METHYLPREDNISOLONE REDUCES THE INFLAMMATORY RESPONSE TO CARDIOPULMONARY BYPASS IN NEONATAL PIGLETS: TIMING OF DOSE IS IMPORTANT

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Introduction: Cardiopulmonary bypass produces an inflammatory response that can cause significant postoperative pulmonary dysfunction and total body edema. This study evaluates the efficacy of preoperative methylprednisolone administration in limiting this injury in neonates and compares the effect of giving methylprednisolone 8 hours before an operation to the common practice of adding methylprednisolone to the cardiopulmonary bypass circuit prime. **Methods:** A control group of neonatal pigs (control; $n = 6$) received no preoperative medication. One experimental group ($n = 6$) received methylprednisolone sodium succinate (30 mg/kg) both 8 and 1.5 hours before the operation. A second experimental group received no preoperative treatment, but methylprednisolone (30 mg/kg) was added to the cardiopulmonary bypass circuit prime. All animals underwent cardiopulmonary bypass and 45 minutes of deep hypothermic circulatory arrest. Hemodynamic and pulmonary function data were acquired before cardiopulmonary bypass and at 30 and 60 minutes after bypass. **Results:** In the control group, pulmonary compliance, alveolar-arterial gradient, and pulmonary vascular resistance were significantly impaired after bypass ($P < .01$ for each by analysis of variance). In the group that received methylprednisolone, compliance ($P = .02$), alveolar-arterial gradient ($P = .0003$), pulmonary vascular resistance ($P = .007$), and extracellular fluid accumulation ($P = .003$) were significantly better after bypass when compared with the control group. Results for the group that received no preoperative treatment fell between the control group and the group that received methylprednisolone. **Conclusions:** When given 8 hours and immediately before the operation, methylprednisolone improves pulmonary compliance after bypass, alveolar-arterial gradient, and pulmonary vascular resistance compared with no treatment. The addition of methylprednisolone to the cardiopulmonary bypass circuit prime is beneficial but inferior to preoperative administration. (J Thorac Cardiovasc Surg 1999;117:515-22)

Cardiopulmonary bypass (CPB) continues to be associated with significant morbidity despite the many advances made in perfusion techniques. Neonates and

infants may be particularly susceptible to the adverse affects of CPB. It is well documented that CPB is an inflammatory stimulus and that its use provokes a whole body inflammatory reaction with endothelial cell injury, adhesion molecule up-regulation,¹ neutrophil activation,² and initiation of the coagulation cascade.³ Patients may also incur an ischemic injury to the lungs during the course of CPB. These processes may result in pulmonary dysfunction and excessive total body edema, which in turn may result in increased ventilatory and oxygen requirements and an inability to close the chest.

Many investigators have documented in clinical studies and experimental preparations that the levels of a

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Read at the Seventy-eighth Annual Meeting of The American Association for Thoracic Surgery, Boston, Mass, May 3-6, 1998.

Received for publication April 6, 1998; revisions requested July 9, 1998; revisions received Oct 7, 1998; accepted for publication Nov 6, 1998.

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0022-5223/99 \$8.00 + 0 12/6/95759

number of inflammatory mediators are elevated during and after CPB.⁴⁻⁶ Although the significance of the elevated levels is uncertain, it is clear that a substantial inflammatory response is occurring. Efforts have also been made to develop methods for reducing the inflammatory reaction caused by CPB in hopes that this will reduce bypass-induced morbidity. These have included the use of antibodies to specific cytokines or adhesion molecules,^{7,8} soluble complement receptor,⁹ and biocompatible coatings for the extracorporeal circuit.¹⁰ Some of these strategies, including the use of glucocorticoids, have been shown to reduce the levels of circulating inflammatory mediators such as interleukins 6 and 8, C3a, and tumor necrosis factor- α (TNF- α) after CPB, but few have correlated reduced levels of cytokines with improved outcome. In addition, most of the strategies tested would be limited in their clinical application because of the lack of general availability or the prohibitive expense of the proposed agent or method, and not to mention mechanisms too specific to inhibit the redundant inflammatory cascade.

