and complement (C4). The remaining 3 mL of blood (of the first and third samples) and the second and fourth samples (3 mL each) were put in a heparin-coated green-top tube and were immediately taken and put in a Beckman CPR Centrifuge (Beckman Coulter Inc, Fullerton, CA) at 4°C and spun at 2000 rpm for 15 minutes. The clear supernatant was transferred to a 1.5-mL Eppendorf tube and stored at -80°C until the end of the study when IL-6, IL-8, IL-10, TNF- α , and ET-1 were assayed for all samples in 1 setting.

Frozen plasma samples were thawed and analyzed. Plasma concentrations of IL-6, IL-8, IL-10, and TNF- α were measured using cytokine-specific enzyme-linked immunosorbent assays (Endogen Inc, Woburn, MN). Plasma concentrations of ET-1 were measured by using a commercial enzyme linked immunoassay kit (Biomedica, BI-20052, Vienna, Austria) per the manufacturer's instructions. Concentrations exceeding 10 fmol/mL were diluted with assay buffer and reassayed with a compatible standard curve. Intra-assay coefficient of variation was ~5%, and the interassay variability was 12%. All samples were measured in parallel and in duplicate to avoid interassay variance. The CRP assay was performed by using a Roche/Hitachi Modular System (Hitachi Ltd, Mito, Japan). The lower detection limit is 0.3 mg/dL. The serum concentration of C-4 was measured by the Nephelometry/Beckman IMMAGE Immunochemistry System (Beckman Coulter Inc). After calibration, the peak rate signal for a particular assay is automatically converted to concentration units by the analyzer (Brea, CA). The lower limit of detection is 2 mg/dL with a range between 1.67 and 4,680 mg/dL.

NO was collected at 3 different times, and, for each time, 2 duplicate samples were obtained. The first sample was taken as a baseline from the patient before they entered the operating room. The exhaled gases were collected in Mylar bags (Physiologic Measurement Systems, Bay Village, OH) using an inspiratory breath-hold maneuver. The patients were seated and instructed to inhale to total lung capacity and then exhale against 10 cmH₂O pressure into a Mylar collection bag. The second sample was obtained 15 minutes after the aorta was unclamped while the patient was on CPB. One liter of air was introduced into each patient's lungs via a syringe directly attached to the endotracheal tube. The passively exhaled gas was collected in a Mylar bag. The third sample was taken 1 hour after intensive care unit (ICU) admission. Two tidal breaths of exhaled gas were collected from the expiratory port of the ventilator, either a Servo 300 ventilator (Siemens Elema, Sweden) or a Puritan Bennett 7200 ventilator (Puritan-Bennett Co, Carlsbad, CA). Exhaled NO gas levels were measured immediately in the pulmonary department using a chemiluminescence analyzer (Sievers Instruments, Boulder, CO) sensitive to 1 ppb of NO.²⁵ Because of technical difficulties, the authors were only able to collect at least 1 measure of exhaled NO for 41 patients.

A sample size of 78 was chosen to give 90% power at the 0.05 significance level to detect a difference of 35% or more between groups in the incidence of AF, assuming that the true percent in the lower group was 18% for patients undergoing combined CABG and valve surgery.²³ Logistic regression, adjusting for preoperative severity score, was used to assess the relationship between AF and the baseline value concentration of inflammatory mediators as well as the change from baseline. Wilcoxon rank-sum tests or Student *t* tests were used to compare groups on continuous variables and Pearson chi-square or exact unconditional tests for categorical variables, as appropriate. Median (quartiles) or mean (standard deviation [SD]) were used to describe continuous variables. A 95% confidence interval (CI) using the exact binomial method was used for categorical variables. Spearman correlation coefficients (*r*) and corresponding a 95% CI were used to assess the relationship between the following continuous variables: (1) baseline inflammatory mediators and the preoperative severity score of illness for extended CABG surgery patients and (2) baseline and change from baseline inflammatory mediators with ICU intubation time, total ICU, and postoperative hospital length of stay (LOS), adjusting for the preoperative severity score. Treatment groups were also compared on time to AF using Kaplan-Meier analysis.

