Traditionally, corticosteroids have been administered to patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) to ward off detrimental physiologic alterations associated with activation of the systemic inflammatory response, yet few well-controlled investigations exist, and use of these drugs in this setting remains controversial. This review article critically examines the results of clinical investigations in this area, and certain conclusions are suggested. The constellation of findings indicate that corticosteroids offer no clinical benefits to patients undergoing cardiac surgery with CPB and in fact may be detrimental. Further directions for clinical research in this area are also suggested.

Key words: cardiopulmonary bypass; corticosteroids; systemic inflammatory response syndrome

Abbreviations: CABG = coronary artery bypass grafting; CI = cardiac index; CPB = cardiopulmonary bypass; IL = interleukin; P(A-a)O\textsubscript{2} = alveolar-arterial oxygen gradient; SIRS = systemic inflammatory response syndrome; SVR = systemic vascular resistance; \dot{V}O\textsubscript{2} = oxygen consumption

Cardiopulmonary bypass (CPB) exposes blood to large areas of synthetic materials that trigger the production and release of numerous chemotactic and vasoactive substances.\textsuperscript{1,2} This ensuing abnormal whole-body inflammatory response can complicate the postoperative period by causing major organ dysfunction. Traditionally, corticosteroids have been administered to patients undergoing cardiac surgery to ward off these detrimental physiologic alterations, yet few well-controlled investigations exist, and use of these drugs in this setting remains controversial.\textsuperscript{3–48} This review article critically examines the results of clinical investigations in this area. Well-controlled clinical investigations\textsuperscript{3,5,10} (prospective, randomized, double-blind, placebo-controlled) indicate that use of corticosteroids in this setting causes detrimental postoperative hemodynamic, pulmonary, and metabolic alterations and prolongs postoperative tracheal extubation time. Thus, new evidence indicates that routine administration of corticosteroids not only offers no clinical benefits to patients undergoing cardiac surgery with CPB, their use in this setting may in fact be contraindicated.\textsuperscript{3,5,10}

**Detrimental Physiologic Effects of CPB**

It has been known for many years that CPB induces a systemic inflammatory response syndrome (SIRS) in patients following cardiac surgery that can lead to major organ injury and postoperative morbidity.\textsuperscript{1,2} Initiation of CPB sets in motion an extremely complex and multifaceted response involving complement activation (both classic and alternative pathways) along with activation of platelets, neutrophils, monocytes, and macrophages, thus initiating the coagulation, fibrinolytic, and kallikrein cascades, increasing blood levels of various endotoxins and cytokines (interleukins [ILs]), tumor necrosis factor, etc.), and increasing endothelial cell permeability. Transvascular migration of activated leukocytes occurs into tissues; various proteases and neutrophil elastase are released, which causes additional vascular and parenchymal damage. The ensuing
SIRS is further amplified by release of additional mediators (endotoxins, cytokines, etc.).

The basic physiologic insults caused by CPB have been associated with major postoperative morbidity, including neurologic dysfunction, pulmonary dysfunction, renal dysfunction, and/or hematologic abnormalities. Additional clinical manifestations associated with the SIRS include increased metabolism (fever), fluid retention, myocardial edema, and detrimental hemodynamic alterations.

Over the years, a wide variety of anti-inflammatory treatment options have been used in patients subjected to CPB in hopes of attenuating the SIRS, including leukocyte depletion techniques, neutrophil adhesion molecule blockade, heparin coating of CPB circuitry, and, most recently, use of monoclonal antibodies directed specifically against various inflammatory mediators. Although results from animal work appear promising, definite clinical benefit in humans has yet to be demonstrated. Corticosteroids, potent anti-inflammatory agents that possess multi-inhibitory effects on numerous components of the inflammatory response, represent an appealing treatment option in this scenario.

**Pharmacokinetics and Pharmacodynamics of Corticosteroids**

Two types of corticosteroids exist: mineralocorticoids (primarily regulate electrolyte homeostasis) and glucocorticoids (primarily regulate carbohydrate metabolism).49 The prototype mineralocorticoid is desoxycorticosterone, and the prototype glucocorticoid is cortisol. It is must be emphasized that the biological characteristics of corticosteroids range over a spectrum from that of a strictly mineralocorticoid type to that of a strictly glucocorticoid type. Cortisone was the first corticosteroid used (around 1950) for its anti-inflammatory effect. Subsequent modification and manipulation of structure has yielded a wide variety of synthetic analogs with an increased ratio of anti-inflammatory effects to electrolyte and metabolic effects. Organic chemists have synthesized a bewildering number of such modified corticosteroids that exhibit substantial anti-inflammatory properties yet do not initiate serious electrolyte disturbances even at large doses. Of these synthetic corticosteroid analogs, methylprednisolone and (to a much lesser extent) dexamethasone represent the two most commonly utilized agents in patients subjected to CPB in hopes of attenuating the SIRS.