Clinical and laboratory experience has suggested that the use of methylprednisolone sodium succinate given before CPB may improve the course of CPB, leading to less postoperative morbidity. This may have an impact on ventilator time, intensive care unit and hospital stays, and hospital costs. Methylprednisolone has the advantage of being readily available and inexpensive. Compared with many of the other selective anti-inflammatory agents that have been studied, it also offers the advantage of inhibiting the inflammatory response at many levels. Anecdotal evidence and several studies suggest that, when used, methylprednisolone is frequently administered either just before CPB or into the extracorporeal circuit prime only. However, on the basis of the mechanism of action of methylprednisolone, a matter of several hours should be required before its peak effect is realized.

We hypothesized that administering methylprednisolone before a cardiac operation would reduce the inflammatory response to CPB in infants and that this effect would cause a measurable improvement in pulmonary function after bypass. Furthermore, we believed that administering methylprednisolone before the operation would be more beneficial than giving it in the circuit prime only. This laboratory study used an infant pig model to test these hypotheses.

Material and methods

Animal preparation. One-week-old piglets were used for all experiments with the approval of the institution's Animal Care and Use Committee. All animals were treated according to "Guide for the Care and Use of Laboratory Animals"

(National Institutes of Health publication No. 85-23, revised 1985). Animals were premedicated with intramuscular ketamine hydrochloride (20 mg/kg) and acepromazine maleate (1 mg/kg). After endotracheal intubation and establishment of an intravenous line, intravenous boluses of fentanyl citrate (100 μ g/kg) and pancuronium bromide (0.3 mg/kg) were administered, and mechanical ventilation was begun with an infant pressure cycled ventilator (Sechrist Industries, Anaheim, Calif). Ventilator settings were adjusted to maintain a PO_2 of 200 to 250 mm Hg and a P_{CO_2} of 35 to 45 mm Hg. Blood gases and hematocrit were measured with a GEM-Stat Blood Gas/Electrolyte Monitor (Mallinckrodt Sensor Systems Inc, Ann Arbor, Mich). Anesthesia was maintained with a fentanyl citrate infusion (100 μ g/kg per hour).

An 18-gauge catheter was inserted into the right femoral artery for pressure and blood gas monitoring. A median sternotomy was performed, and a perivascular ultrasonic pulmonary artery flow probe (Transonics, Inc, Ithaca, NY) was fitted for cardiac output measurement. Micromanometers (Millar Instruments, Houston, Tex) were inserted into the left atrium, pulmonary artery, and right ventricle.

Experimental design. Piglets were initially divided into 2 groups. The control group received no additional premedication before CPB. The experimental group (Preop-MP) received 30 mg/kg of methylprednisolone intravenously both 8 hours before the operation and immediately after the induction of anesthesia (approximately 1.5 hours before CPB). A second experimental group (Prime-MP) received no methylprednisolone before the operation, but 30 mg/kg of methylprednisolone was added to the extracorporeal circuit prime. Animals from each group underwent identical instrumentation and were each subjected to CPB and 45 minutes of deep hypothermic circulatory arrest. After deep hypothermic circulatory arrest, the animals were rewarmed and weaned from CPB.

Data collection. After instrumentation was complete and the animals were observed for hemodynamic stability, baseline data were collected that included an arterial blood gas, arterial blood pressure, heart rate, and ventilator settings. Data from the flow probe and micromanometers were digitized at 500 Hz for 8 seconds and stored as a computer file for later analysis. Static pulmonary compliance was measured with a pediatric pulmonary function laboratory (Sensor-medics, Inc, Yorba Linda, Calif). The same data were again collected at 30 and 60 minutes after discontinuation of CPB.

Each computer file containing pressure and flow data was analyzed with custom software and a personal computer. Left atrial pressure (LAP), mean pulmonary artery pressure (MPAP), cardiac output, and pulmonary vascular resistance (PVR) were derived for each experimental stage. The cardiac output was indexed by dividing by the animals' preoperative body weight.