Multivariable models were fit to assess the association between baseline inflammatory mediators and their interaction with treatment on the outcomes of AF, initial ICU intubation time, postoperative hospital LOS, and total ICU LOS. Variables with a univariable significance of *p* < 0.15 were considered. A logistic regression was used for AF, and

Table 1. Demographics, Preoperative Severity Score of Illness, and Surgical Data

Variable	Placebo (n = 34) Median (Q1, Q3)	Dexamethasone (n = 37) Median (Q1, Q3)	p Value†
Age (y)	74.2 (64, 79)	69.2 (62, 78)	NA
Sex			NA
Males/Females (n [%])	(25/9) (73.5/26.5)	(31/6) (83.8/16.2)	
Preoperative Weight (kg)	79.0 (70, 89)	78.0 (69, 86)	NA
Department Preoperative Severity Score of Illness*	4.0 (3, 6)	3.0 (3, 5)	NA
Type of surgery			NA
CABG and AV (n [%])	24 (70.6)	23 (62.2)	
CABG and MV (n [%])	5 (14.7)	12 (32.4)	
CABG, AV, and MV (n [%])	5 (14.7)	2 (5.4)	
Cardiopulmonary bypass time (min)	111 (94, 136)	116 (96, 132)	0.77
Cross-clamp time (min)	86 (66, 97)	98 (81, 108)	0.08
Lowest cardiopulmonary bypass Temperature (°C)	35 (34, 36)	35 (34, 36)	0.64

Abbreviations: NA, statistical comparisons not meaningful on baseline variables in randomized study; AV, aortic valve; MV, mitral valve.

*Assigned to predict patient outcome after CABG surgery (highest possible score is 33).

†Wilcoxon rank-sum test, unless noted.

linear regression was used for the other 3 outcomes, adjusting for treatment in each model and other variables when $p < 0.05$. The continuous outcomes were log transformed to better meet model assumptions. The overall significance level was 0.05 for all hypotheses, and Bonferroni correction was used for multiple comparisons. Analysis was performed with SAS 8.2 (SAS Institute Inc, Cary, NC), and graphics were produced with S-PLUS 6.0 (Insightful Corp, Seattle, WA).

RESULTS

The 2 study groups were predominantly male (74% in PL group and 84% in DEX group) and were comparable on demographic and surgical characteristics (Table 1) and in the uses of preoperative statins, nonsteroidal antiinflammatory drugs, or digoxin. Similarly, no significant differences were found in the perioperative hemodynamics or fluid balance on POD 1 (Table 2). No differences were found between the groups in regards to

intubation time, ICU and postoperative hospital LOS, major morbidity, and mortality (Tables 2 and 3). One DEX patient with a history of chemotherapy and radiotherapy for Hodgkin's lymphoma developed acute respiratory distress syndrome on POD 2 and died 5 days later.

No significant difference was detected in the incidence of postoperative AF between the PL and DEX groups (41% v 30%, respectively; difference [95% CI] = 11.5% [−11%, 34%], $p = 0.31$). Comparing groups on the time to AF using Kaplan-Meier analysis was also nonsignificant (log-rank p value = 0.36). Similarly, intention-to-treat analysis showed no significant difference between the 2 groups in the incidence of postoperative AF (39% v 31%, $p = 0.42$) in placebo and DEX groups, respectively. Patients with or without AF did not differ significantly in preoperative (60% v 45.7%, $p = 0.25$, respectively) or postoperative (69.6% v 62.2%, $p = 0.56$, respec-

Table 2. Perioperative Hemodynamics and Postoperative Outcomes

Variable	Placebo (n = 34) Mean ± SD or Median (Q1, Q3)	Dexamethasone (n = 37) Mean ± SD or Median (Q1, Q3)	p Value*
Heart rate on postoperative day 1 (beats/min)	90 (78, 96)	87 (76, 90)	0.51
Cardiac index (L/min/m ²)			
Baseline	2.4 (2.2, 2.6)	2.4 (2.1, 2.7)	NA
After cardiopulmonary bypass	2.8 (2.3, 3.3)	2.8 (2.4, 3.1)	0.69
4 h after ICU admission	2.8 ± 0.5	2.9 ± 0.6	0.54†
Net fluid gain (mL)	1277 ± 2558	1356 ± 1739	0.88†
Intubation time (h)	8.3 (4.8, 13)	6.4 (4.3, 13)	0.21
ICU LOS (h)	29 (24, 52)	34 (25, 77)	0.33
Postoperative Hospital LOS (d)	8 (6, 10)	6 (5, 10)	0.09
Highest body temperature			
Day of surgery	37.7 ± 0.4	37.3 ± 0.5	<0.001†‡
Postoperative day 1	37.7 (37, 38)	37.5 (37, 38)	0.27
Postoperative day 2	37.3 (37, 38)	37.4 (37, 38)	0.99
Postoperative day 3	37.2 ± 0.5	37.2 ± 0.5	0.89†

Abbreviation: NA; statistical comparisons not meaningful on baseline variables in randomized study.

*Wilcoxon rank-sum test, unless noted.

†Student t test.

‡Significant ($p < 0.05$).

