

Case Report

Systemic Inflammatory Response Syndrome (SIRS) Following Emergency Cardiopulmonary Bypass: A Case Report and Literature Review

Joseph J. Sistino, MPA, CCP; Jeffrey R. Acsell, BS, CCP

Program in Extracorporeal Circulation Technology, Medical University of South Carolina, Charleston, South Carolina

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ABSTRACT

A complication of emergency resuscitation is the development of the Systemic Inflammatory Response Syndrome (SIRS). In the past, this has been identified as multiple organ failure, with symptoms similar to sepsis. The hallmark of this syndrome is peripheral vasodilation, which is associated with a breakdown of capillary membranes and the accumulation of excess interstitial fluid.

This case report discusses the development of SIRS in a patient following emergency cardiopulmonary bypass (CPB). The patient was a 53 year old male with significant left main coronary artery disease who developed sudden bradycardia and hypotension in the operating room and was emergently placed on cardiopulmonary bypass. During CPB, the patient was peripherally vasodilated, and required continuous alpha-adrenergic support to maintain normal systemic vascular resistance. In addition, metabolic acidosis was present despite high flow rates, high hematocrit, addition of colloids, and hemoconcentration. Despite excellent neurological and myocardial recovery following surgery, the patient died one week later in renal and hepatic failure.

Several mechanisms for the development of this syndrome have been hypothesized. One of these theories is that the ischemic injury in the gastrointestinal tract disturbs the gut barrier function and allows enteric bacterial endotoxins to pass into the circulation producing sepsis-like symptoms. Other theories relate to the release patterns of cytokines associated with CPB. These mechanisms and the treatment of SIRS with new pharmacological agents and perfusion techniques are reviewed.

Address correspondence to:
Joseph J. Sistino, MPA, CCP
Medical University of South Carolina
101 Doughty Street, 2nd Floor
Charleston, SC 29401-5797

INTRODUCTION

Multiple organ failure due to infection, sepsis, or inflammation has been termed the Systemic Inflammatory Response Syndrome (SIRS). This is actually a combination of many diseases that lead to multiple organ dysfunction (MODS), multiple organ system failure, and ultimately death. These disease entities are activated "nonspecifically by a host of abnormalities ranging from trauma to infection to myocardial infarction or to a low cardiac output by patients who have undergone surgery for cardiac disease" (1).

SIRS may also be a complication of emergency cardiopulmonary resuscitation. Because of the limited time available to restore the circulation before ischemic injury to the brain tissue, resuscitative efforts are focused on the restoration of cerebral blood flow as quickly as possible. The use of vasoconstrictors to increase arterial blood pressure during cardiogenic shock may preserve cerebral perfusion at the expense of the visceral organs (2). Ischemic and reperfusion injury to the gastrointestinal tract or the lower extremities produce further damage to a remote organ such as the lung from the release of inflammatory mediators (3). This selective perfusion may contribute to the development of SIRS (4).

In the past, SIRS has been identified as multiple organ failure, with symptoms very similar to sepsis (5,6). SIRS is manifested by "2 or more of the following conditions: a temperature lower than 36°C or higher than 38°C; a heart rate more than 90 beats per minute; a respiratory rate more than 20 breaths per minute or a PaCO₂ less than 32 mmHg, which usually means hypoxic hyperventilation; or a white blood cell count more than 12.0x10⁹/L or less than 4.0x10⁹/L or the presence of greater than 10% immature or band forms" (7,8,9). The hallmark of this syndrome is peripheral vasodilation. As multiple organ system dysfunction develops, interstitial fluid increases due to the breakdown of capillary membranes, with the development of generalized edema. Due to acute renal and hepatic failure, this syndrome is accompanied by metabolic acidosis and a severe coagulopathy. The mortality rate at this stage is extremely high (10,11,12).

The SIRS has been associated with increased levels of endotoxins and cytokines such as tumor necrosis factor (TNF), interleukin-6 (IL-6) and interleukin-8 (IL-8) (13). Proinflammatory cytokines induce increased neutrophil and endothelial surface adhesive molecule expression, promoting enhanced neutrophil-endothelial adherence. Neutrophil-endothelial adherence is the initial step in this response, and leads to the migration of leukocytes into the extravascular space where they release toxins that damage the surrounding tissues. The cytokines also increase the cellular expression of inducible nitric oxide synthase, increasing cellular production of nitric oxide (3).

