METHYLPREDNISOLONE DOES NOT BENEFIT PATIENTS UNDERGOING CORONARY ARTERY BYPASS GRAFTING AND EARLY TRACHEAL EXTUBATION

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Objective: We sought to determine whether methylprednisolone, when administered to patients undergoing cardiac surgery, is able to ward off the detrimental hemodynamic and pulmonary alterations associated with cardiopulmonary bypass.

Methods: After institutional review board approval and informed consent was obtained, 90 patients scheduled for elective cardiac surgery were randomized to 1 of 3 groups. Group 30MP patients received 30 mg/kg intravenous methylprednisolone during sternotomy and 30 mg/kg during initiation of cardiopulmonary bypass, group 15MP patients received 15 mg/kg methylprednisolone at the same 2 times, and group NS patients received similar volumes of isotonic sodium chloride solution at the same 2 times. Perioperative care was standardized, and all caregivers were blinded to treatment group. Various hemodynamic and pulmonary measurements were obtained perioperatively, as well as fluid balance, weight, peak postoperative blood glucose level, and tracheal extubation time.

Results: Demographic and clinical characteristics of patients and intraoperative data were similar among the 3 groups. Patients receiving methylprednisolone (either dose) exhibited significantly increased cardiac index ($P = .0006$), significantly decreased systemic vascular resistance ($P = .0005$), and significantly increased shunt flow ($P = .0020$) during the immediate postoperative period. All 3 groups exhibited significant increases in alveolar-arterial oxygen gradient ($P < .0001$), significant decreases in dynamic lung compliance ($P < .0001$), and significant decreases in static lung compliance ($P < .0001$) during the immediate postoperative period, with no differences between groups. Perioperative fluid balance and weights were similar between groups. A statistically significant difference in peak postoperative blood glucose level existed ($P = .016$) among group NS (234 ± 96 mg/dL), group 15MP (292 ± 93 mg/dL), and group 30MP (311 ± 90 mg/dL). In patients extubated within 12 hours of intensive care unit arrival, a statistically significant difference in extubation times existed ($P = .025$) between group NS (5.7 ± 2.3 hours), group 15MP (5.9 ± 2.2 hours), and group 30MP (7.5 ± 2.7 hours).

Conclusions: Methylprednisolone, as used in this investigation, offers no clinical benefits to patients undergoing elective coronary artery bypass grafting with cardiopulmonary bypass and may in fact be detrimental by initiating postoperative hyperglycemia and possibly hindering early postoperative tracheal extubation for undetermined reasons. (J Thorac Cardiovasc Surg 2001;121:561-9)

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Cardiopulmonary bypass (CPB) exposes blood to large areas of synthetic materials that trigger the production and release of numerous chemotactic and vasoactive substances.¹ This ensuing abnormal whole-body inflammatory response can complicate the postoperative period by causing major organ dysfunction. Traditionally, methylprednisolone has been administered to patients undergoing cardiac surgery to ward off these detrimental physiologic alterations, yet few well-controlled investigations exist, and use of the drug in this setting remains controversial. Our group was the first to rigorously examine use of methylprednisolone in patients undergoing coronary artery bypass grafting (CABG) and early extubation.^{2,3} Somewhat surprisingly, we found that methylprednisolone (30 mg/kg during sternotomy and 30 mg/kg during initiation of CPB) caused larger increases in postoperative alveolar-arterial (A-a) oxygen gradient and shunt flow, was unable to prevent postoperative decreases in lung compliance, was associated with a higher likelihood of requiring postoperative hemodynamic support, and prolonged tracheal extubation times when compared with placebo controls.^{2,3} These results indicate that use of the drug in this setting may hinder early tracheal extubation.^{2,3} This study was undertaken to determine whether these unexpected results could be duplicated and possibly ascertain why methylprednisolone was detrimental in this setting. Because larger doses of methylprednisolone may induce sodium and water retention, which may initiate pulmonary edema in susceptible patients,⁴ this investigation assessed perioperative fluid balance and weights in study patients along with standard pulmonary and hemodynamic parameters. Furthermore, 2 different doses of methylprednisolone (30 mg/kg twice and 15 mg/kg twice) are compared with placebo controls.

