Cardiac Vasoplegia Syndrome: Pathophysiology, Risk Factors and Treatment

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Abstract: Vasoplegia syndrome is a well known complication after cardiac surgery and has a significant morbidity and mortality. It is characterized by profound vasodilation and loss of systemic vascular resistance leading to hypotension. The pathogenesis of vasoplegia involves the activation of contact, coagulation and complement systems and the activation of leukocytes, platelets and endothelial cells resulting in an imbalance in the regulation of the vascular tone leading to postcardiac surgery vasoplegia. Multiple risk factors have been identified that help predict vasoplegia. Treatment requires mainly vasopressors, but hypotension can be refractory to vasopressors. Some studies suggest that methylene blue can reverse refractory hypotension in these patients and may prevent the development of the syndrome, but more studies are needed with this drug. In this review, we will discuss the pathophysiology of the vasoplegia syndrome and associated risk factors for this complication and briefly outline current therapeutic strategies.

Key Indexing Terms: Vasoplegia; Cardiopulmonary bypass; Vasopressin; Methylene blue. **[Am J Med Sci 2015;349(1):80–88.]**

Cardiac vasoplegia syndrome is a form of vasodilatory shock that occurs in 9% to 44% of patients after cardiopulmonary bypass (CPB) surgery.[1,2] These patients have profound vasodilation and loss of systemic vascular resistance, resulting in severe hypotension despite high cardiac outputs and adequate fluid resuscitation. This leads to inadequate tissue perfusion and metabolic acidosis. Treatment often requires high doses of vasopressors to maintain adequate blood pressure postoperatively, and sometimes, this vasoplegia becomes refractory to vasopressors, resulting in high morbidity and mortality.[3] This complication is largely managed by cardiac anesthesiologists and cardiac surgeons. We provide a brief review for primary care physicians and intensivists who may participate in the care of these patients.

DISCUSSION

Pathophysiology

Cardiac vasoplegia syndrome has become a well-recognized complication of cardiac surgery requiring CPB and is characterized by significant hypotension, high or normal cardiac outputs, low systemic vascular resistance and an increased requirement for vasopressors.[4] This syndrome reflects the complex interactions among plasma proteins, leukocytes, platelets and endothelial cells. Surgical trauma and the use of CPB with exposure of blood to foreign surfaces in the pump and tubing activate multiple enzyme pathways and stimulate production of systemic inflammatory mediators and neurohumoral factors.[1] The pathophysiologic basis for this syndrome also depends on patient characteristics and the surgical procedure. The net result is a systemic inflammatory response syndrome (SIRS) and transient vascular dysfunction resulting in vasodilation and resistance to vasopressors.[5]

Plasma proteins are immediately absorbed to biomembranes when blood passes through the CPB equipment. This protein layer is densely packed and immobile, and some proteins undergo confirmation changes and express "receptors" for cells and other proteins.[6,7] This results in the activation of the contact system, the extrinsic coagulation pathway, the intrinsic coagulation pathway, complement and fibrinolysis. Activation of the contact pathway produces bradykinin and kallikrein. Activation of the extrinsic and intrinsic coagulation systems produces thrombin and results in the deposition of fibrin. Activation of the complement pathway results in the formation of C5a and the terminal complement complex. These cascades interact with one another and have multiple cellular effects.[8]

Leukocytes, platelets, macrophages and endothelial cells are also activated during CPB. Neutrophils are activated by multiple agonists, especially kallikrein and C5a.[8] Activated neutrophils release proteolytic enzymes and reactive oxygen species and adhere to membrane surfaces and endothelial surfaces.[9] Platelets are activated by thrombin and other agonists and undergo shape changes, express surface receptors and secrete granular contents.[10–12] These platelets adhere to other platelets, neutrophils and exposed basement membranes.[13] Activated macrophages secrete cytokines which in turn activate neutrophils and lymphocytes. Multiple factors, including thrombin, C5a and cytokines, activate endothelial cells that produce vasoactive substances, including nitric oxide (NO) and prostacyclin, and express surface receptors.[14,15]