With the availability of cardiopulmonary bypass (CPB), rapid initiation of CPB can restore vital blood flow while efforts at cardiac resuscitation are maximized. CPB alone has been associated with complement activation, endotoxin release, leu-

kocyte activation, expression of adhesion molecules, release of inflammatory mediators including oxygen free radicals, cytokines, platelet activating factor, nitric oxide, and endothelins (14-19). The combination of emergency resuscitation and exposure to CPB may increase the risk of SIRS.

Ischemia and reperfusion are a major stimulus for the release of cytokines. During CPB, endotoxemia occurs at the time of aortic cross-clamp release and peaks shortly before the end of bypass (20). There is a correlation between the duration of cross-clamping and a decrease in the oncotic pressure (21). There is evidence that splanchnic ischemia does occur routinely during CPB and may disturb the gut barrier function (22-27). Peak endotoxin levels during bypass have been shown to be a predictor of protracted hospital stay when compared with other hemodynamic and tissue perfusion factors (16).

There is a strong correlation between endotoxin exposure and decreased systemic vascular resistance (SVR) due to impaired endothelial function (28). Decreased response to phenylephrine following shock in animal models has been demonstrated. Nitric oxide synthase expression is known to occur in the liver during endotoxemia, and a decreased vasoconstrictive response to phenylephrine has been reported in isolated liver preparations exposed to endotoxins. In control livers using the isolated liver preparation, nitric oxide produced a similar vasodilation (29,30). Incubation of rat aortic rings in endotoxin also induced a delayed and prolonged release of nitric oxide and resulted in a decrease in contractile response to phenylephrine (31).

Endotoxins are considered the main trigger for release of IL-6, IL-8 and granulocyte elastase that have been found to be detrimental to respiratory function (32). Postoperative circulatory instability has been associated with IL-6 release (33). Increased endotoxin and TNF levels have been associated with depressed myocardial performance in the elderly (34). According to Menasche et al, cytokine levels were consistently higher in patients undergoing normothermic bypass and increased pressor support was required in normothermic patients (35). A strong correlation exists between the mean arterial pressure and endotoxin concentration after 10 minutes on CPB. The concentration of endotoxins after CPB was found to be related to three factors: the degree of vasoconstriction, the duration of aortic cross-clamping, and the degree of hypo-oncotic hemodilution (36). Factors identified to prevent endotoxin release include adequate flow (cardiac index > 2.4 L/min/m² at normothermia) and perfusion pressure > 60 mmHg (37).

The source of the endotoxin release has not been well established. No significant differences between mixed venous and hepatic endotoxin levels have been found. No difference in IL-6 and IL-8 has been found between coronary sinus and arterial blood in spite of increased levels of these mediators after CPB. Therefore, one researcher has concluded that the myocardium is not a predominant source of IL-6 and IL-8 release (38). Others have shown that the levels of TNF, IL-6 and IL-8 are positively correlated with the duration of cardiac ischemia and conclude that the myocardium is the major source of these three

cytokines (39). During lung reperfusion, no difference in the cytokine levels was found between the left atrium and the radial artery, which is evidence that the lung is not the source of cytokine release (40).

CASE REPORT

A 53 year old male with a history of hypertension presented to the hospital with chest burning and abdominal pain. After some relief with IV nitroglycerin, the patient underwent a cardiac catheterization which revealed an isolated 80% lesion of his left main coronary artery. His ejection fraction was 50%. He was taken to the operating room for emergency bypass surgery. Shortly after the harvest of the left internal mammary artery (LIMA), the patient developed severe myocardial ischemia and bradycardia, which quickly degraded into ventricular fibrillation. The patient was quickly cannulated and placed on CPB. The fibrillating heart was noted to be markedly distended. The left ventricle was vented through the left atrial appendage and after several attempts at defibrillation, the aorta was cross-clamped and 1000 ml of warm blood cardioplegia enriched with aspartate and glutamate was injected both antegrade and retrograde, followed by 1200 ml of cold retrograde blood cardioplegia. Two coronary artery bypass grafts were placed, a LIMA to the left anterior descending (LAD) and a vein graft to the first diagonal branch. Warm blood cardioplegia (900 ml) was again given before the release of the cross-clamp. Weaning off CPB necessitated the use of an intra-aortic balloon pump. The heart was allowed to rest on CPB for approximately one hour until the transesophageal echocardiogram (TEE) demonstrated that the stunned anterior and lateral walls were recovering. The patient was weaned off CPB with good ventricular function assessed by TEE. He was transferred to the Surgical Intensive Care Unit on epinephrine .05 mcg/kg/min, amrinone 5 mg/kg/min, and dobutamine 4.5 mcg/kg/min.