Methods

After institutional review board approval and informed consent were obtained, 90 patients scheduled for elective CABG and early extubation were studied. At our institution, we view all patients scheduled for elective CABG as candidates for early extubation, including those undergoing reoperations and those with decreased left ventricular function (ejection fraction < 40%). Patients receiving preoperative steroids or who had undergone previous lung surgery were excluded from participation. Patients requiring preoperative intravenous inotropic or vasoactive drugs, intra-aortic balloon support, supplemental oxygen, or mechanical ventilation were excluded.

Each patient was randomized to 1 of 3 groups. Two groups received intravenous methylprednisolone sodium succinate (A-Methapred; Abbott Laboratories, North Chicago, Ill), and 1 group received intravenous isotonic sodium chloride solu-

tion. Group 30MP patients received 30 mg/kg intravenous methylprednisolone during sternotomy and 30 mg/kg during initiation of CPB, group 15MP patients received 15 mg/kg of intravenous methylprednisolone at the same 2 times, and group NS patients received similar volumes of intravenous isotonic sodium chloride solution at the same 2 times. An anesthesia research nurse performed the randomization and prepared the 2 syringes of blinded solution that were administered by the anesthesiologist managing the case. All physicians and nursing staff caring for the patients perioperatively were unaware of treatment group.

The intraoperative anesthetic technique was standardized and consisted of intravenous fentanyl (20 mg/kg), midazolam (150 mg/kg), and vecuronium bromide. All of the fentanyl was administered before sternotomy. Regarding midazolam, approximately 70% of the calculated dose was administered before sternotomy, and the balance was administered during rewarming. If required, inhaled isoflurane, intravenous nitroglycerin, or both were used for blood pressure control before initiation of CPB. Hypothermic CPB (to a lowest temperature of 26°C) with a membrane oxygenator and crystalloid prime (2.0 L of lactated Ringer's solution and 50 mEq sodium bicarbonate) was used in all patients. Nonpulsatile flows were maintained between 2.4 and 2.8 L · min⁻¹ · m⁻², and if needed, isoflurane was used by the perfusionist to maintain perfusion pressure in the range of 50 to 70 mm Hg. Intermittent antegrade hypothermic crystalloid cardioplegia was used in all patients. Alpha-stat blood gas management was used in all patients. The lungs were allowed to deflate during CPB. Separation from CPB was facilitated with intravenous dobutamine, norepinephrine, nitroglycerin, or some combination thereof at the discretion of the anesthesiologist managing the case.

Hemodynamic and pulmonary measurements were obtained at 4 times: 10 minutes after intubation (time A), 10 minutes after sternotomy (time B), 10 minutes after sternal closure (time C), and 60 minutes after intensive care unit (ICU) arrival (time D). A pulmonary artery catheter (Swan-Ganz Thermodilution Paceport Catheter; Baxter Healthcare Corporation, Irvine, Calif) was used in all patients to facilitate data collection. Hemodynamic measurements included heart rate, mean arterial pressure, central venous pressure, mean pulmonary artery pressure, and pulmonary artery occlusive pressure. Cardiac outputs were obtained at end-expiration in triplicate and averaged. Cardiac index (CI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and shunt flow were calculated by using standard equations (Appendix I). Pulmonary measurements included A-a oxygen gradient, arterial carbon dioxide tension, dynamic lung compliance, and static lung compliance computed by standard equations (Appendix II). Mechanical ventilation parameters were standardized (respiratory rate, 8 breaths/min; tidal volume, 10 mL/kg; fraction of inspired oxygen [FIO₂], 1.0; positive end-expiratory pressure, +5 cm H₂O; and inspiratory/expiratory ratio, 1:3) for at least 10 minutes before each measurement. In each patient the inspiratory flow was adjusted so that the calculated tidal volume was delivered during the entire inspiratory cycle (creating the lowest peak airway pressure).

Perioperative fluid balance and weights were recorded in all patients. Total operating room intravenous input (eg, crystalloid and blood products) and total operating room urine output, as well as total intravenous input (eg, crystalloid and blood products) and total output (urine and chest tube) during the initial 24 postoperative hours, were recorded. All patients were weighed 3 times: immediately before transfer to the operating room (baseline) and at 2 and 24 hours after ICU arrival. The same sling scale (Scale-Tronix 2001 Sling Scale; Scale-Tronix, Inc, Wheaton, Ill) was used for every weight measurement.