Changes in corticosteroid molecular structure may bring about changes in biological potency as a result of alterations in absorption, protein binding, rate of metabolic transformation, rate of excretion, ability to traverse membranes, and/or intrinsic effectiveness of the molecule at its site of action. In plasma, a large percentage of corticosteroid is reversibly bound to two proteins under normal circumstances (corticosteroid-binding globulin and albumin). Globulin has high affinity yet low total binding capacity, while albumin has low affinity yet relatively large binding capacity. Consequently, at low or normal concentrations of corticosteroids, most of the hormone is bound to globulin. When the amount of corticosteroid is increased, concentrations of both free and albumin-bound steroid increase with little change in the concentration of that bound to globulin. The free corticosteroid, as opposed to the protein-bound corticosteroid, is biologically active and available for hepatic metabolism and renal excretion. Corticosteroids, like other steroid hormones, are thought to exert their influence by controlling the rate of synthesis of proteins by stimulating transcription of RNA.

The physiologic effects of corticosteroids are numerous and widespread (Table 1). They influence carbohydrate metabolism, protein metabolism, lipid metabolism, electrolyte and water balance, the cardiovascular system, skeletal muscle, the CNS, the formed elements of blood, and they possess anti-inflammatory properties and affect other organs and tissues in a wide variety of ways. In essence, corticosteroids endow the organism with the capacity to resist many types of noxious stimuli and environmental change. The actions of corticosteroids are often complexly related to functions of other hormones, and a given dose of corticosteroid may by physiologic or pharmacologic depending on the environment and activities of the organism.

Corticosteroids have evolved to protect glucose-dependent cerebral functions by stimulating formation of glucose, diminishing its peripheral utilization, and promoting its storage as glycogen. Glucocorticoids promote gluconeogenesis by both peripheral and hepatic actions. Corticosteroids also promote redistribution of body fat and facilitate the effect of

<table>
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<th>Table 1—Functions Affected by Corticosteroid Treatment</th>
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<td>Carbohydrate metabolism</td>
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adipokineti
cs in adipose tissue. Mineralocorticoids act on the
distal tubules of the kidney to enhance reabsorption
of sodium ions from the tubular fluid into the
plasma, thus increasing urinary excretion of both
potassium and hydrogen ions. Physiologic conse-
quences include positive sodium balance, expansion
of extracellular fluid volume, normal or slight in-
crease in plasma sodium concentration, hypokale-
mia, and alkalosis. Glucocorticoids decrease absorp-
tion of calcium from the intestine and increase its
renal excretion, thus producing a negative balance of
the cation.

The cardiovascular effects of corticosteroids are
primarily secondary to consequences of regulation of
renal sodium ion excretion and volume shifts. Corti-
co
corticoid-induced hypertension may be the result
of prolonged, excessive sodium retention and/or
edema within the walls of arterioles (reducing their
lumina and increasing peripheral vascular resis-
tance). Another possibility is that salt retention, or
mineralocorticoids themselves, sensitize blood ves-
sels to pressor agents, in particular angiotensin and
catecholamines. Corticosteroids also exert important
actions on the various elements of the circulatory
system, including capillaries, arterioles, and myocar-
dium. In the absence of corticosteroids, there is
increased capillary permeability, inadequate vasomo-
tor response of small vessels, and reduction in
cardiac size and output.

When glucocorticoids are administered for pro-
longed periods of time in high doses (or endog-
енно secreted in large amounts), wasting of skel-
etal muscle occurs (the mechanism of which is
unknown). Corticosteroids can also affect the CNS in
a number of indirect ways, in particular via glucose
homeostasis, maintaining adequate circulation, and
electrolyte homeostasis. They may also have direct
effects, but these are as yet, poorly defined. An array
of reactions, varying in degree and kind, is observed
in patients administered glucocorticoids for therapeu-
tic purposes. Most patients respond with an

elevated mood, yet others exhibit euphoria, insom-
nia, restlessness, and increased motor activity. Some
patients may become anxious, depressed, or even
psychotic. Also, corticosteroids have been shown to
affect brain excitability and alter the EEG.

Glucocorticoids increase the hemoglobin and red-
cell content of blood, an effect that may be second-
ary to the capacity of these corticosteroids to retard
erythropagocytosis. Glucocorticoids also increase
the number of polymorphonuclear leukocytes in the
blood as a result of an increased rate of entrance into
the blood from the marrow and a diminished rate of
removal from the circulation. In contrast, lympho-
cyes, eosinophils, monocytes, and basophils in blood
decrease in number following administration of glu-
cocorticoids (secondary to redistribution, not de-
struction).