Each animal was weighed to the nearest 10 g both before and after the experiment to determine total body weight gain. Peripheral lung biopsy specimens weighing 1 to 2 g were taken from the anterior right middle lobe of each animal at the conclusion of each experiment. The lung biopsy specimens were weighed wet, then desiccated in a warming oven,

Table I. Hemodynamic data

Variable	Stage	Control	Prime-MP	Preop-MP
LAP (mm Hg)	Baseline	5.2 ± 2.1	4.1 ± 2.1	4.7 ± 2.6
	Post 30	4.2 ± 1.6	3.8 ± 1.7	4.4 ± 1.5
	Post 60	4.3 ± 1.7	3.1 ± 1.6	3.9 ± 1.3
MPAP (mm Hg)	Baseline	8.0 ± 4.3	9.6 ± 1.9	6.7 ± 3.0
	Post 30	30.3 ± 3.6	19.5 ± 7.0	12.2 ± 2.4
	Post 60	29.7 ± 4.3	19.6 ± 5.9	17.2 ± 5.4
Cardiac index (mL · min ⁻¹ · kg ⁻¹)	Baseline	112 ± 21	105 ± 23	126 ± 28
	Post 30	87 ± 9	93 ± 12	110 ± 38
	Post 60	76 ± 18	69 ± 24	96 ± 31
Heart rate (beats/min)	Baseline	163 ± 30	169 ± 22	124 ± 15
	Post 30	176 ± 25	170 ± 21	147 ± 15
	Post 60	189 ± 28	166 ± 29	151 ± 17

Values expressed as mean ± standard deviation.

and reweighed dry to determine lung water content. A careful record was kept of the extracorporeal circuit fluid balance for each animal.

CPB. The extracorporeal circuit included a Minimax Plus Hollow Fiber Oxygenator/Heat Exchanger (Medtronic, Inc, Anaheim, Calif) and a standard roller pump (Stöckert-Shiley, Irvine, Calif). It was primed with fresh donor pig whole blood and lactated Ringer's solution mixed to obtain a hematocrit of 23% to 25%, 2000 U heparin sodium, 400 µg fentanyl citrate, 2 mg pancuronium bromide, and sodium bicarbonate to achieve a pH of approximately 7.40. The donor blood was filtered with a high efficiency leukocyte removal filter (model RCXLTM2; Pall Biomedical, Inc, Fajardo, Puerto Rico).

After instrumentation, baseline data acquisition, and systemic heparinization (300 units/kg), the aortic root and right atrial appendage were cannulated through purse-string sutures. Normothermic CPB was established at a flow rate of 100 mL · kg⁻¹ · min⁻¹. The animal was perfusion cooled to 18°C over 20 minutes then exsanguinated to the cardiectomy reservoir. After 45 minutes of circulatory arrest, the animal was reperfused and rewarmed over approximately 40 minutes to normothermia. After reaching 36°C, CPB was discontinued. During cooling and rewarming, alpha-stat strategy was used to manage arterial blood gases.

Statistical analysis. Variables measured at only 1 point in the study (eg, lung water content) were made by single factor analysis of variance. Post-hoc comparisons between the groups were made by unpaired *t* test with the Bonferroni modification. All variables measured over the course of the experiment were compared between groups by 2-way repeated measures of analysis of variance. Post-hoc comparisons, where appropriate, were made by the Scheffé test. Results for each group are expressed as the mean ± SD.

Results

Pulmonary hemodynamics. There were no differences between the groups at baseline in cardiac index (*P* = .32), LAP (*P* = .70), MPAP (*P* = .39), or PVR (*P* = .13), although PVR tended to be lower and cardiac

index tended to be higher in the Preop-MP group than in the other 2 groups (Table I). There were no significant differences in LAP between any of the groups over the course of the study (*P* = .63).