After completion of CABG, patients were transferred to the ICU, where postoperative care was standardized and tracheal extubation was accomplished at the earliest clinically appropriate time. Criteria for extubation in our ICU include an appropriate sensorium, normothermia, hemodynamic stability, adequate pulmonary function (arterial partial pressure of oxygen, >60 mm Hg with an Fio_2 of 0.4), adequate urine output, and minimal chest tube output. If a patient had hypertension, tachycardia, and/or excessive movement at a time when tracheal extubation was not yet appropriate (for any reason), the ICU nurse was free to administer small amounts of intravenous midazolam. In patients who were not extubated within 24 hours of ICU arrival, the reason for prolonged intubation (eg, hemodynamic instability and oxygenation difficulties) was ascertained.

Postoperative complications and treatments were recorded daily until hospital discharge. All patients had a creatine kinase (CK) level assayed (by means of coupled enzymatic reactions on the basis of Rosalki's modification of the Oliver procedure) and an electrocardiogram recorded at 4 AM on the first postoperative day. If the total CK level was greater than 200 IU/L, CK-MB levels were assayed (by using the monoclonal antibody technique), and the CK-MB index was calculated ($\text{CK-MB}/\text{total CK} \times 100$). If the initial total CK was greater than 200 IU/L, 2 additional total CK and CK-MB levels were measured 6 and 12 hours later. Sensitivity of the CK-MB assay in our laboratory is 0.4 ng/mL. Perioperative myocardial infarction was defined as a postoperative CK-MB index of greater than 3.0, postoperative electrocardiographic evidence (new Q waves or ST segment elevation) of infarction, or both.

The Pearson χ^2 or Fisher exact tests were applied to categorical data. One-way analysis of variance (ANOVA) was used to test the difference between means in the 3 groups regarding demographic and clinical characteristics of patients and appropriate perioperative data. To account for repeated measurements of perioperative hemodynamic and pulmonary data, repeated-measures ANOVA was used, along with statistical construct, to compare mean measurements 10 minutes after intubation and 60 minutes after ICU arrival (with and without the Bonferroni correction). Results are expressed as the mean $\pm$ 1 SD or, when indicated in the appropriate table, the number of patients, unless otherwise indicated.

Results

Thirty patients were randomized to each group. One patient in group NS and 1 patient in group 15MP were omitted from statistical analysis because of deviation

Table I. Demographic and clinical characteristics of patients

	Group NS (n = 29)	Group 15MP (n = 29)	Group 30MP (n = 30)
Preoperative history			
Age, y (range)	67 $\pm$ 10 (43-85)	62 $\pm$ 12 (37-81)	67 $\pm$ 9 (54-81)
Male	22	24	22
Female	7	5	8
Height (cm)	172 $\pm$ 8	173 $\pm$ 9	169 $\pm$ 11
Weight (kg)	85 $\pm$ 20	84 $\pm$ 15	79 $\pm$ 16
Smoking history (packs/y)			
10-20	9	5	7
21-40	3	6	5
41-60	3	5	7
>60	5	3	5
Actively smoking	5	3	5
Never smoked	9	10	6
Preoperative medications			
β -Blocker	14	18	18
Calcium channel blocker	5	3	7
Nitrate	12	16	15
ACE inhibitor	5	12	12
Digitalis preparation	4	2	7
Diuretic	7	4	7
Oral hypoglycemic	8	6	5
Insulin	3	3	5
Inhaled bronchodilators	1	2	1
None	2	1	0

ACE, Angiotensin-converting enzyme.

from the study protocol. Demographic and clinical characteristics of patients and intraoperative data are presented in Tables I and II, respectively. Statistical analysis with the Pearson χ^2 and Fisher exact test and 1-way ANOVA revealed no differences between groups regarding demographic and clinical characteristics and intraoperative data.

Perioperative hemodynamic data are presented in Tables III and IV. Regarding Table III, repeated-measures ANOVA revealed that differences over time (times A, B, C, and D) within groups in heart rate ($P < .0001$), mean arterial pressure ($P < .0001$), central venous pressure ($P < .0001$), mean pulmonary artery pressure ($P < .0001$), and pulmonary artery occlusive pressure ($P < .0001$) were statistically significant, yet there were no differences between groups. Regarding Table IV, repeated-measures ANOVA revealed that differences over time (times A, B, C, and D) within groups in CI ($P = .0001$), SVR ($P = .0098$), PVR ($P = .0049$), and shunt flow ($P < .0001$) were statistically significant. When mean measurements at time A and time D were compared by statistically constructed repeated-measures ANOVA, differences in CI