Cortisol and synthetic analogs of cortisol prevent/
suppress development of local heat, redness, swelling,
and tenderness by which inflammation is recog-
nized. At the microscopic level, inhibition of the
early phenomenon of the inflammatory process oc-
curs (edema, fibrin deposition, capillary dilatation,
migration of leukocytes into the inflamed area, and
phagocytic activity), as well as inhibition of late
phenomenon (capillary proliferation, fibroblast pro-
liferation, collagen deposition). Corticosteroids in-
hbit the inflammatory response whether the inciting
agent is radiant, mechanical, chemical, infectious, or
immunologic. It is this suppression of inflammation
and its consequences that have made corticosteroids
such valuable therapeutic agents (at times, lifesav-
ing). The anti-inflammatory effects depend on the
direct local action of the corticosteroids. The most
important factor in the anti-inflammatory effect of
glucocorticoids may be their ability to inhibit recruit-
ment of neutrophils and monocytes-macrophages
into the affected area. Neutrophils also have a
diminished tendency to adhere to capillary endothelial
cells in areas of inflammation. Glucocorticoids
also block the effects of migration inhibitory factor
(produced by activated lymphocytes) on macro-
phages. Thus, the movement of macrophages is no
longer impeded and they do not accumulate locally.
Low concentrations of glucocorticoids also inhibit
the formation of plasminogen activator by neutro-
phils. This enzyme converts plasminogen to plasmin,
which is thought to facilitate entrance of leukocytes
into areas of inflammation by hydrolysis of fibrin and
other proteins. Glucocorticoids may also inhibit
phospholipase A₂ and thereby diminish the release
of arachidonic acid from phospholipids. This de-
creases formation of prostaglandins, leukotrienes,
and related compounds such as prostaglandin endo-
deroxides and thromboxane, which play important
roles in chemotaxis and inflammation.

Corticosteroid toxicity can be caused by either
withdrawal of the drug or continued use of large
doses. Withdrawal of the drug may initiate signs and
symptoms of acute adrenal insufficiency. Continued
use of large doses of drug may lead to suppression of
the pituitary-adrenal axis, fluid and electrolyte dis-
turbances, hyperglycemia/glycosuria, increased sus-
ceptibility to infections, peptic ulcers, osteoporosis,
mopathy, behavioral disturbances, posterior sub-
capsular cataracts, arrest of growth, and Cushòing's
habitus, among others. However, a single dose of
corticosteroid, even a large one, is virtually without
harmful effects; and a few days of therapy, in the
absence of specific contraindications, is unlikely to produce harmful effects except at the most extreme doses.

**Historical Overview of Corticosteroid Use During CPB**

In the early 1960s, animal and human studies revealed the beneficial physiologic effects of corticosteroid administration in shock and sepsis models. Soon thereafter, investigators studied the effects of corticosteroid treatment during CPB, which at that time was thought to induce detrimental physiologic alterations similar to shock and sepsis. In dogs, Moses et al. reported that hydrocortisone (or its equivalent in methylprednisolone) attenuated detrimental physiologic effects (acidosis, elevated lactate levels, etc.) associated with extracorporeal perfusion and foreshadowed application to humans: “... it is conceivable that such administration before prolonged cardiopulmonary bypass in humans would be of value.” Subsequently, in humans, Replogle et al. reported that dexamethasone (“massive doses”) attenuated lysosomal enzyme release (β-glucuronidase) associated with CPB. In these early investigations, the specific corticosteroid chosen was empirical and the dose administered often massive. In the late 1960s, methylprednisolone became the drug of choice because of its anti-inflammatory potency and minimal tendency to induce sodium and water retention. An IV dose of 30 mg/kg was at this time deemed “optimal” because this amount was shown to be beneficial in clinical shock studies yet possesses no detrimental systemic effects when administered to a small group (n = 12) of healthy volunteers (no larger doses were studied, however).

A pivotal study was published in 1970 by Dietzman et al. who reported that methylprednisolone, 30 mg/kg, was effective in treating “low output syndrome” in dogs and humans following cardiac surgery. Specifically, in 98 dogs, methylprednisolone administration decreased systemic vascular resistance (SVR), increased cardiac index (CI), improved tissue perfusion, and increased survival from 22 to 65%. In 19 humans, following cardiac valve replacement, the same beneficial hemodynamic effects were observed. The authors justifiably conclude that on “the basis of this experimental and preliminary clinical evidence this treatment plan merits further investigation.”

The initial clinical investigation describing beneficial effects of methylprednisolone pretreatment prior to CPB appeared the following year, in 1971. Wilson et al. studied 50 patients undergoing CPB procedures and found that administration of methylprednisolone, 15 mg/kg, to patients prior to CPB prevented detrimental pulmonary vascular and alveolar architectural changes as assessed via perioperative lung biopsies (light microscopy, electron microscopy, enzyme studies) when compared to patients not receiving the drug. This encouraging initial investigation, along with others that followed in the 1970s, prompted many clinicians to routinely administer methylprednisolone, 30 mg/kg, to patients who were to undergo CPB. In the early 1980s, Thompson et al. assayed blood samples in patients receiving methylprednisolone, 30 mg, prior to CPB and found that plasma concentrations of the drug declined substantially (approximately 50%) with initiation of CPB (secondary to pump prime dilution), yet plasma concentrations were well maintained into the postoperative period if a repeat dose of 30 mg/kg was administered during initiation of CPB. Obviously, the plasma concentration of methylprednisolone that is “effective” is not known. Thus, by 1982, the dose of methylprednisolone was empirically set at 30 mg/kg twice and remains the standard to this day.