MPAP was significantly higher than baseline at 30 minutes and 60 minutes after CPB in both the control group (*P* < .0001 for both) and the Prime-MP group (*P* = .01 and .03, respectively) but not in the Preop-MP group. The increase in MPAP over the course of the study was significantly greater in the control group than in either experimental group (*P* = .00001 vs Preop-MP and *P* = .0004 vs Prime-MP) but was also significantly greater in the Prime-MP group than in the Preop-MP group (*P* = .05).

PVR was significantly higher at 30 and 60 minutes after CPB compared with baseline in the control group (*P* = .0002 for both) and the Prime-MP group (*P* = .05 and *P* = .0002, respectively) but was not significantly higher than baseline in the Preop-MP group. The increase in PVR after CPB was greater in both the control group (*P* = .007) and the Prime-MP group (*P* = .04) compared with the Preop-MP group. There was no difference in the increase in PVR between the control and Prime-MP groups. These data are shown in Fig 1.

The cardiac index was significantly lower than baseline at 60 minutes after CPB in the control (*P* = .02) and prime (*P* = .002) groups, but not in the Preop-MP group.

Pulmonary function. There were no significant differences between the groups in static pulmonary compliance (*C*_{stat}) or alveolar-arterial oxygen gradient (A-a gradient) at baseline. *C*_{stat} was significantly worse (lower) at 30 and 60 minutes after bypass in the control (*P* < .00001 for both) and Prime-MP (*P* = .004 and .002, respectively) groups but not in the Preop-MP group. The decrement in *C*_{stat} over the course of the study was significantly different between the control and Preop-

Fig 1. The PVR is shown for each group at each experimental stage. PVR is significantly higher than baseline in the control and Prime-MP groups. PVR in the Preop-MP group is significantly lower compared with the control group at 30 minutes (*Post 30*) and at 60 minutes after CPB (*Post 60*). * $P < .05$; † $P = .013$; ‡ $P = .036$.

Fig 2. The static pulmonary compliance is shown for each group at each experimental stage. Measurements were made at before CPB (*baseline*) and at 30 minutes (*Post 30*) and 60 minutes (*Post 60*) after CPB. The C_{stat} is significantly lower than baseline at *Post 30* and *Post 60* in the control and the Prime-MP groups, but not in the Preop-MP group. * $P < .0001$; † $P = .004$; ‡ $P = .002$.

MP groups ($P = .016$). The Prime-MP group, which fell between the control and Preop-MP groups, did not differ significantly from either group with respect to the change in C_{stat} over time. These data are shown in Fig 2.

The A-a gradient was significantly higher than baseline at 30 and 60 minutes after CPB in the control group ($P = .0001$ for both). In the Prime-MP group, the A-a gradient only tended toward higher than baseline at 30 minutes after CPB ($P = .07$) but was significantly greater at 60 minutes after CPB ($P = .02$). In the Preop-MP group, the A-a gradient after CPB was not significantly higher than baseline. With respect to the increase

Fig 3. The A-a gradient is shown for each group at each experimental stage. In the control group, the A-a gradient was significantly higher than before CPB (*baseline*) and at 30 minutes (*Post 30*) and 60 minutes (*Post 60*). In the Prime-MP group, the A-a gradient was significantly higher than baseline at *Post 60*, although in the Preop-MP group, A-a gradient was not significantly higher than baseline at either stage after CPB. * $P = .0001$; † $P = .02$.

Fig 4. The net extracorporeal circuit fluid balance is shown for each group. Each group had a positive ending balance. The pump balance for the Preop-MP group was significantly lower than that of the control group. The balance for the Prime-MP group was intermediate between the control and Preop-MP groups, but the differences did not reach statistical significance. * $P = .001$; † $P = .07$ versus control and .05 versus Preop-MP.

in the A-a gradient over the course of the study, there was a statistically significant difference between the control and Preop-MP groups ($P = .0003$) and the control and Prime-MP groups ($P = .01$). The A-a gradient in the Prime-MP group increased relative to the Preop-MP group, but this difference was not statistically significant ($P = .07$). These data are shown in Fig 3.