Table II. Intraoperative data

	Group NS (n = 29)	Group 15MP (n = 29)	Group 30MP (n = 30)
Anesthetic drugs			
Fentanyl ($\mu\text{g/kg}$)	20 $\pm$ 0.3	20 $\pm$ 0.3	20 $\pm$ 0.4
Midazolam ($\mu\text{g/kg}$)	150 $\pm$ 39	150 $\pm$ 21	139 $\pm$ 23
Vecuronium ($\mu\text{g/kg}$)	431 $\pm$ 186	468 $\pm$ 167	436 $\pm$ 182
Before CPB			
Isoflurane use	29	26	29
Nitroglycerin use	6	8	9
During CPB			
Lowest temperature ($^{\circ}\text{C}$)	28.8 $\pm$ 1.8	27.9 $\pm$ 1.6	27.9 $\pm$ 1.8
Highest ACT (s)	608 $\pm$ 141	653 $\pm$ 181	633 $\pm$ 129
Total heparin (mg)	295 $\pm$ 93	379 $\pm$ 99	311 $\pm$ 120
Total cardioplegia (mL)	3176 $\pm$ 1086	3034 $\pm$ 932	3309 $\pm$ 991
Countershocks required	14	16	12
Crossclamp time (min)	84 $\pm$ 18	82 $\pm$ 29	83 $\pm$ 17
CPB time (min)	108 $\pm$ 25	107 $\pm$ 30	102 $\pm$ 22
After CPB			
Dobutamine use	20	23	20
Norepinephrine use	3	4	6
Nitroglycerin use	1	2	2
Isoflurane use	6	6	5
Total protamine (mg)	310 $\pm$ 84	348 $\pm$ 88	315 $\pm$ 87
Surgical data			
Saphenous vein grafts (range)	1-4	0-5	1-4
LITA	26	26	24

ACT, Activated clotting time; LITA, left internal thoracic artery.

Table III. Perioperative hemodynamic data

	Time A	Time B	Time C	Time D
Heart rate (beats/min)				
Group NS	58.9 $\pm$ 10.7	62.6 $\pm$ 12.6	91.9 $\pm$ 16.5	89.2 $\pm$ 12.5
Group 15MP	58.4 $\pm$ 10.2	61.0 $\pm$ 13.8	90.5 $\pm$ 15.3	86.0 $\pm$ 16.0
Group 30MP	59.9 $\pm$ 13.1	68.0 $\pm$ 13.4	90.0 $\pm$ 15.0	87.0 $\pm$ 15.7
Mean arterial pressure (mm Hg)				
Group NS	68.4 $\pm$ 11.6	79.6 $\pm$ 10.9	81.0 $\pm$ 10.1	80.9 $\pm$ 13.8
Group 15MP	71.9 $\pm$ 9.7	82.1 $\pm$ 12.6	77.4 $\pm$ 8.9	78.3 $\pm$ 14.4
Group 30MP	73.3 $\pm$ 7.1	79.3 $\pm$ 10.8	76.3 $\pm$ 12.2	73.2 $\pm$ 12.2
Central venous pressure (mm Hg)				
Group NS	13.2 $\pm$ 3.3	12.8 $\pm$ 4.8	13.5 $\pm$ 4.3	8.9 $\pm$ 3.7
Group 15MP	13.5 $\pm$ 3.4	14.0 $\pm$ 3.4	14.4 $\pm$ 3.7	8.4 $\pm$ 2.6
Group 30MP	12.2 $\pm$ 2.8	13.1 $\pm$ 3.6	14.3 $\pm$ 3.9	8.2 $\pm$ 4.1
Mean pulmonary artery pressure (mm Hg)				
Group NS	22.5 $\pm$ 4.8	22.6 $\pm$ 5.3	22.2 $\pm$ 5.0	18.7 $\pm$ 4.2
Group 15MP	22.8 $\pm$ 7.6	23.4 $\pm$ 6.0	24.1 $\pm$ 4.4	18.8 $\pm$ 5.3
Group 30MP	21.0 $\pm$ 4.9	24.1 $\pm$ 7.5	24.3 $\pm$ 6.0	18.6 $\pm$ 4.4
Pulmonary artery occlusive pressure (mm Hg)				
Group NS	15.7 $\pm$ 4.1	15.5 $\pm$ 5.4	8.1 $\pm$ 5.7	11.3 $\pm$ 3.9
Group 15MP	14.8 $\pm$ 3.4	15.6 $\pm$ 3.3	7.8 $\pm$ 4.2	10.4 $\pm$ 3.0
Group 30MP	14.5 $\pm$ 3.6	15.0 $\pm$ 4.4	9.5 $\pm$ 5.3	11.1 $\pm$ 3.8

Time A, 10 minutes after intubation; Time B, 10 minutes after sternotomy; Time C, 10 minutes after sternal closure; Time D, 60 minutes after ICU arrival.