**Clinical Investigations in the 1970s**

Following the provocative studies published in 1970 by Dietzman et al. and in 1971 by Wilson et al. indicating that methylprednisolone administration may benefit patients undergoing CPB, many investigators began to focus on this area. Initial clinical results however, were not encouraging. Coffin et al. in 1975 prospectively administered methylprednisolone, 30 mg/kg, to 50 patients prior to CPB and compared perioperative data with 50 historical control subjects not receiving the drug. These investigators found that patients receiving methylprednisolone experienced longer periods of postoperative respiratory support (mean ± SD, 85 ± 181 h vs 27 ± 16 h, p = 0.05), a higher incidence of low cardiac output syndrome (24% vs 12%, p = 0.01), and higher operative mortality (22% vs 16%, not statistically significant) when compared to historical control subjects. However, the design of this study (prospective administration of drug, historical control subjects) does not eliminate the possibility that patients receiving methylprednisolone were at higher risk to begin with. In a small (31 patients) prospective study, Enderby et al. found no beneficial effects on perioperative pulmonary function (Paw, Paco2, alveolar-arterial oxygen gradient [P(A-a)O2], shunt) in patients receiving methylprednisolone, 30 mg/kg, when compared to patients not receiving the drug. In contrast to these discouraging studies, other clinical investigations revealed potential benefits of
methylprednisolone. A large (427 patients) observational study published in 1975 by Dietzman et al. revealed that, when compared to control patients, patients receiving methylprednisolone, 30 mg/kg, prior to CPB exhibited significantly less (p < 0.01) vasoconstriction (assessed via total peripheral resistance index, skin color, urine output) and significantly improved (p < 0.0005) perfusion flows (assessed via calibration curve of CPB arterial pump). Clinically, patients receiving methylprednisolone "were mentally alert earlier, required less pulmonary support, and left the ICUs earlier than the control group" yet no definitive data were presented. Two years later, in 1977, another large (150 patients) observational study by Rao et al. suggested that, when compared to control patients, patients receiving methylprednisolone, 1 g, prior to CPB exhibited a lesser incidence of myocardial infarction, cardiac arrhythmia, cerebral vascular accident, and pulmonary embolism perioperatively and had significantly better (p = 0.05) heart function at the end of CPB (rated as "good," "fair," or "poor" by the investigators) and significantly fewer (p = 0.05) total incidents of postoperative complications.

Stimulated by emerging data revealing an anti-ischemic effect of steroids on the infarcted area of myocardium in both animal and human investigations, Morton et al. published the first well-designed (prospective, randomized, double-blind, placebo-controlled) investigation involving methylprednisolone and CPB. They studied 95 patients undergoing coronary artery bypass grafting (CABG), with half receiving methylprednisolone (2 g or 30 mg/kg) immediately prior to induction of anesthesia and half receiving placebo at the same time. However, there was no difference between the two groups regarding ease of separation from CPB, postoperative blood levels of cardiac enzymes and isoenzymes, postoperative ECG evidence of myocardial infarction, or postoperative respiratory insufficiency. In contrast to this study, another clinical investigation published 2 years later, in 1978, revealed that methylprednisolone may possess cardioprotective properties. Fecht et al. studied 50 patients undergoing CABG, half receiving methylprednisolone (1 g early during CPB, 1 g late during CPB) and half receiving mannitol (600 mg twice, at the same two times). Perioperative myocardial biopsies with subsequent electron microscopy revealed that methylprednisolone helped preserve cardiac cellular integrity (less mitochondrial damage). Furthermore, patients receiving methylprednisolone exhibited improved bypass graft flow rates (56% higher), improved postoperative urine output (67% higher), and fewer postoperative chest radiographic abnormalities.

The decade of the 1970s closed with publication by Niazi et al. of the second well-designed investigation involving methylprednisolone and CPB. Ninety patients undergoing elective cardiac surgery were randomized to receive an injection prior to CPB: 30 patients received methylprednisolone, 30 mg/kg; 30 patients received dexamethasone, 6 mg/kg; and 30 patients received placebo therapy. Patients receiving methylprednisolone exhibited a higher mean CI before (p < 0.01) and after (p < 0.05) CPB as well as a lower mean total peripheral vascular resistance before (p < 0.10) and after (p < 0.20) CPB when compared to the other two groups. While there was no difference between the three groups regarding perioperative oxygen consumption (V̇O₂), postoperative blood levels of lactic acid were higher in patients receiving methylprednisolone (p < 0.005), a finding the authors attributed to improved microcirculatory flow ("washout" phenomenon). Patients receiving dexamethasone behaved no differently than patients receiving placebo regarding all important perioperative physiologic variables.

**Clinical Investigations in the 1980s**

The decade of the 1980s began with publication by Toledo-Pereyra et al. of a relatively large (95 patients), well-designed investigation involving adult and pediatric patients undergoing a wide variety of cardiac surgeries. Forty-seven patients randomly received methylprednisolone, 30 mg/kg, seven times perioperatively: 1 h preoperatively, 5 min prior to CPB, immediately after CPB, and then every 6 h for the next 24 h. Forty-eight patients randomly received placebo in an identical, blinded manner. There was no difference between the two groups regarding perioperative laboratory data (arterial blood gases, serum sodium, serum potassium), perioperative complications (urinary tract infection, fever, pneumonia, stress ulcer, sepsis), or discharge day (methylprednisolone group, 15.5 ± 8.6 days [mean ± SD]; placebo group, 16.7 ± 13.1 days). However, the methylprednisolone group had significantly less deaths than the placebo group (two deaths vs eight deaths, respectively; p < 0.05), a finding the authors were unable to explain.