At the onset of bypass the systemic vascular resistance was 2737 dynes sec cm^{-5} . This high resistance was thought to be a residual effect of epinephrine that was given during emergency resuscitation. During the first 30 minutes of bypass the systemic vascular resistance (SVR) returned to the normal range. (Figure 1). Following this, the patient became hypotensive and required significant alpha-adrenergic support with phenylephrine to maintain the systemic vascular resistance within a normal range. Metabolic acidosis was present despite high blood flow rates, high hematocrit (30%), hemoconcentration, and the addition of

Figure 1: Venous oxygen saturation and systemic vascular resistance on cardiopulmonary bypass

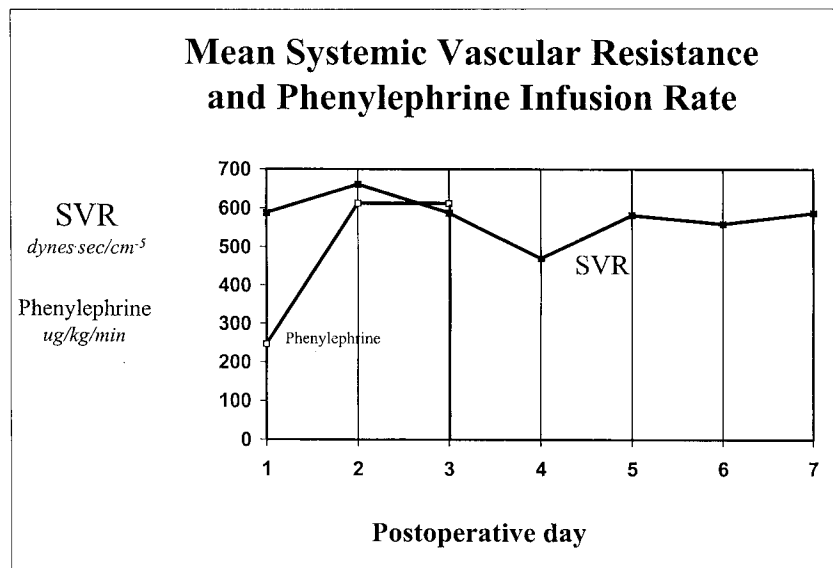


Table 1: Postoperative renal/hepatic laboratory values

	creat mg/dl	bilirubin mg/dl	ast IU/L	alt IU/L	ammonia umol/L
preop					
PO day 1					
PO day 2	10.7				
PO day 3	10.1	8.1	10630	8378	10.7
PO day 4	10	11	4052	4403	
PO day 5	9.2	14.7	1552	2571	
PO day 6	10.5				63
PO day 7	12.6				99
Normal Range	0.8-1.5	0.2-1.3	15-59	21-72	9-33

colloids. Urine output was decreased on bypass despite diuretic therapy. The mixed venous oxygen saturation was maintained > 70% throughout bypass.

The neurological exam on post-op day #1 showed that the patient was alert and responded appropriately to commands. However, there was significant renal and hepatic dysfunction (Table 1). Despite an excellent cardiac index with the IABP, the SVR averaged 588 dynes sec cm^{-5} the first 24 hours post-op with high dose phenylephrine infusion (Figure 2). Although cardiac function improved, the balloon pump could not be removed due to a persistent coagulopathy related to the liver dysfunction. Serum creatinine levels became elevated and a renal consult was obtained. On post-op day 3, the patient appeared septic with a low SVR and a fever of 102°F. Continuous veno-venous hemofiltration was started for fluid overload and hyperkalemia. Improvement in these values occurred, but the patient developed

Figure 2: Postoperative mean systemic vascular resistance and phenylephrine infusion rate

Postoperative Renal/Hepatic Laboratory Values

	creat	bilirubin	ast	alt	ammonia
	mg/dl	mg/dl	IU/L	IU/L	umol/L
preop					
PO day 1					
PO day 2	10.7				
PO day 3	10.1	8.1	10630	8378	10.7
PO day 4	10	11	4052	4403	
PO day 5	9.2	14.7	1552	2571	
PO day 6	10.5				63
PO day 7	12.6				99
Normal Range	0.8 - 1.5	0.2 - 1.3	15 - 59	21 - 72	9 - 33

Table 2: Postoperative laboratory values

	temp	wbc K/cumm	plat K/cumm
preop		7.4	222
PO day 1	38.8	22.8	249
PO day 2	38.1	13.5	71
PO day 3	39.2	11.2	40
PO day 4	38.3	9.3	86
PO day 5	36	17.3	63
PO day 6	39.3	40.9	52
PO day 7	40.1	50.8	33

a decreased platelet count, possibly secondary to heparin-induced thrombocytopenia, which required the discontinuation of dialysis (Table 2). The patient expired two days later.