Table 3. Major Morbidities and Mortalities*

Variable	Placebo (n = 34) % Yes (95% CI)	Dexamethasone (n = 37) % Yes (95% CI)	p Value†
Atrial fibrillation (during first 3 postoperative days)	41 (25, 59)	30 (16, 47)	0.31‡
Hospital mortality	0 (0, 10)	2.7 (0.1, 14)	>0.99
Pulmonary morbidity	5.9 (0.7, 20)	2.7 (0.1, 14)	0.55
Renal morbidity	0 (0, 10)	0 (0, 9.5)	>0.99
Cardiac morbidity	0 (0, 10)	2.7 (0.1, 14)	>0.99
Neurologic morbidity	5.9 (0.7, 20)	0 (0, 9.5)	0.16
Infection morbidity	0 (0, 10)	0 (0, 9.5)	>0.99

*See text for explanation.

†Exact unconditional test, unless noted.

‡Pearson chi-square test.

tively) use of β -blockers. Only those patients who developed postoperative AF received treatment with amiodarone. There were no significant relationship between baseline or postoperative levels of inflammatory mediators and the incidence of postoperative AF.

Peak body temperature was significantly lower in the DEX group on the day of surgery (Table 2). Blood glucose levels were significantly higher on ICU admission in the DEX group than in the PL group (195 ± 50 v 165 ± 53 mg/100 mL, $p = 0.02$, respectively). As a result, insulin use was higher in the DEX group than in the PL group (65% v 38%, $p = 0.02$, respectively). In the CVICU, the target range for blood glucose (75-150 mg/dL) was the same for all patients as per standard insulin titration protocol.

Both groups were comparable on baseline values for the inflammatory mediators (Table 4). The postoperative changes from baseline in cytokines and chemokines are shown in Figures 1 and 2. With the exception of ET-1 in the DEX group on POD 2, postoperative levels of IL-6, IL-8, IL-10, and ET-1 as well as CRP and C-4 increased significantly from baseline within both PL and DEX groups. Exhaled NO level 1 hour after ICU admission as well as TNF- α on POD 1 were significantly lower than baseline in the DEX group. Postoperative changes from baseline were significantly higher in PL versus DEX for IL-6, IL-8, and IL-10, CRP, and exhaled NO. However, there were no differences between both groups for TNF- α , ET-1, or C-4 (Figs 1 and 2). CRP was the only baseline inflammatory mediator that was found to be significantly correlated with the preoperative severity score (r [95% CI] = 0.30 [0.07, 0.53]) (Fig 3).

Increased levels of IL-8 and IL-10 on POD 1 were positively

correlated with the intubation time (r [95% CI] = 0.31 [0.08, 0.54]) and (r [95% CI] = 0.30 [0.07, 0.53]), respectively. Conversely, the intubation time was inversely correlated with the POD 2 change from baseline of C-4 ($r = -0.32$ [-0.55, -0.09]). Postoperative hospital LOS was significantly correlated with IL-10 levels on POD 3 compared with baseline ($r = 0.30$ [0.07, 0.53]). Total ICU LOS was inversely correlated with the POD 2 change from baseline of C-4 ($r = -0.30$ [-0.53, -0.07]). After adjusting for treatment intervention, the preoperative departmental Severity Score ($p = 0.02$) was positively correlated with postoperative hospital LOS.

DISCUSSION

Valvular heart disease increases the risk of postoperative AF.²⁶ The authors previously reported in a post hoc study that in patients undergoing combined CABG and valvular surgery, DEX was associated with a statistically significant reduction of new-onset postoperative AF from 52.6% to 18.2%.²³ Because reporting of AF in the previous study was based on chart review, the authors expected the incidence of AF in the present prospective study to be the same or higher. However, the present report shows that the incidence of AF as well as the difference between groups is much less than in the previous study. As a result, the difference in the incidence of AF between groups is not statistically significant in the present study, although the results favored the DEX group. The sample size that was based on the authors' earlier findings of a large observed treatment effect was not large enough to detect a smaller but potentially useful clinical effect noted in this study. Although the reasons for this difference cannot be identified, with certainty, the authors believe that changes in the manage-

Table 4. Cytokines and Chemokines at Baseline

Variable	Dexamethasone		Placebo	
	n	Mean (Q1, Q3)	n	Median (Q1, Q3)
IL-6 (pg/dL)	37	0.0 (0.0, 0.4)	34	0.0 (0.0, 0.5)
IL-8 (pg/dL)	37	5.9 (3.3, 9.2)	34	4.6 (1.8, 9.3)
IL-10 (pg/dL)	37	0.0 (0.0, 0.8)	34	0.2 (0.0, 1.3)
TNF- α (pg/dL)	37	0.9 (0.0, 2.0)	34	1.0 (0.0, 2.4)
Endothelin-1 (fmol/mL)	37	0.7 (0.3, 3.5)	34	0.6 (0.3, 2.0)
CRP (mg/dL)	37	0.3 (0.3, 0.8)	32	0.3 (0.3, 0.8)
C4 (mg/dL)	37	23.0 (20.0, 28.0)	33	22.0 (20.0, 30.0)
NO (ppb)	17	15.6 (12.9, 22.1)	15	14.8 (13.3, 21.5)