($P = .0006$), SVR ($P = .0005$), and shunt flow ($P = .0020$) were statistically significant. Further statistical analysis of data at time A and time D by using the Bonferroni correction revealed significant differences between group NS and group 30MP regarding CI

($P < .0001$), SVR ($P < .0001$), and shunt flow ($P = .0030$) and between group 15MP and group 30MP regarding shunt flow ($P = .0260$). There were no differences among group NS, group 15MP, and group 30MP in the number of patients requiring dobutamine

Table IV. Perioperative hemodynamic data

	Time A	Time B	Time C	Time D
CI ($L \cdot \min^{-1} \cdot m^{-2}$)				
Group NS	2.4 ± 0.7	2.5 ± 0.7	2.7 ± 1.0	2.6 ± 0.7
Group 15MP	2.4 ± 0.6	2.6 ± 0.7	3.2 ± 0.9	3.1 ± 0.8
Group 30MP	2.3 ± 0.4	2.5 ± 0.7	3.4 ± 1.2	3.4 ± 1.0*
SVR ($\text{dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$)				
Group NS	1027 ± 396	1225 ± 452	1181 ± 564	1260 ± 550
Group 15MP	1027 ± 283	1171 ± 382	875 ± 316	968 ± 324
Group 30MP	1181 ± 345	1201 ± 388	883 ± 406	913 ± 470*
PVR ($\text{dynes} \cdot \text{s}^{-1} \cdot \text{cm}^{-5}$)				
Group NS	125 ± 47	133 ± 56	252 ± 147	124 ± 67
Group 15MP	139 ± 101	141 ± 111	232 ± 102	118 ± 67
Group 30MP	123 ± 61	168 ± 121	213 ± 129	96 ± 46
Shunt flow (%)				
Group NS	15.9 ± 6.1	16.0 ± 6.0	21.6 ± 9.1	23.1 ± 7.7
Group 15MP	15.3 ± 7.6	14.1 ± 5.4	21.4 ± 9.7	24.1 ± 8.5
Group 30MP	14.9 ± 6.9	16.8 ± 6.6	27.3 ± 9.6	30.1 ± 8.8†‡

Time A, 10 minutes after intubation; Time B, 10 minutes after sternotomy; Time C, 10 minutes after sternal closure; Time D, 60 minutes after ICU arrival.

* $P < .0001$, group 30MP versus group NS.

† $P = .0030$, group 30MP versus group NS.

‡ $P = .0260$, group 30MP versus group 15MP.

(10, 12, and 15, respectively), norepinephrine (8, 9, and 9, respectively), or nitroglycerin (8, 3, and 7, respectively) during the initial 24 hours of ICU stay.

Perioperative pulmonary data are presented in Table V. Repeated-measures ANOVA revealed that differences over time (times A, B, C, and D) within groups in A-a oxygen gradient ($P < .0001$), arterial carbon dioxide tension ($P < .0001$), dynamic lung compliance ($P < .0001$), and static lung compliance ($P < .0001$) were statistically significant, yet there were no differences between groups.

Perioperative fluid balance and weights are presented in Table VI. One-way ANOVA revealed no differences between groups regarding perioperative fluid balance. All 3 groups experienced equivalent significant ($P < .0001$) postoperative increases in weight.

Extubation times are presented in Table VII. When all extubated patients and patients extubated within 24 hours of ICU arrival were analyzed, there was no statistically significant difference between groups despite a trend toward prolonged extubation times in patients receiving methylprednisolone. However, when patients extubated within 12 hours of ICU arrival were analyzed, 1-way ANOVA revealed a statistically significant difference in extubation times ($P = .025$) between groups, and Bonferroni correction comparing group NS with group 30MP yielded a P value of .038. Midazolam administration from arrival in the ICU to extubation was similar among group NS (5.4 ± 7.2 mg), group 15MP (3.9 ± 4.7 mg), and group 30MP (2.9

± 5.6 mg). More patients in group 30MP (14) required no midazolam before extubation than in group 15MP (11) and group NS (7).

