The Inflammatory Response to CPB: Why Am I So Vasodilated?

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Learning Objectives:

1. To describe the pathogenesis of the inflammatory response to CPB.
2. To understand the mechanism and consequences of contact activation induced by CPB.
3. To explore biochemical pathways that lead to refractory vasodilatory shock.
4. To review the role of, and evidence for, norepinephrine, arginine vasopressin and methylene blue therapy in vasodilatory shock.

THE INFLAMMATORY RESPONSE TO CPB

The inflammatory response to cardiopulmonary bypass (CPB) is characterized by profound, sometimes refractory vasodilation, known as vasodilatory shock or vasoplegia. In its extreme manifestation, it can result in a systemic inflammatory response syndrome (SIRS). Vasodilatory shock may accompany heart failure, especially with protracted cardiogenic shock; sepsis; occur as an idiosyncratic response to cardiopulmonary bypass (CPB) or after prolonged CPB; with extracorporeal membrane oxygenation (ECMO) or ventricular assist device (VAD) insertion (Fig. 1). It may be exacerbated by certain vasodilatory drugs, e.g. angiotensin converting enzyme (ACE) inhibitors or milrinone.

Figure 1: Inflammatory Response to Cardiopulmonary Bypass. SBE = subacute bacterial endocarditis, ACEI = angiotensin converting enzyme inhibitors, CPB = cardiopulmonary bypass, ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device, SIRS = systemic inflammatory response syndrome.
CPB AND CONTACT ACTIVATION

The inflammatory response to CPB appears to be mediated by complement activation, neutrophil migration, cytokine production and arachidonic acid metabolites. Contact activation of the blood by the extracorporeal circuit (Fig. 2) triggers a series of amplification cascades mediated by proteolytic enzymes, especially serine proteases.

Figure 2. Contact Activation. DIC = disseminated intravascular coagulation, C’ = complement.

Contact activation with the foreign surface of CPB triggers the activation of Hageman (Factor XII), which simultaneously activates the intrinsic pathway of coagulation, fibrinolysis and the complement system. Contact activation may be continued beyond CPB by the insertion of devices such as ECMO or a VAD.

Activation of the intrinsic pathway immediately triggers thrombogenesis, so full anticoagulation is essential to prevent lethal macroclot during CPB. However, microclot formation may proceed despite heparinization, resulting in consumption of circulating procoagulants (consumption coagulopathy), obstruction of the microcirculation (DIC), bleeding and organ injury. Hagemann Factor simultaneously activates kallikrein, an enzyme that cleaves plasminogen to plasmin, inducing fibrinolysis. Recognition of the central role of fibrinolysis activation during CPB has led to the ubiquitous administration of antifibrinolytic agents such as epsilon aminocaproic acid (EACA) or tranexamic acid. An endogenous kallikrein inhibitor, aprotinin, was used for many years during CPB for its potent antifibrinolytic and anti-inflammatory actions, but it is being currently withheld from the US market on the basis of an adverse outcomes study.

Activation of complement, especially the C’3a and C’5a anaphylatoxins, triggers vasospasm and leukocyte activation. Leukocytes may also be activated by shear stress and contact with the CPB circuit. Levels of neutrophil elastase, a measure of neutrophil activation, peak at the end of CPB and are associated with intrapulmonary shunt and postoperative pulmonary dysfunction. The consequence is leukocyte degranulation, adhesion, aggregation and embolization, and release of toxic oxygen free radicals and
Activated leukocytes also produce peptide cytokines such as tumor necrosis factor-alpha (TNF-alpha) and interleukins (IL). Elevated levels of TNF-alpha, IL-6 and IL-8 are observed after CPB. Cytokines exacerbate the inflammatory response by exacerbating neutrophil adhesion and aggregation. Complement activation and neutrophil arachidonic acid metabolites (e.g. leukotriene B4) increase vascular permeability and cause mast cell degranulation. The net result is an acute inflammatory response, which may culminate in SIRS, and characterized by abnormal vascular response, capillary leak syndrome with diffuse interstitial edema, and multiorgan dysfunction. Plasma complement concentrations, duration of CPB, and the degree of elevation of C’3a levels have been correlated with the degree of postoperative organ dysfunction.

**PATHOGENESIS OF VASODILATORY SHOCK**

There are multiple mechanisms of vasodilatory shock, but three are most important: (1) opening of potassium-adenosine triphosphate (K\textsubscript{ATP}) channels; (2) acute arginine vasopressin (AVP) deficiency and (3) widespread activation of inducible nitric oxide synthase (iNOS) and massive release of nitric oxide.