DISCUSSION

This patient exhibited a number of symptoms consistent with SIRS. Although he was successfully resuscitated with CPB and coronary artery bypass surgery after cardiac arrest, he developed severe hepatic and renal failure with peripheral vasodilation after surgery. In the early postoperative period, there appeared to be excellent neurological and cardiac recovery. However, due to the progression of multiple organ failure, treatment with high dose alpha-adrenergic support, fluid replacement therapy, and dialysis was unsuccessful.

This example of the systemic inflammatory response is a complicated scenario with many possible interventions, both preventative and therapeutic. There have been several strategies that

have been shown to mediate the release of either endotoxins or cytokines (41,42,43). There are pharmacological agents being tested to reduce the inflammatory response following ischemia. In addition, there are perfusion strategies that may decrease the incidence of this complication. They are outlined below.

PHARMACOLOGICAL INTERVENTIONS

Enoximone, a Type III phosphodiesterase inhibitor improves splanchnic oxygen utilization. It improves the barrier function of the gut and reduces the endotoxin levels in the liver venous blood (44).

Dopexamine, a dopamine receptor agonist selectively activates beta 2 adrenergic receptors. It produces selective vasodilation of the intestinal mucosa and improves oxygen uptake in the splanchnic circulation. This has been shown to lower

the postoperative level of IL-6 (45).

Ketanserin, an inhibitor of serotonin-induced vasoconstriction and a weak alpha-1 sympathetic blocker, reduces endotoxin levels and postoperative oxygen consumption in cardiac surgery patients (46).

Methylprednisilone, which suppresses the expression of adhesion molecules by endotoxin-activated endothelial cells, decreases the degree of endotoxemia produced by CPB. (47). Preoperative steroids have been shown to significantly reduce cytokine release and vasodilation in normothermic CPB, through a decrease in IL-8 and TNF, and increase in IL-10 (48).

Antibiotics have been used to reduce the gut content of enterobacter, with complete elimination after 3 days. Reduction in intestinal bacteria is associated with a significant reduction in endotoxin release (49,50).

Aprotinin at high doses was found to lower cytokine and cellular activation associated with the acute inflammatory response of CPB. Low dose aprotinin only modifies hemostasis and does not reduce inflammatory cytokines (51,52). High dose aprotinin has been shown to inhibit complement activation, neutrophil elastase release, and kallikrein production.

Nafamostat mesilate, a serine protease inhibitor, decreases both IL-6 and IL-8 release (53).

Methylene blue, which inhibits nitric oxide (NO) has been used successfully to treat the vasodilation associated with SIRS. Inducible nitric oxide synthase is activated by endotoxins and cytokines and produces large quantities of nitric oxide. Methylene blue inhibits guanylate cyclase and blocks the vasodilatory effects of nitric oxide in the smooth muscle. Based on the observed clinical improvements in peripheral vascular resistance after treatment with methylene blue, nitric oxide is thought to be the final mediator of SIRS (54,55).

Vasopressin deficiency has been shown to be present in patients with vasodilatory shock that are resistant to catecholamines (56). Although vasopressin has little effect in normal subjects, it is an effective agent in patients with low arterial pressure. CPB is associated with a reduction in vasopressin concentration. The high sensitivity following CPB to low doses of vasopressin confirms this deficiency. Treatment with vasopressin significantly increased the arterial blood pressure and reduced catecholamine requirements in patients with refractive vasodilatory shock (57).

CARDIOPULMONARY BYPASS INTERVENTIONS

Heparin bonded circuits have been shown to reduce complement activation via the alternative pathway, and the terminal pathway. They have also shown less granulocyte activation and reduction in the release of the inflammatory cytokines TNF, IL-6 and IL-8 (58,59).

Pulsatile flow has been shown to decrease the endogenous endotoxin levels that occur with the intestinal congestion and ischemia of nonpulsatile flow. With pulsatile blood flow, there was no increase in endotoxin levels after aortic cross-clamping (60,61).

Ultrafiltration may reduce cytokine levels of TNF and IL-6. High volume hemofiltration showed early removal of factors triggering the inflammatory response (62).

This list of interventions is not all-inclusive. There are many avenues of research into the complexities of this syndrome, which combine the immune system's response to extracorporeal circulation and ischemic injury. As we begin to understand the complexities of ischemic injury and the triggers of the inflammatory response, a combination of these agents will become available to prevent the secondary organ dysfunction and stop the progression to multiple organ system failure and death.

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