Weight gain/lung water. There was no significant difference in preoperative body weight between the groups. The body weights in each group were signifi-

Table II. Body weight and lung water content data

Variable	Stage	Control	Prime-MP	Preop-MP
Body weight (kg)	Baseline	2.5 ± 0.2	2.3 ± 0.3	2.5 ± 0.4
	Post	2.9 ± 0.2*	2.7 ± 0.3*	2.5 ± 0.4†
Water weight gain/body weight (g/kg)	Post	160 ± 27‡	150 ± 30§	96 ± 14
Lung water (%)	Post	86.4 ± 1.5	83.9 ± 0.7¶	82.9 ± 0.5

**P* < .001 vs baseline.

†*P* = .003 vs baseline.

‡*P* = .003 vs Preop-MP.

§*P* = .01 vs Preop-MP.

^{||}*P* = .001 vs Preop-MP.

¶*P* = .026 vs Preop-MP.

cantly higher at the end of the study than the preoperative body weights (Table II). This was attributed to an increase in total body water. The animals in the Preop-MP group gained significantly less water weight per kilogram than the control group (96 g/kg vs 160 g/kg; *P* = .003) and the Prime-MP group (96 g/kg vs 150 g/kg; *P* = .01). There was no significant difference between the control and Prime-MP groups (Table II).

There was also a significant difference between the groups in lung water content at the end of the study (*P* = .0002). The lungs in the Preop-MP group contained significantly less water than the control group (82.9% vs 86.4%; *P* = .001) and the Prime-MP group (82.9% vs 83.9%; *P* = .026). There was no significant difference in lung water content between the Preop-MP and Prime-MP groups.

Pump balance. Each group had a net positive pump balance at the end of CPB. There was a significant difference between the groups in the magnitude of the positive pump balance (*P* = .002). The control group had a significantly more positive balance (per body weight) than the Preop-MP group (120 mL/kg vs 61 mL/kg; *P* = .0010). The Prime-MP group fell between the control and Preop-MP groups (94 mL/kg) and was significantly different from the Preop-MP group (*P* = .053) but not the control group (*P* = .070). These data are shown in Fig 4.

Discussion

Few would debate that CPB causes a substantial inflammatory response. In infants, 2 of the most morbid manifestations of this host response are pulmonary dysfunction and increased total body water gain. These can result in longer mechanical ventilation requirements and longer intensive care unit stays and in pulmonary and cardiac dysfunction and may necessitate delayed chest closure. All of these increase the likelihood of complications and increase hospital costs. Numerous techniques have been investigated with the

goal of finding one that reduces this inflammatory response to CPB. A desirable method would be one that is not only effective, but available, relatively easy to implement, and not prohibitively expensive and that works at multiple levels of the inflammatory cascade.

Studies have shown that circulating levels of various cytokines (interleukin-6 [IL-6], IL-8, IL-10, tumor necrosis factor- α , C-reactive protein) and products of complement activation are all elevated in response to CPB. Because of the strong anti-inflammatory effect of glucocorticoids, it is logical to assume that the administration of these agents would blunt this inflammatory response. Many studies have in fact been done to investigate the role of steroids in ameliorating the inflammatory response to CPB. The earliest of these studies¹¹⁻¹³ used relatively crude or nonspecific measures such as graft flows, urine output, and chest radiograph appearance to evaluate the effect of glucocorticoids administered before or during CPB. Although these studies suggested a beneficial effect from glucocorticoid administration, this received little attention in the literature until recently.

With the discovery of cytokines as inflammatory mediators and the ability to measure many of these molecules, investigators were able to document the ability of glucocorticoids to blunt the CPB-related increases in circulating levels of many of these inflammatory mediators, including IL-6, IL-8, TNF- α , CD11b, leukotriene B₄, and tissue plasminogen activator.^{4,6,14-19} Most of these studies, however, fail to correlate measures of physiologic injury with the reduction of cytokine levels. It is not clear, for example, if reducing the circulating level of TNF- α by 50% is sufficient to prevent severe postoperative pulmonary hypertension or an increase in total body edema and therefore to improve outcome. Numerous studies suggest that lung injury is a result of inflammatory mediators. In 2 studies by Brigham,^{21,22} lung injury in a model of endotoxemia was correlated with increased levels of various cytokines. These stud-

ies suggest that the administration of corticosteroids is more effective in ameliorating this insult than either cyclooxygenase inhibitors or leukocyte depletion.