These acute responses subside as CPB be continues. However, a 2nd or late response also occurs during CPB. The reinfusion of cardiotomy blood from the thoracic wound contributes to the pathogenesis of cardiac vasoplegia. This blood has hemolyzed erythrocytes and macroaggregates consisting of denatured proteins, fat globules and platelet and leukocyte aggregates. These cell fragments and particulates potentially plug small capillaries and stimulate inflammatory responses. In addition, after the cross clamp on the aorta is released, reperfusion of the heart and lung causes an ischemia-reperfusion syndrome with neutrophil adherence to activated endothelial cells and the release of reactive oxygen species, which can cause direct protein, lipid and nucleic acid damage. This increases capillary permeability and causes interstitial edema and reduced intravascular volume. Finally, during CPB, endotoxin released from bacteria in the gastrointestinal tract is translocated into the circulation and stimulates inflammation.

The systemic inflammatory response associated with cardiac surgery using CPB causes the formation of fibrin clots and microemboli and produces vascular dysregulation. The inflammatory mediators also cause cardiac, central nervous system, pulmonary, platelet and renal dysfunction. Intraoperative myocardial ischemia, reperfusion and myocardial

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inflammation–associated elevated troponin I levels after cardiac surgery independently predict in-hospital death and major postoperative complications.[16,17] These cardiac-related outcomes are likely explained in part by impaired contractility leading to postoperative hemodynamic instability. Interleukin (IL) 6 and IL-8 produced during SIRS have negative inotropic effects, which can lead to poorer cardiac outcomes.[18] However, the primary initial problem in patients with cardiac vasoplegia involves hypotension. Reduced plasma levels of arginine vasopressin (AVP) and excess NO production cause vasodilation after cardiac surgery.[19] The low plasma vasopressin (VP) concentration in these patients has been attributed to reduced VP secretion, possibly secondary to impaired baroreflex-mediated VP secretion. Alternatively, excessive secretion of VP in the early stages of the shock state may have depleted pituitary VP stores.[20,21] Increased levels of NO and the deficiency of VP lead to the activation of the adenosine triphosphate (ATP)-sensitive K^+ channel (KATP) in the plasma membrane of vascular smooth muscle. Opening this channel hyperpolarizes vascular smooth muscle and reduces Ca^{2+} entry through voltage-gated Ca^{2+} channels, which induces vasodilation.[20] NO and other vasodilators, such as atrial natriuretic peptide, cause dephosphorylation of the light chain of myosin by increasing the production cyclic GMP. This prevents actin and myosin interaction and ultimately prevents muscle contraction leading to vasodilation and hypotension.[22] All of these mechanisms contribute to the development of catecholamine-resistant postoperative cardiac vasoplegia. These complex interactions are depicted in part in Figure 1.

The pathogenesis and clinical features of cardiac vasoplegia resemble severe sepsis and septic shock. Severe sepsis is defined to sepsis-induced tissue hypoperfusion and/or organ dysfunction. Septic shock is defined as a severe sepsis with hypotension, which is refractory to adequate fluid resuscitation. Sepsis creates an intense inflammatory response with the release of the same mediators causing activation of plasma protein systems and cells seen in the cardiac vasoplegia syndrome. Sepsis is, of course, complicated by the active replication of bacteria and the release of exotoxins and endotoxins, but studies in septic patients and models are likely relevant to the investigation and management of cardiac vasoplegia.