Two investigations by the same group from London in the early 1980s revealed the importance of administering a supplemental dose of methylprednisolone with initiation of CPB to compensate for hemodilution (and thus maintain blood levels of the drug). In the first observational investigation, Thompson and Brodbent found that, when compared to patients receiving saline solution, patients...
receiving methylprednisolone, 30 mg/kg, prior to CPB exhibited significantly increased ($p < 0.001$) $\text{VO}_2$ immediately following CPB and significantly increased ($p < 0.05$) serum phosphate levels in the immediate postoperative period. The authors attributed the increased $\text{VO}_2$ associated with methylprednisolone to improved tissue perfusion because at this time there was no difference between groups regarding CI.36 Additionally, there was no difference between groups regarding perioperative hemoglobin 2,3-diphosphoglycerate levels, standard partial oxygen pressure values, or oxygen availability.36 In a subset of four patients receiving methylprednisolone, plasma radioimmunoassays revealed a rapid decline in drug levels (1 to 2 h after administration) that was further exacerbated with initiation of CPB.36 The second observational study by the same group revealed that plasma levels of methylprednisolone were well maintained throughout CPB if two doses were administered (30 mg/kg after anesthesia induction and 30 mg/kg at CPB initiation).34 However, marked differences in plasma levels of methylprednisolone were observed between individual patients 5 min after administration of the initial injection, despite a standardized, weight-related dose (range, 140 to 330 $\mu$g/mL).34 As with their previous study, there was no difference between the methylprednisolone and placebo groups regarding perioperative hemoglobin 2,3-diphosphoglycerate levels, standard partial oxygen pressure values, or CI.34

In the early 1980s, important research performed at the University of Alabama in Birmingham revealed the pivotal role that complement activation plays in the basic physiologic insults caused by CPB.60,61 These investigators discovered that initiation of CPB was associated with complement activation, neutrophilia, transpulmonary neutropenia, and pulmonary-vascular sequestration of complement-associated granulocytes, and theorized that the major postoperative morbidity associated with CPB (neurologic dysfunction, pulmonary dysfunction, renal dysfunction, and/or hematologic abnormalities) was related in part to complement activation.60,61 Subsequently, a majority of the investigations involving methylprednisolone and CPB in the 1980s focused on complement activation. Many small observational studies29,30,35,38 involving adult and pediatric patients during this time indicated that a single dose of methylprednisolone, 30 mg/kg, prior to CPB was unable to prevent complement activation associated with CPB. Another small observational study also revealed that higher doses suggested by studies by Boscoe et al33 (30 mg/kg after anesthesia induction and 30 mg/kg at CPB initiation) were unable to prevent complement activation associated with CPB. One investigation actually hinted that methylprednisolone, 30 mg/kg, may actually increase complement activation.32 However, two studies did suggest that methylprednisolone may confer benefits despite inability to inhibit complement activation.29,30 One revealed that methylprednisolone may be able to attenuate complement-mediated neutrophil activation (assessed in vitro and in vivo) associated with CPB.30 The other study revealed that, when compared to control patients, patients receiving methylprednisolone exhibited significantly increased ($p < 0.01$) postoperative blood granulocyte levels (indicating less complement-mediated aggregation and/or adherence) and significantly decreased ($p < 0.01$) postoperative bronchial lavage fluid granulocyte levels (indicating less alveolar influx of granulocytes).29

However, two investigations in the late 1980s revealed that methylprednisolone may inhibit complement activation associated with CPB and bubble oxygenators.28,31 Cavarocchi et al31 in 1986 randomly divided 91 patients undergoing a wide variety of cardiac surgeries into three groups: 30 patients received bubble oxygenators, 31 patients received bubble oxygenators and methylprednisolone (30 mg/kg prior to CPB), and 30 patients received membrane oxygenators. The two groups receiving methylprednisolone or membrane oxygenators behaved similarly; both groups, when compared to the bubble oxygenator group, exhibited significantly decreased ($p < 0.0001$) complement activation and significantly decreased ($p < 0.0001$) transpulmonary leukocyte sequestration associated with CPB.31 Another small observational study using bubble oxygenators revealed that, when compared to control subjects, patients receiving methylprednisolone, 30 mg/kg, prior to CPB exhibited significantly decreased ($p < 0.01$) complement activation and significantly increased ($p < 0.01$) blood levels of circulating endotoxins during CPB.28 The issue regarding bubble oxygenators vs membrane oxygenators should be emphasized. Many of the older studies involving corticosteroids and CPB utilized bubble oxygenators, whereas the current standard of practice is to utilize membrane oxygenators. There is no doubt that bubble oxygenators possess greater capability of inducing the SIRS associated with CPB,1,2 and this fact should be accounted for when analyzing and interpreting studies involving corticosteroids and CPB.