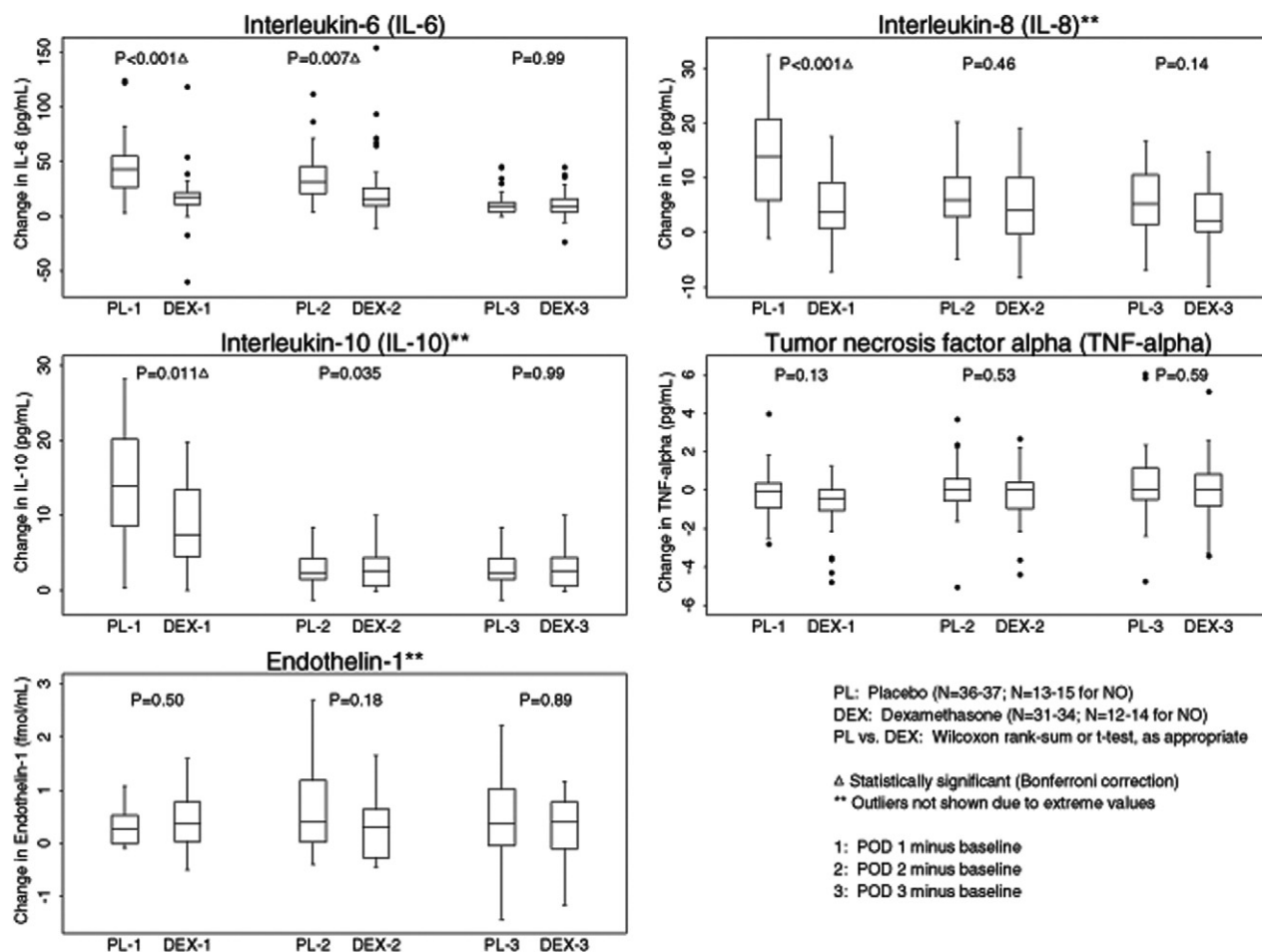


Fig 1. Cytokine and chemokine changes from baseline.

ment of temperature during CPB may have altered the inflammatory response²⁷; the mean of the lowest temperature reached on CPB was 35°C versus 33.4°C in the present and previous studies, respectively. Moreover, the cross-clamp time for each group was identical in the previous study (83 ± 32 minutes for both groups), whereas it was much longer in the DEX group in the present study, although the difference was not statistically significant. Longer cross-clamp time has been identified as a risk factor for the occurrence of postoperative AF.^{3,28,29}