Risk Factors

Multiple risk factors for vasoplegia have been identified (Table 1). Levin et al[23] retrospectively analyzed 2,823 adult cardiac surgery cases. Twenty percent of these patients developed vasoplegia syndrome after separation from CPB. They found that 1,645 patients (58.3%) had a clinically significant decrease in mean arterial pressure after starting CPB and were more likely to become vasoplegic (23.0% versus 16.9%; odds ratio [OR], 1.26; 95% confidence interval [CI], 1.12–1.43; $P < 0.001$). These vasoplegic patients had more in-hospital mortality and/or more frequent lengths of stay >10 days (OR, 3.30; 95% CI, 1.44–7.57; $P = 0.005$). They described 3 patterns of hypotension during CPB in patients with vasoplegia. Group 1 patients had a steep initial drop in BP but responded to an increase in perfusion pressure and vasoconstrictors. This response likely reflects an acute transient hypersensitivity reaction secondary to exposure of blood to nonphysiological surfaces. Group 2 patients had more gradual but prolonged BP drop and responded poorly to clinical interventions. Patients in this

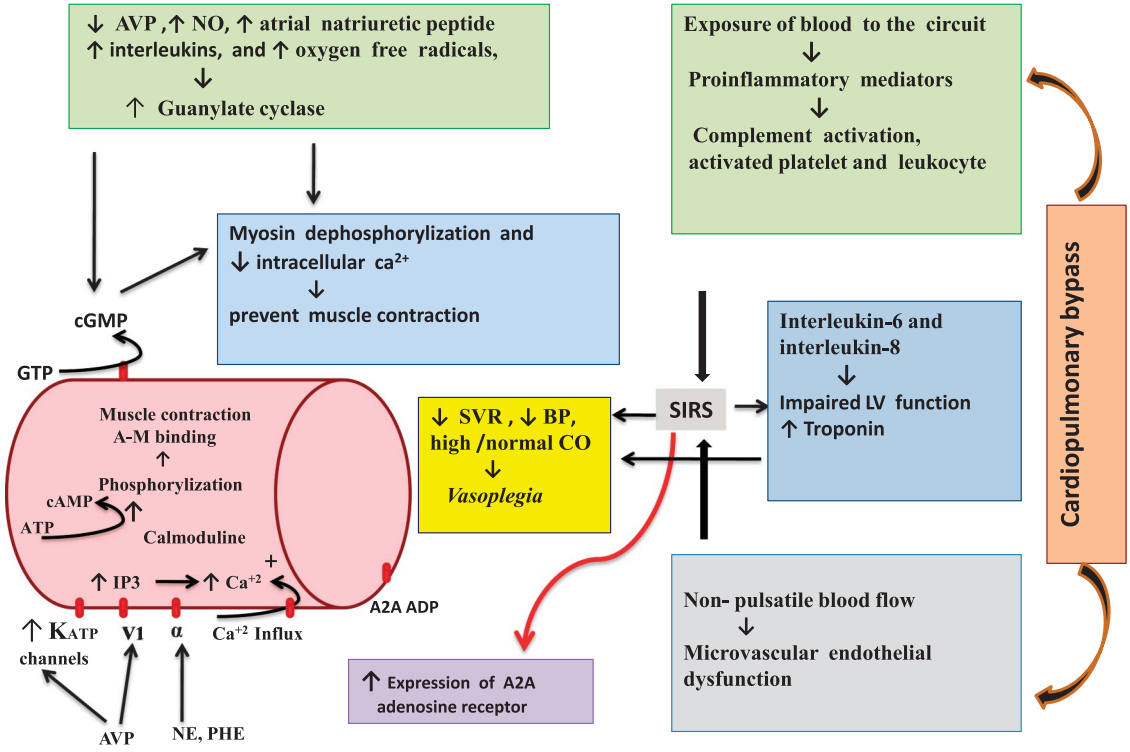

FIGURE 1. Pathophysiology of postcardiac surgery vasoplegia syndrome. AVP, arginine-vasopressin; NE, norepinephrine; PHE, phenylephrine; V1, vasopressin receptor; α, alpha receptor; A2A ADP, adenosine receptor; NO, nitric oxide; SVR, systemic vascular resistant; CO, cardiac output; BP, blood pressure; LV, left ventricular; SIRS, systemic inflammatory response syndrome; A-M, actin-myosin; IP3, inositol triphosphate; KATP; adenosine triphosphate–sensitive potassium channel; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; GTP, guanosine triphosphate; cGMP, cyclic guanosine monophosphate.