**Clinical Investigations From 1990 to the Present**

Numerous investigations3–27 during the last 11 years have explored the potential clinical benefits of routine administration of methylprednisolone to patients un-
derng undergoing cardiac surgery with CPB. A fair proportion of these investigations have been prospective, randomized, double-blind, placebo-controlled clinical trials. Most of the clinical investigations in the early 1990s continued to focus on the potential ability of methylprednisolone to attenuate the SIRS associated with CPB. Most recent clinical investigations continue to assess the effects of the drug on the SIRS, yet also have begun to assess clinical outcomes.

One can assess the SIRS that is associated with CPB in a wide variety of ways. Most commonly, this is performed by assaying blood levels of numerous proinflammatory and/or anti-inflammatory mediators. While a few investigations have shown no effect, the vast majority of investigations have revealed the ability of methylprednisolone to beneficially alter the balance of these mediators in the blood of patients following exposure to CPB (by attenuating increases in proinflammatory mediators and/or augmenting increases in anti-inflammatory mediators). Numerous observational studies have shown that methylprednisolone (in a wide variety of dosing schedules) can attenuate increases in the proinflammatory mediators IL-1, IL-6, IL-8, tumor necrosis factor, and plasma endotoxin, yet augment increases in the anti-inflammatory mediators IL-4 and IL-10 associated with CPB. Additional observational studies have revealed that the drug attenuates complement activation, and decreases bronchial epithelial nitric oxide concentration, and decreases neutrophil CD11b surface glycoprotein upregulation associated with CPB, all of which should be beneficial. Clinical benefits suggested by these observational studies include an increased CI, a decreased pulmonary capillary wedge pressure, and a decreased incidence of postoperative hyperthermia, yet postoperative hyperglycemia may ensue. Lastly, these studies suggest that preoperative administration (as much as 8 h) may be important when optimizing beneficial effects.

Several well-designed (prospective, randomized, double-blind, placebo-controlled) clinical trials have supported and extended the results of these observational studies. In 1991, Jensen et al revealed that, when compared to control subjects receiving placebo treatment, patients receiving methylprednisolone (30 mg/kg following anesthesia induction) had significantly lower blood levels of leukotriene B4 (p < 0.05) and tissue plasminogen activator (p < 0.01) yet similar blood levels of complement C3a and elastase following exposure to CPB. Two years later, in 1993, Jorens et al reported that patients receiving methylprednisolone (30 mg/kg following anesthesia induction) had significantly lower blood levels of IL-8 (p < 0.05) and significantly less neutropenia (p < 0.05) yet similar blood levels of complement C3a on exposure to CPB, when compared to control subjects receiving placebo. Furthermore, they also discovered that harvested alveolar macrophages from patients administered methylprednisolone released significantly less IL-8 (p < 0.05) than did macrophages from control subjects receiving placebo.

Most recent clinical investigations continue to assess the effects of methylprednisolone on the SIRS yet also have begun to assess clinical outcomes. In 1997, Mayumi et al revealed that, when compared to control subjects receiving placebo, patients receiving methylprednisolone (20 mg/kg twice) had significantly increased blood levels of WBCs (p = 0.04) and natural killer cells (p = 0.01) yet significantly decreased blood levels of IL-2 (p = 0.04), C-reactive protein (p < 0.0001), and phytohemagglutinin response (p < 0.01) following exposure to CPB. Because their constellation of findings suggested that the drug may promote an immunocompromised state (yet no postoperative wound infections were observed), postoperatively, patients receiving methylprednisolone had significantly higher blood glucose (p < 0.01) and lactate (p < 0.05) levels and a significantly decreased incidence of postoperative hyperthermia (p = 0.001) when compared to control subjects receiving placebo. There was no difference between the methylprednisolone and placebo groups regarding perioperative CI, water balance, arterial blood gas levels, electrolytes, nor extubation time (1.42 ± 0.64 days vs 1.30 ± 0.46 days, respectively). In 1999, Tassani et al revealed that, when compared to control subjects receiving placebo, patients receiving methylprednisolone (1 g prior to CPB) had significantly decreased blood levels of IL-6 (p < 0.05) and IL-8 (p < 0.05) and significantly increased blood levels of IL-10 (p < 0.05) on exposure to CPB. Clinically, patients receiving methylprednisolone exhibited decreased F(A-a)O2 (376 mm Hg vs 428 mm Hg, respectively; p < 0.05), increased pulmonary compliance (44 mL/mm Hg vs 39 mL/mm Hg, respectively; p < 0.05), and increased CI (4.1 vs 3.6 L/min/m2, respectively; p < 0.05) following exposure to CPB, when compared to control subjects receiving placebo. Postoperatively, patients receiving methylprednisolone exhibited increased blood glucose concentrations (203 mg/dL vs 146 mg/dL, respectively; p < 0.001) and similar extubation times (8.1 h vs 9.2 h, respectively) when compared to control subjects receiving placebo. While the investigation of Tassani et al revealed potential clinical benefits of methylprednisolone...
(improved oxygenation, improved pulmonary compliance, increased CI, etc.), the study can be criticized because of lack of standardization in key areas (mechanical ventilation parameters) and the routine use of aprotinin (known to attenuate the SIRS associated with CPB) in all patients.