An increased risk of postoperative AF has been associated with elevated preoperative CRP and a postoperative increase in complement C-4 and CRP.^{9,11} Recently, combined use of methylprednisolone and DEX has been shown to decrease the incidence of AF in CABG surgery patients.³⁰ Similar to methylprednisolone,^{19,31,32} DEX attenuated the increase in inflammatory mediators, but the authors could not show its effectiveness in reducing the incidence of AF. A significant difference in postoperative C-4 between groups was not detected, a finding that is consistent with some but not all studies.^{19,33,34} The association between ET-1 levels and AF noted in nonsurgical patients with congestive heart failure¹⁰ was not observed after cardiac surgery in patients. The lack of effect of DEX on the release of ET-1 suggests that inflammation may not be the primary determinant of its release.

The correlation observed between elevated preoperative CRP and the department's preoperative Severity Score of Illness was statistically significant but weak. Although CRP may reflect the severity of atherosclerotic heart disease,³⁵ the present study patients had concomitant severe valvular disease, which is known to impact their outcome. To the authors' knowledge, the influence of CRP values on the outcome of patients with combined coronary and valvular disease has not been studied.

The importance of the proinflammatory mediators as markers of the severity of illness and predictors of outcome is shown by the positive correlation observed between postoperative change from baseline of IL-8 and duration of postoperative intubation on POD 1. This finding is consistent with reports that IL-8 correlates with ICU LOS after lung transplant³⁶ and predicts mortality in patients with signs of systemic inflammatory response syndrome admitted to the emergency department.³⁷

It was also found that intubation time and postoperative hospital LOS were correlated with lower values of C-4 on POD 2 and higher values of IL-10 on POD 3, respectively. This may suggest that patients with delayed immunosuppression have worse outcome. This is consistent with reports of delayed immunosuppression associated with poor outcome after cardiac surgery^{38,39} and by studies that show that high IL-10 levels correlate with the severity