These observations led us to design this study that used methylprednisolone as a potent anti-inflammatory agent and to measure pulmonary function both as an indicator of postbypass inflammation and of outcome. Smith,²³ in a study of butylated hydroxytoluene-induced lung injury in mice, suggested that the timing of the dose of steroids is important in producing an effect. In light of this observation we found it surprising that in most studies steroids were given in close proximity to CPB. Glucocorticoids exert their anti-inflammatory effects by a mechanism of action that involves binding to an intracellular receptor. The steroid-receptor complex is then transported into the nucleus where it affects mRNA transcription and, consequently, protein translation. Because alterations in the translation of specific proteins is required, it is unlikely that the maximum effect of the administered steroid would be realized immediately. Despite this, virtually all studies examining the effect of glucocorticoids on the inflammatory response to CPB involve administration of the drug only shortly before the inflammatory stimulus—usually either on induction of anesthesia, only minutes before CPB, or into the CPB pump prime itself—and sometimes not until after perfusion had commenced.^{4,11,19,24-27} Because the activation of blood elements occurs when they contact the artificial surfaces of the extracorporeal circuit, it is logical to assume that to have an optimal effect, glucocorticoids should be administered hours before the initiation of CPB.

Our study is unique in that it uses a neonatal model, that steroids are given in 2 doses beginning 8 hours before the operation, and that specific measures of pulmonary function are taken. The dosing regimen was somewhat arbitrary but was based on the presumed need to give at least 1 dose of methylprednisolone sufficiently early that its maximal effects would be achieved. The adverse effects of CPB in this model (including the highly reproducible severe pulmonary hypertension and associated poor lung compliance) and extracellular fluid accumulation are clinically similar to what is sometimes observed in infants undergoing CPB. In virtually every variable measured in this study, a protective effect was observed in the Preop-MP group, that is from administering high-dose methylprednisolone beginning 8 hours before the operation. In addition, in the case of each parameter measured, the outcome for the Prime-MP group was intermediate between the control and Preop-MP groups, indicating that administering methylprednisolone in the pump

prime only (correlating with the onset of the inflammatory stimulus) conferred a beneficial effect, but that the maximum benefit of the glucocorticoid treatment is not achieved with this dosing strategy. The mechanism responsible for the partial salutary effect observed in the Prime-MP group is not clear but may involve the immediate release of immunomodulating substances after receptor binding.

One limitation of the current study is that inflammatory mediators were not measured to correlate with the physiologic indicators of the inflammatory response to CPB. Although this is somewhat more difficult in the pig than in human beings or mice because of the availability of reagents, work is in progress to document the levels of IL-6 and TNF- α . In addition, some may argue that the risks of high-dose glucocorticoid administration may outweigh the benefits. Mayumi and colleagues²⁸ suggest that the combination of CPB and high-dose methylprednisolone is immunosuppressive based on blood cell count and cytokine production. There are also concerns about gastric ulceration. However, there are no data to suggest that patients receiving steroids and undergoing CPB have higher infectious complications, and it is generally believed that administration of a single high dose of glucocorticoids does not carry the risks of wound-healing complications and ulcerogenesis as long-term use does. An additional limitation of our study is that it was not randomized or blinded to the dosing regimen. The reason for this was that the experiment was first conducted with just the control and Preop-MP groups. It was clear even before the data were analyzed that the experimental group tolerated CPB better than the control group, so a second experimental group was added to determine whether differences existed between the novel and more conventional dosing strategies. The findings must be considered with this fact in mind.