Most recent clinical investigations by Chaney et al. indicate that routine administration of methylprednisolone to patients undergoing cardiac surgery with CPB not only offers no clinical benefits, its use in the era of early tracheal extubation may in fact be contraindicated. In their first studies, these investigators in prospective, randomized, blinded fashion administered methylprednisolone (30 mg/kg twice) to 30 patients undergoing elective CABG while 30 similar patients received placebo. Perioperative care was standardized, including intraoperative baseline anesthetic and mechanical ventilation parameters. They found that patients receiving methylprednisolone had significantly larger increases in postoperative P(A-a)O_2 (199 to 420 mm Hg vs 237 to 360 mm Hg, respectively; p = 0.001), shunt (12 to 27% vs 14 to 21%, respectively; p = 0.001), and CI (2.1 to 3.0 L/min/m^2 vs 2.1 to 2.5 L/min/m^2, respectively; p = 0.04), yet significantly smaller increases in postoperative SVR (1,199 to 1,045 dyne/cm^2 vs 1,247 to 1,312 dyne/cm^2, respectively; p = 0.05) when compared to control subjects receiving placebo. Furthermore, the drug was unable to prevent significant peripereoperative increases in blood C3a levels (p < 0.01) and significant postoperative decreases in dynamic lung compliance (p < 0.000001). Lastly, when compared to control subjects receiving placebo, patients receiving methylprednisolone required significantly more dobutamine (24 patients vs 15 patients, respectively; p = 0.02), significantly less nitroglycerin (4 patients vs 12 patients, respectively; p = 0.02), and had prolonged extubation times (12.8 h vs 10.1 h, respectively; p = 0.05) during the postoperative period.

Thus, this constellation of findings unexpectedly revealed that methylprednisolone may initiate detrimental pulmonary and hemodynamic effects that may hinder early tracheal extubation following cardiac surgery. In this study, 90 patients were prospectively randomized into three groups: one group received methylprednisolone (30 mg/kg twice), one group received the drug at half that dose (15 mg/kg twice), and the last group received placebo in a blinded fashion. Once again, the perioperative care was standardized including intraoperative baseline anesthetic and mechanical ventilation parameters. The results on this investigation were similar. Patients receiving methylprednisolone (either dose) exhibited significantly increased CI (p = 0.0006), significantly decreased SVR (p = 0.0005), and significantly increased shunt (p = 0.002) during the immediate postoperative period. All three groups exhibited significant increases in P(A-a)O_2 (p < 0.0001), significant decreases in dynamic lung compliance (p < 0.0001) 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 = 0.016) among the group receiving 30 mg/kg twice (mean ± SD, 311 ± 90 mg/dL), the group receiving 15 mg/kg twice (292 ± 93 mg/dL), and the group receiving placebo (234 ± 96 mg/dL). Lastly, in patients extubated within 12 h of ICUs arrival, a statistically significant difference in extubation times existed (p = 0.025) between the group receiving 30 mg/kg twice (7.5 ± 2.7 h), the group receiving 15 mg/kg twice (5.9 ± 2.2 h), and the group receiving placebo (5.7 ± 2.3 h). Thus, the findings of this investigation support and extend the previous studies by the same group and indicate that methylprednisolone offers no clinical benefits to patients undergoing cardiac surgery with CPB, and may in fact be detrimental by initiating postoperative hyperglycemia and possibly hindering early postoperative tracheal extubation for undetermined reasons.

**Summary**

Prospective, randomized, double-blind, placebo-controlled clinical investigations involving methylprednisolone and patients undergoing cardiac surgery with CPB are summarized in Table 2. As can be seen, all involved small numbers of patients and most did not tightly control perioperative management (intraoperative baseline anesthetic technique, mechanical ventilation parameters, technique of CPB, etc.). Despite these facts, the results of these clinical investigations, along with the results of less well-controlled clinical investigations, suggest certain conclusions. It appears that methylprednisolone is able to reliably (and beneficially) alter the balance of proinflammatory and anti-inflammatory mediators in the blood of patients subjected to CPB, indicating that the drug decreases the SIRS associated with CPB. However, whether or not suppression of the SIRS is clinically beneficial remains to be determined. Specific hemodynamic benefits (increased CI, decreased SVR) seem to be associated with use of the drug in this setting yet these alterations may increase the need for postoperative IV hemodynamic agents (vasoconstrictors, etc.). From a pulmonary perspective, it is also important to consider the potential for the drug to increase the need for postoperative IV hemodynamic agents (vasoconstrictors, etc.).
perspective, the use of methylprednisolone in this setting does not appear to offer any clinical benefits and may be detrimental. The drug is unable to reliably prevent postoperative decreases in pulmonary compliance and increases in P(A-a)O₂ (perhaps by increasing pulmonary shunt) and may hinder early postoperative tracheal extubation for undetermined reasons. Lastly, while methylprednisolone is unable to beneficially affect perioperative fluid balance (and weight), it is clear that the drug will increase perioperative blood glucose levels (possible increasing morbidity). Thus, this constellation of findings indicate that methylprednisolone offers no clinical benefits to patients undergoing cardiac surgery with CPB and in fact may be detrimental by initiating postoperative hyperglycemia and possibly hindering early postoperative tracheal extubation for undetermined reasons.