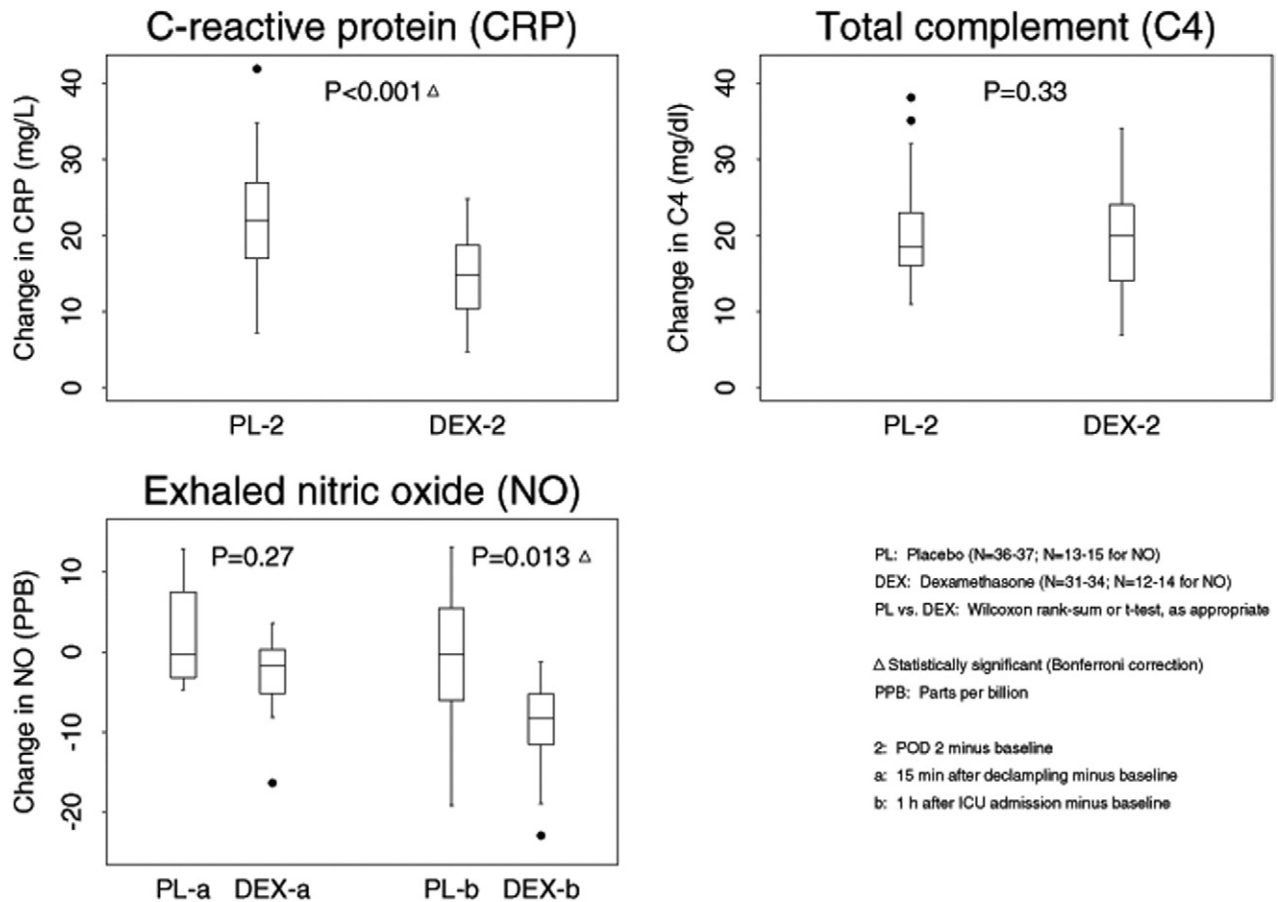


Fig 2. Inflammatory marker changes from baseline.

of sepsis, organ failure, and death.⁴⁰ These findings may indicate that modulation of the inflammatory response may have different results depending on the time that modulation occurs. Therefore, these observations suggest that an elevated proinflammatory response in the early post-CPB period as well as subsequent immunosuppressed state can both be associated with adverse outcomes. Expression of inducible NO synthase is increased by proinflammatory cytokines and can be inhibited by corticosteroids.²² The observed postoperative changes in exhaled NO are consistent with some but not all studies.^{22,41,42} In view of the differences in NO sampling techniques known to affect the accuracy and reproducibility of the measurements, such differences in results are not surprising. However, it must be noted that because of the large number of secondary analyses that were performed, it is possible that some of the significant results are because of chance alone.

Corticosteroids have antipyretic and hyperglycemic effects.^{32,33,43} On the day of surgery, the antipyretic effect was statistically and clinically significant. This corticosteroid-mediated effect that prevents postoperative fever is advantageous in cardiac surgery patients because oxygen consumption is directly related to body temperature.⁴⁴ The increased insulin requirements in the DEX group emphasize the importance of insulin titration protocols to maintain euglycemia because postoperative hyperglycemia has been linked to adverse outcome.⁴⁵

The major limitation of this study was inadequate sample size. Moreover, because a single dose of dexamethasone was used, the authors were unable to confirm recently published data³⁰ that show that sustained suppression of the inflammatory response with repeated doses of DEX can impact the incidence of AF. Moreover, the study was not powered to detect the possible impact of DEX on major morbidities and mortality.

In conclusion, this clinical trial does not provide evidence that a single preoperative dose of DEX markedly reduces the incidence of postoperative AF in patients undergoing combined CABG and valve surgery. The present study, given the sample size, does not assess whether DEX has a potentially modest or small effect on postoperative AF. Dexamethasone decreased the release of inflammatory mediators and caused a minor postoperative reduction of temperature on the day of surgery. The association of slower postoperative recovery with increased proinflammatory mediator concentrations in the early postoperative period, as well as decreased proinflammatory mediators at a later stage of postoperative recovery after cardiac surgery, may be clinically important.

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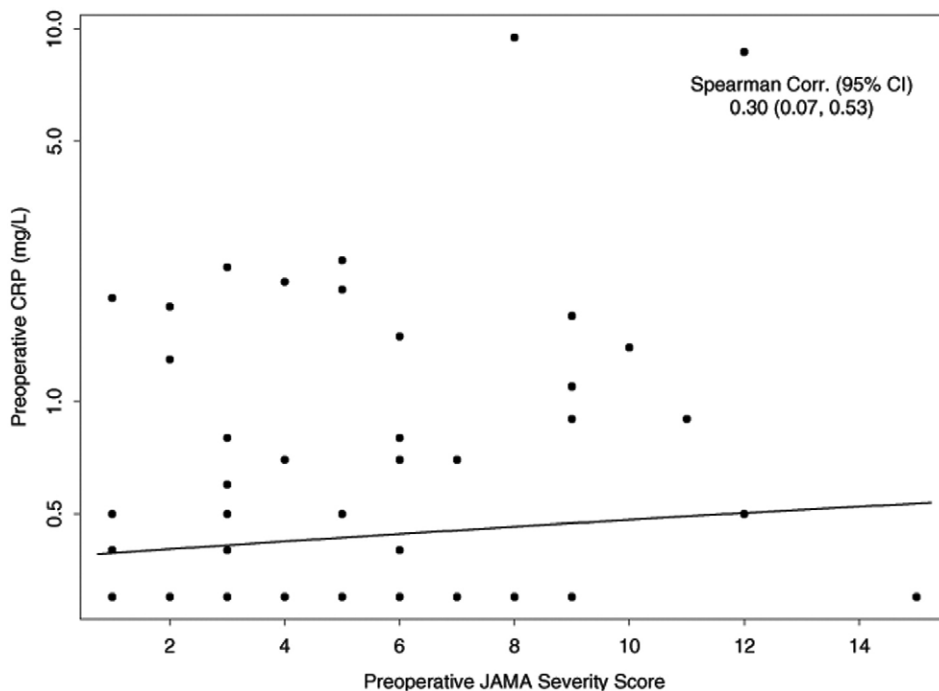


Fig 3. Association of preoperative JAMA Severity Score and CRP.