During the initial 24 ICU hours, 1-way ANOVA revealed a statistically significant difference in peak postoperative blood glucose level ($P = .016$) among patients in group NS (234 ± 96 mg/dL), group 15MP (292 ± 93 mg/dL), and group 30MP (311 ± 90 mg/dL). Postoperative atrial fibrillation occurred in 9 group NS patients, 8 group 15MP patients, and 9 group 30MP patients. One patient in group NS had a perioperative myocardial infarction (electrocardiographic changes) yet otherwise had an uneventful postoperative course. One patient in group NS and 1 patient in group 30MP had a postoperative cerebral infarction. Both patients were eventually discharged to a chronic care facility. One patient in group NS died. This patient was initially extubated uneventfully yet became asystolic late on the first postoperative day. Re-exploration revealed dysfunctional saphenous vein grafts, and the patient died on the fifth postoperative day. Of the 88 patients, 87 were eventually discharged from the hospital. The mean duration of postoperative hospital stay among patients in group NS (6.5 ± 4.6 days), group 15MP (6.0 ± 4.8 days), and group 30MP (6.7 ± 3.4 days) was similar.

Discussion

This prospective randomized double-blind placebo-controlled clinical study reveals that administration of methylprednisolone to patients undergoing elective

Table V. Perioperative pulmonary data

	Time A	Time B	Time C	Time D
A-a oxygen gradient (mm Hg)				
Group NS	254.2 ± 95.1	246.7 ± 91.4	352.3 ± 123.0	393.3 ± 83.7
Group 15MP	219.3 ± 111.9	219.4 ± 96.1	318.8 ± 127.4	364.1 ± 106.0
Group 30MP	233.7 ± 119.6	243.7 ± 128.9	373.6 ± 145.5	413.7 ± 126.5
Arterial carbon dioxide tension (mm Hg)				
Group NS	35.9 ± 4.4	34.2 ± 5.9	38.0 ± 4.9	45.2 ± 7.7
Group 15MP	37.5 ± 4.2	35.1 ± 4.3	39.8 ± 4.9	46.2 ± 6.7
Group 30MP	36.8 ± 3.6	35.4 ± 4.1	40.4 ± 4.5	45.5 ± 6.4
Dynamic lung compliance (mL/cm H ₂ O)				
Group NS	49.4 ± 14.3	47.7 ± 12.8	43.2 ± 12.2	33.1 ± 8.5
Group 15MP	48.3 ± 10.5	47.0 ± 9.2	41.4 ± 8.3	36.5 ± 6.1
Group 30MP	48.1 ± 12.6	47.7 ± 12.9	41.7 ± 10.1	35.7 ± 6.4
Static lung compliance (mL/cm H ₂ O)				
Group NS	71.4 ± 27.7	68.2 ± 28.7	61.5 ± 26.0	49.3 ± 13.1
Group 15MP	69.4 ± 41.0	61.6 ± 17.3	55.5 ± 24.1	57.0 ± 13.9
Group 30MP	73.6 ± 44.6	75.4 ± 59.4	63.2 ± 38.3	54.8 ± 13.3

Time A, 10 minutes after intubation; Time B, 10 minutes after sternotomy; Time C, 10 minutes after sternal closure; Time D, 60 minutes after ICU arrival.

Table VI. Perioperative fluid balance and weights

	Group NS (n = 29)	Group 15MP (n = 29)	Group 30MP (n = 30)
Total OR IV input (mL)	2660 ± 505	3096 ± 1739	3097 ± 964
Total OR urine output (mL)	844 ± 564	976 ± 770	819 ± 583
Initial 24-h ICU total IV input (mL)	3714 ± 1450	3671 ± 1677	3491 ± 1432
Initial 24-h ICU total output (mL)	3281 ± 1004	3668 ± 1301	3491 ± 1193
Baseline weight (kg)	85.5 ± 20.3	84.0 ± 14.9	78.9 ± 16.4
Weight 2 h after ICU arrival (kg)	90.7 ± 18.4*	90.9 ± 15.3*	85.6 ± 16.8*
Weight 24 h after ICU arrival (kg)	91.3 ± 20.3*	88.7 ± 15.7*	84.6 ± 17.1*

OR, Operating room; IV, intravenous.