**Future Directions**

Additional well-designed (prospective, randomized, double-blind, placebo-controlled) clinical investigations (with large numbers of patients and tightly-controlled perioperative management) involving corticosteroids and patients undergoing cardiac surgery with CPB need to be done. Whether or not suppression of the SIRS associated with CPB with corticosteroids (or any other drug/technique) is clinically desirable and beneficial remains to be determined. Why these drugs appear to prolong extubation time and whether or not the increased perioperative blood glucose levels caused by the drugs are clinically detrimental are questions that need answers. Lastly, over the past few years, the trend in cardiac surgery has been to perform CABG ("off-pump" cardiac surgery) in

<table>
<thead>
<tr>
<th>Source</th>
<th>Year</th>
<th>Total Patients, No.</th>
<th>Methyldprednisolone Dosing</th>
<th>Main Parameters Evaluated</th>
<th>Perioperative Management</th>
<th>Main Results of Methyldprednisolone Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chaney et al³</td>
<td>2001</td>
<td>90</td>
<td>30 mg/kg twice 15 mg/kg twice</td>
<td>Respiratory, hemodynamic, fluid balance, weight, blood glucose</td>
<td>Standardized</td>
<td>Increased extubation time Increased shunt Increased CI Decreased SVR Increased blood glucose levels</td>
</tr>
<tr>
<td>Chaney et al⁵,¹⁰</td>
<td>1999</td>
<td>60</td>
<td>30 mg/kg twice</td>
<td>Respiratory, hemodynamic, inflammatory mediators</td>
<td>Standardized</td>
<td>Increased extubation time Increased P(A-a)O₂ Increased shunt Increased CI Decreased SVR Increased hemodynamic support Decreased P(A-a)O₂</td>
</tr>
<tr>
<td>Chaney et al⁵,¹⁰</td>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td>Standardized</td>
<td>Increased P(A-a)O₂ Increased CI Decreased SVR Increased hemodynamic support Decreased P(A-a)O₂</td>
</tr>
<tr>
<td>Tassani et al⁷</td>
<td>1999</td>
<td>52</td>
<td>1.0 g</td>
<td>Respiratory, hemodynamic, inflammatory mediators, blood glucose</td>
<td>Not well standardized</td>
<td>Decreased P(A-a)O₂ Increased pulmonary compliance Increased CI Decreased IL-6 levels Decreased IL-8 levels Increased IL-10 levels Increased blood glucose levels</td>
</tr>
<tr>
<td>Mayumi et al¹¹</td>
<td>1997</td>
<td>24</td>
<td>20 mg/kg twice</td>
<td>Respiratory, hemodynamic, inflammatory mediators, blood glucose</td>
<td>Not well standardized</td>
<td>Increased WBC levels Increased NKC levels Decreased IL-2 levels Decreased C-reactive protein levels Increased blood glucose levels</td>
</tr>
<tr>
<td>Jorens et al²⁵</td>
<td>1993</td>
<td>26</td>
<td>30 mg/kg</td>
<td>Inflammatory mediators, blood glucose</td>
<td>Not well standardized</td>
<td>Decreased IL-8 levels Decreased neutropenia Decreased leukotriene B₄ levels Decreased TPA levels</td>
</tr>
<tr>
<td>Jansen et al²⁷</td>
<td>1991</td>
<td>24</td>
<td>30 mg/kg</td>
<td>Inflammatory mediators</td>
<td>Not well standardized</td>
<td></td>
</tr>
<tr>
<td>Toledo-Pereyra et al²⁷</td>
<td>1980</td>
<td>95</td>
<td>30 mg/kg seven times</td>
<td>Wide variety of clinical outcomes</td>
<td>Not well standardized</td>
<td>Decreased mortality</td>
</tr>
<tr>
<td>Niazi et al³⁰</td>
<td>1979</td>
<td>90</td>
<td>30 mg/kg</td>
<td>Hemodynamic, metabolic</td>
<td>Not well standardized</td>
<td>Increased CI Decreased SVR</td>
</tr>
<tr>
<td>Morton et al¹⁴</td>
<td>1976</td>
<td>95</td>
<td>2.0 g or 30 mg/kg</td>
<td>Wide variety of clinical outcomes</td>
<td>Not well standardized</td>
<td>No difference between groups</td>
</tr>
</tbody>
</table>

* NKC = natural killer cells; TPA = tissue plasminogen activator.
hopes of avoiding the known detrimental physiologic effects of CPB. While cardiac surgery without CPB was initially thought not to induce the SIRS \(^{63,64}\), recent clinical investigations suggest otherwise \(^{65,66}\) (that is, the SIRS is indeed induced with this technique). Thus, the potential clinical benefits of corticosteroids to patients undergoing cardiac surgery without CPB has yet to be (and should be) investigated.

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