REFERENCES

1. Olshansky B: Management of atrial fibrillation after coronary artery bypass graft. *Am J Cardiol* 78:27-34, 1996
2. Mathew JP, Fontes ML, Tudor IC, et al: A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 291:1720-1729, 2004
3. Creswell LL, Schuessler RB, Rosenbloom M, et al: Hazards of postoperative atrial arrhythmias. *Ann Thorac Surg* 56:539-549, 1993
4. Jones EL, Weintraub WS, Craver JM, et al: Coronary bypass surgery: Is the operation different today? *J Thorac Cardiovasc Surg* 101:108-115, 1991
5. Hravnak M, Hoffman LA, Saul MI, et al: Resource utilization related to atrial fibrillation after coronary artery bypass grafting. *Am J Crit Care* 11:228-238, 2002
6. Connolly SJ, Cybulsky I, Lamy A, et al: Double-blind, placebo-controlled, randomized trial of prophylactic metoprolol for reduction of hospital length of stay after heart surgery: The Beta-Blocker Length Of Stay (BLOS) study. *Am Heart J* 145:226-232, 2003
7. Hill LL, Kattapuram M, Hogue CW Jr: Management of atrial fibrillation after cardiac surgery: Part I: Pathophysiology and risks. *J Cardiothorac Vasc Anesth* 16:483-494, 2002
8. Downing SW, Edmunds LH Jr: Release of vasoactive substances during cardiopulmonary bypass. *Ann Thorac Surg* 54:1236-1243, 1992
9. Lo B, Fijnheer R, Nierich AP, et al: C-reactive protein is a risk indicator for atrial fibrillation after myocardial revascularization. *Ann Thorac Surg* 79:1530-1535, 2005
10. Tuinenburg AE, Van Veldhuisen DJ, Boomsma F, et al: Comparison of plasma neurohormones in congestive heart failure patients with atrial fibrillation versus patients with sinus rhythm. *Am J Cardiol* 81:1207-1210, 1998
11. Bruins P, te Velthuis H, Yazdanbakhsh AP, et al: Activation of the complement system during and after cardiopulmonary bypass surgery: Postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. *Circulation* 96:3542-3548, 1997
12. Psychari SN, Apostolou TS, Sinos L, et al: Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol* 95:764-767, 2005
13. Cremer J, Martin M, Redl H, et al: Systemic inflammatory response syndrome after cardiac operations. *Ann Thorac Surg* 61:1714-1720, 1996
14. Wan S, Izzat MB, Lee TW, et al: Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *Ann Thorac Surg* 68:52-56, 1999; discussion 56-57
15. Kirklin JK, Westaby S, Blackstone EH, et al: Complement and the damaging effects of cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 86:845-857, 1983
16. Deng MC, Dasch B, Erren M, et al: Impact of left ventricular dysfunction on cytokines, hemodynamics, and outcome in bypass grafting. *Ann Thorac Surg* 62:184-190, 1996
17. te Velthuis H, Jansen PG, Oudemans-van Straaten HM, et al: Myocardial performance in elderly patients after cardiopulmonary bypass is suppressed by tumor necrosis factor. *J Thorac Cardiovasc Surg* 110:1663-1669, 1995
18. Wan S, LeClerc JL, Vincent JL: Cytokine responses to cardiopulmonary bypass: Lessons learned from cardiac transplantation. *Ann Thorac Surg* 63:269-276, 1997
19. Eppinger MJ, Ward PA, Bolling SF, et al: Regulatory effects of interleukin-10 on lung ischemia-reperfusion injury. *J Thorac Cardiovasc Surg* 112:1301-1305, 1996; discussion 1305-1306
20. Engleman RM, Rousou JA, Flack JE, et al: Influence of steroids on complement and cytokine generation after cardiopulmonary bypass. *Ann Thorac Surg* 60:801-804, 1995
21. Fosse E, Mollnes TE, Osterud A, et al: Effects of methylprednisolone on complement activation and leukocyte counts during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 2:255-261, 1987
22. Hill GE, Snider S, Galbraith TA, et al: Glucocorticoid reduction of bronchial epithelial inflammation during cardiopulmonary bypass. *Am J Respir Crit Care Med* 152:1791-1795, 1995