**P* < .0001 when compared with baseline weight.

CABG with CPB increases postoperative CI, decreases postoperative SVR, increases postoperative shunt flow, is unable to prevent postoperative pulmonary dysfunction (increased A-a oxygen gradient and decreased dynamic and static lung compliance) or prevent postoperative weight gain, initiates postoperative hyperglycemia, and prolongs tracheal extubation time. Thus, methylprednisolone, as used in this investigation, offers no clinical benefits to patients undergoing elective CABG with CPB and may in fact be detrimental by initiating postoperative hyperglycemia and possibly hindering early postoperative tracheal extubation.

Patients undergoing cardiac surgery experience an abnormal whole-body inflammatory response after initiation of CPB, which causes detrimental postoperative changes in pulmonary function and hemodynamics.¹ Inhibition of detrimental CPB-induced physiologic effects may be possible with corticosteroids. In the 1960s, methylprednisolone became the drug of choice because of its clinical efficacy in shock and sepsis and

its advantageous side effect profile.⁵ The dose used, 30 mg/kg, was empirically chosen and remains the standard. However, a supplemental dose must be administered at initiation of CPB to maintain adequate plasma levels of drug into the postoperative period.⁶ Although many studies have investigated use of methylprednisolone in preventing detrimental CPB-induced physiologic effects, it is still unclear whether the drug truly is beneficial in this setting.⁷⁻³²

Whether administration of methylprednisolone before CPB enhances postoperative hemodynamic stability remains controversial.* The observed hemodynamic changes in this investigation regarding CI, SVR, and shunt flow were similar to those in our previous investigation.³ Other investigators have documented increases in CI,^{24,32} decreases in SVR,^{24,29,32} increases in shunt flow,^{25,33,34} and decreased incidence of

*References 3,5,6,12,19,22,24,28-30,32

arrhythmias²⁸ when methylprednisolone is used in this setting. Postoperative vasodilation, although having certain beneficial physiologic effects (decreased afterload and decreased left ventricular end-diastolic volume and pressure), may increase postoperative use of pharmacologic agents to support mean arterial pressure,³ increase postoperative A-a oxygen gradient because of increased shunt fraction,^{2,3} or both. Indeed, after cardiac surgery, there is a significant correlation ($r = 0.82$) between shunt flow and A-a oxygen gradient.³³

Whether administration of methylprednisolone before CPB attenuates pulmonary damage is also controversial.^{2,15,16,25,26} Some investigators document decreased neutrophil activation,¹⁶ decreased postoperative radiographic abnormalities,²⁶ and improvement in postoperative oxygenation² in patients who received methylprednisolone, whereas others reveal the drug does not prevent interleukin 8-mediated pulmonary neutrophil infiltration¹⁵ or postoperative oxygenation abnormalities.²⁵ As in our previous investigation,² we again found that methylprednisolone was unable to prevent postoperative increases in A-a oxygen gradient and postoperative decreases in dynamic and static lung compliance.

The stimulus for this investigation was the unexpected findings of our previous investigation.^{2,3} Our group was the first to rigorously examine use of methylprednisolone in patients undergoing cardiac surgery and early extubation, and we found that the drug significantly prolonged extubation time when compared with placebo controls (12.8 ± 4.9 hours vs 10.1 ± 5.2 hours, respectively; $P = .05$).^{2,3} Using the same perioperative study protocol (with an additional group receiving the drug at half the original dose), we again found that methylprednisolone significantly prolonged extubation time. Because large doses of methylprednisolone may induce sodium and water retention, which may initiate pulmonary edema in susceptible patients,⁴ we also assessed perioperative fluid balance and weights. However, there was no difference between groups regarding these perioperative variables. Two previous observational studies further suggest that methylprednisolone prolongs extubation time in this setting.^{10,30} One found that patients who received 1.0 g of methylprednisolone immediately before CPB followed by 4 doses of dexamethasone (4.0 mg each) every 6 hours after CPB had prolonged extubation times compared with control patients who did not receive steroids (13.1 ± 2.3 hours vs 10.5 ± 1.0 hours, respectively), although the difference was not statistically significant.¹⁰ The other found that patients who received 30 mg/kg methylprednisolone after the induction of anesthesia required significantly prolonged respiratory support in