In summary, the administration of high-dose methylprednisolone 8 hours and immediately before operations involving CPB in infants offers a relatively inexpensive and readily available means of protection from the inflammatory response to CPB compared with no treatment. Furthermore, the use of this dosing strategy is superior to one in which methylprednisolone is administered at or around the time of the inflammatory stimulus of CPB. The use of this strategy may substantially reduce morbidity after CPB and hospital costs, especially if used in selected high-risk patients.

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Discussion

Dr Carl L. Backer (Chicago, Ill). Our experience at Children's Memorial Hospital used a slightly intermediate technique where we administered intravenous dexamethasone (Decadron) 1 to 2 hours before CPB. We found that this resulted in findings similar to yours. There was a decrease in inflammatory mediator release of both IL-6 and tumor necrosis factor and also an improved clinical course as evidenced by less postoperative fever, less fluid administration, and fewer days of ventilation.

If you had to pick either the single dose in the prime or an oral dose preoperatively, which would you choose? I noted that in several of the results, the dose in the prime did significantly improve the outcome.

What do you think about administering the dexamethasone 1 to 2 hours before CPB, which is relatively easy to facilitate?

Dr Lodge. If I had to choose between preoperative oral dose and an intravenous dose, which was given only 1 or 2 hours before bypass, I would probably choose the oral dose given 8 hours before bypass, simply based on the results that we have seen here and the known mechanism of action of steroids, which then take probably 48 hours to reach peak effect.

The answer to your second question is relatively similar, but there is no question that our results showed some benefit to giving steroids in the pump prime. I would expect that similar results would be observed if an intravenous dose was administered, say, at the induction of anesthesia. On the basis of those data, there is some benefit to doing that. However, if it is feasible, a dose that was begun significantly before the induction of anesthesia (the timing that we used was 8 hours) would be more beneficial.

Dr John H. Calhoon (*San Antonio, Tex*). We have been using steroids while the patient is undergoing bypass for years for children's hearts and intraoperatively during our transplantations. In San Antonio (after a fortuitous visit to Duke about 8 months ago), we started using the steroids the night before as they had been doing clinically. We, too, like Dr Backer's group in Chicago, saw a dramatic decrease in postoperative weight gain and ventilator and fluid requirements.

I think this article is going to be an important one. It should make us all think carefully about our approach to CPB conduct and probably transplantation with its attendant ischemia-reperfusion response.

Why is there an intermediate response with steroids given at the time of pump institution? Could you share with us any of the clinical results that you all have started having?

Dr Lodge. The effect observed in the intermediate group was inconsistent, but I think the data show that there was some benefit to administering steroids in the prime. There may be two reasons for that. First, more recent work on the mechanism of action of steroids has shown that there may be some membrane receptors that may mediate some of the earlier effects. In addition, steroids are thought to have a membrane-stabilizing effect and most important, in this case perhaps, stabilizing lysosomes that can release toxic products.

As far as the clinical data go, Dr Jagers has actually been collecting some of these data and using this strategy in some of the patients that have undergone operation recently at Duke. His results preliminarily show significant decreases in ventilator time and the need for delayed chest closure, which translated into decreased intensive care unit length of stays and decreased overall costs.

Dr Bradley Allen (*Chicago, Ill*). These findings are similar to those of our recent study, which demonstrated that the inflammatory response in neonates could be decreased by removing white cells from the CPB circuit. If I understood your presentation correctly, the group that received preoperative steroids (Preop-MP) actually received 2 doses of methylprednisolone, whereas the other steroid group (Prime-MP) received only 1 dose. Therefore how do you know that it is the timing of the steroid infusion and not the fact that you gave twice as much methylprednisolone to the Preop-MP group?

Dr Lodge. We do not know that. That is a good question. I think it is worth looking into some of that information, specifically a dose-response curve and the possibility of giving a dose that starts 8 hours before the operation in addition to a dose that is given right before the operation, compared with a group that receives 1 dose right before the operation. We do not have those data and did not include that group in our study.