23. Yared JP, Starr NJ, Torres FK, et al: Effects of single dose, post-induction dexamethasone on recovery after cardiac surgery. *Ann Thorac Surg* 69:1420-1424, 2000
24. Higgins TL, Estafanous FG, Loop FD, et al: Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. *JAMA* 267:2344-2348, 1992
25. Khatri SB, Ozkan M, McCarthy K, et al: Alterations in exhaled gas profile during allergen-induced asthmatic response. *Am J Respir Crit Care Med* 164:1844-1848, 2001
26. Tsang TS, Barnes ME, Bailey KR, et al: Left atrial volume: important risk marker of incident atrial fibrillation in 1655 older men and women. *Mayo Clin Proc* 76:467-475, 2001
27. Tonz M, Mihaljevic T, von Segesser LK, et al: Normothermia versus hypothermia during cardiopulmonary bypass: A randomized, controlled trial. *Ann Thorac Surg* 59:137-143, 1995
28. Salaria V, Mehta NJ, Abdul-Aziz S, et al: Role of postoperative use of adrenergic drugs in occurrence of atrial fibrillation after cardiac surgery. *Clin Cardiol* 28:131-135, 2005
29. Nakai T, Lee RJ, Schiller NB, et al: The relative importance of left atrial function versus dimension in predicting atrial fibrillation after coronary artery bypass graft surgery. *Am Heart J* 143:181-186, 2002
30. Prasongsukarn K, Abel JG, Jamieson WR, et al: The effects of steroids on the occurrence of postoperative atrial fibrillation after coronary artery bypass grafting surgery: A prospective randomized trial. *J Thorac Cardiovasc Surg* 130:93-98, 2005
31. Yamashita Y, Shimada M, Hamatsu T, et al: Effects of preoperative steroid administration on surgical stress in hepatic resection: Prospective randomized trial. *Arch Surg* 136:328-333, 2001
32. Jansen NJ, van Oeveren W, van den Broek L, et al: Inhibition by dexamethasone of the reperfusion phenomena in cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 102:515-525, 1991
33. Bronicki RA, Backer CL, Baden HP, et al: Dexamethasone reduces the inflammatory response to cardiopulmonary bypass in children. *Ann Thorac Surg* 69:1490-1495, 2000
34. Chew MS, Brandslund I, Brix-Christensen V, et al: Tissue injury and the inflammatory response to pediatric cardiac surgery with cardiopulmonary bypass: A descriptive study. *Anesthesiology* 94:745-753, 2001
35. Janoskuti L, Forhecz Z, Hosszofalusi N, et al: High levels of C-reactive protein with low total cholesterol concentrations additively predict all-cause mortality in patients with coronary artery disease. *Eur J Clin Invest* 35:104-111, 2005
36. De Perrot M, Sekine Y, Fischer S, et al: Interleukin-8 release during early reperfusion predicts graft function in human lung transplantation. *Am J Respir Crit Care Med* 165:211-215, 2002
37. Lin KJ, Lin J, Hanasawa K, et al: Interleukin-8 as a predictor of the severity of bacteremia and infectious disease. *Shock* 14:95-100, 2000
38. Tarnok A, Schneider P: Pediatric cardiac surgery with cardiopulmonary bypass: Pathways contributing to transient systemic immune suppression. *Shock* 16:24-32, 2001
39. Mayumi H, Zhang QW, Nakashima A, et al: Synergistic immunosuppression caused by high-dose methylprednisolone and cardiopulmonary bypass. *Ann Thorac Surg* 63:129-137, 1997
40. Doughty L, Carcillo JA, Kaplan S, et al: The compensatory anti-inflammatory cytokine interleukin-10 response in pediatric sepsis-induced multiorgan failure. *Chest* 113:1625-1631, 1998
41. Radomski MW, Palmer RM, Moncada S: Glucocorticoids inhibit the expression of an inducible, but not the constitutive nitric oxide synthase in vascular endothelial cells. *Proc Natl Acad Sci U S A* 87:10043-10047, 1990
42. Brett SJ, Quinlan GJ, Mitchell J, et al: Production of nitric oxide during surgery involving cardiopulmonary bypass. *Crit Care Med* 26:272-278, 1998
43. Yared JP, Starr NJ, Hoffman-Hogg L, et al: Dexamethasone decreases the incidence of shivering following cardiac surgery: A randomized, double-blind, placebo controlled study. *Anesth Analg* 87:795-799, 1998
44. Frank SM, Fleisher LA, Olson KF, et al: Multivariate determinants of early postoperative oxygen consumption in elderly patients. Effects of shivering, body temperature, and gender. *Anesthesiology* 83:241-249, 1995
45. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 345:1359-1367, 2001