Table VII. Extubation times

All extubated patients	
Group NS, h (n = 27)	7.0 $\pm$ 5.1
Group 15MP, h (n = 28)	14.9 $\pm$ 34.7
Group 30MP, h (n = 30)	16.3 $\pm$ 38.7
Patients extubated within 24 h of ICU arrival	
Group NS, h (n = 27)	7.0 $\pm$ 5.0
Group 15MP, h (n = 27)	8.4 $\pm$ 5.4
Group 30MP, h (n = 29)	9.3 $\pm$ 5.0
Patients extubated within 12 h of ICU arrival	
Group NS, h (n = 25)	5.7 $\pm$ 2.3
Group 15MP, h (n = 21)	5.9 $\pm$ 2.2
Group 30MP, h (n = 24)	7.5 $\pm$ 2.7*

* $P = .038$, group 30MP versus group NS.

the immediate postoperative period compared with historical controls (85 ± 181 hours vs 27 ± 16 hours, respectively; $P = .05$).³⁰

Methylprednisolone is an attractive agent for potential suppression of the systemic inflammatory response associated with CPB because of its beneficial effects on neutrophil kinetics and function and because it represents one of the few therapeutic drugs that possess multi-inhibitory effects on numerous components of the inflammatory response.³⁵ Potential anti-inflammatory effects of methylprednisolone, when used in this manner, include decreased complement activation,^{10,19,21} decreased interleukin 6 release,^{7,11,12} decreased interleukin 8 release,^{8-10,12} increased interleukin 10 release,^{8,9} decreased tumor necrosis factor release,^{9,11-13} and decreased neutrophil integrin CD11b up-regulation,^{13,14} among others. However, although results from animal models appear promising, definitive clinical benefits in human subjects have yet to be demonstrated. Our investigation shows that the drug confers no clinical benefit and may in fact be detrimental by delaying postoperative extubation (for undetermined reasons) and initiating postoperative hyperglycemia. Furthermore, methylprednisolone administration is not without other potential risks, which include gastritis, gastrointestinal bleeding, impaired wound healing, increased risk of infection, adverse psychiatric effects, avascular bone necrosis, and aggravation of ischemic brain injury (irrespective of hyperglycemia).³⁶

In conclusion, this prospective randomized double-blind placebo-controlled clinical study reveals that administration of methylprednisolone to patients undergoing elective CABG with CPB increases postoperative CI, decreases postoperative SVR, increases postoperative shunt flow, is unable to prevent postoperative pulmonary dysfunction (increased A-a oxygen gradient and decreased dynamic and static lung com-

pliance) or postoperative weight gain, initiates postoperative hyperglycemia, and prolongs tracheal extubation time (for undetermined reasons). Thus, methylprednisolone, as used in this investigation, offers no clinical benefits to patients undergoing elective CABG with CPB and may in fact be detrimental by initiating postoperative hyperglycemia and possibly hindering early postoperative tracheal extubation.

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Appendix I. Hemodynamic standard equations

$$\text{Cardiac index: CI} = \frac{\text{CO}}{\text{BSA}}$$

$$\text{Systemic vascular resistance: SVR} = \frac{(\text{MAP} - \text{CVP})}{\text{CO}} \times 80$$

$$\text{Pulmonary vascular resistance: PVR} = \frac{(\text{PAP} - \text{PCWP})}{\text{CO}} \times 80$$

$$\text{Shunt flow (\%): } \frac{Q_s}{Q_t} = \frac{C_{cO_2} - C_{aO_2}}{C_{cO_2} - C_{vO_2}}$$

CO, Cardiac output; BSA, body surface area; MAP, mean arterial pressure; CVP, central venous pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; C_{cO_2} , end-capillary oxygen content; C_{aO_2} , arterial oxygen content; C_{vO_2} , mixed venous oxygen content.

Appendix II. Pulmonary standard equations

$$\text{Alveolar-arterial O}_2 \text{ gradient (mm Hg): } P(A-a)O_2 = PAO_2 - PaO_2$$

$$PAO_2 = P_{iO_2} - \frac{PaCO_2}{0.8}$$

$$P_{iO_2} = F_{iO_2} \times (P_B - 47)$$

$$\text{Dynamic lung compliance (mL/cm H}_2\text{O): } C_d = \frac{\text{Tidal volume}}{P_{\text{peak}} - \text{PEEP}}$$

$$\text{Static lung compliance (mL/cm H}_2\text{O): } C_s = \frac{\text{Tidal volume}}{P_{\text{plateau}} - \text{PEEP}}$$

PAO_2 , Alveolar PO_2 ; PaO_2 , arterial PO_2 ; $PaCO_2$, arterial PCO_2 ; 0.8, assumed respiratory quotient; PEEP, positive end-expiratory pressure.

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