**Opening of K\textsubscript{ATP} Channels**

Vasoconstrictors such as norepinephrine (NE) and angiotensin stimulate G-protein coupled endothelial receptors that open cell membrane calcium channels and promote an influx of calcium. This, together with the release of calcium from intracellular stores, activates a kinase that enhances the phosphorylation of myosin and results in muscle contraction and vasoconstriction. In the presence of intracellular acidosis, lactate accumulation and ATP depletion, membrane K\textsubscript{ATP} channels open and allow an efflux of potassium. This hyperpolarizes the membrane and closes the calcium channels, resulting in vasodilation that is refractory to NE.

**Acute AVP Deficiency**

Landry et al. serendipitously found that relatively modest dose AVP infusion (0.5 - 6 units/hr) results in remarkable improvement in blood pressure and urine flow in patients with vasodilated septic shock, allowing rapid tapering of catecholamines.

Normally, AVP exerts an antidiuretic effect on V\textsubscript{2}-receptors in the distal renal tubule and collecting duct in response to tiny (1%) elevations in serum osmolality. Plasma AVP over the range of 1 through 5 pg/L increases urine osmolality from 300 to 1200 mOsm/kg. Severe hypotension induces a baroreceptor response that releases large amounts of AVP from the posterior pituitary. Plasma AVP of 10 through 200 pg/L exerts a vasoconstrictor effect on V\textsubscript{1}-receptors in vasculature and helps to restore blood pressure.

Patients in severe vasodilated septic shock have paradoxically low plasma AVP (about 3 pg/L)\textsuperscript{10}. In animal models of hemorrhagic shock, AVP stores in the posterior pituitary become quite depleted that within an hour of the induction of profound hypotension. Thus, the response to infused AVP is in part accounted for by the restoration of plasma AVP to appropriate levels for the degree of hypotension.

In addition, AVP appears to block the K\textsubscript{ATP} channel, thereby restoring membrane polarity and vascular responsiveness to catecholamines and angiotensin. AVP also has a salutary effect on renal function because it preferentially constricts the efferent arteriole, thereby enhancing glomerular filtration pressure, filtration rate and urinary flow.
Massive Release of Nitric Oxide

Endogenous nitric oxide (NO) is formed by the action of nitric oxide synthase (NOS) on the amino acid arginine. Nitric oxide in turn activates soluble guanosine cyclase (sGC), which acts on guanosine triphosphate (GTP) to produce cyclic guanosine monophosphate (cGMP), which induces vasodilation. A form of constitutive NOS, endothelial NOS (eNOS) is responsible for the continuous (“tonic”) production of low levels of nitric oxide that maintain vascular patency.

Inducible NOS (iNOS) is activated by the action of cytokines on macrophages in sepsis or the systemic inflammatory response syndrome (SIRS) and produces huge amounts of nitric oxide over protracted periods of time. A similar situation is encountered after prolonged cardiogenic shock, CPB or VAD insertion. This induces profound systemic vasodilation refractory to NE, and also inhibits beta-adrenergic inotropy and results in myocardial depression.

In animal models of sepsis, hypotension is reversed and response to catecholamines restored by NOS inhibitors. However, mortality is increased because non-selective NOS inhibitors (e.g. L-NAME, L-NMMA) also suppress eNOS, thus impairing tonic vasodilation and tissue oxygen delivery.

Studies using selective iNOS inhibitors show promise in decreasing the inflammatory and vasodilator response to sepsis while maintaining tissue oxygen delivery.

Therapeutic Options in Post-CPB Vasodilatory Shock

The “standard” treatment of vasodilatory shock after cardiac surgery consists of NE infusion 1-14 mcg/min plus AVP 1-4 units/hr. Concomitant infusion of AVP repletes endogenous AVP, closes K\textsubscript{ATP} channels and restores the response to NE and decreases its dose requirement. When severe hypotension persists despite NE > 14 mcg/min and AVP up to 6 units/hr (maximum dose), a state of vasoplegia is considered to exist and it is at this stage that infusion of methylene blue (MB) is usually considered.

Norepinephrine

Norepinephrine (NE) is a potent alpha-1 agonist that induces dose-related peripheral vasoconstriction. It is also a potent beta-1 inotropic agent that may provide important myocardial support in vasodilatory states associated with myocardial depression. There is considerable evidence in vasodilated, oliguric septic shock that restoration of blood pressure by NE infusion also restores urine flow and glomerular filtration rate (GFR)\textsuperscript{11,12}. However, with increasing doses, NE has the potential to induce a number of adverse effects. These include afferent arteriolar constriction that negates its beneficial effects on GFR; increasing pulmonary vasoconstriction that may progressively impair right ventricular function; and increasing splanchnic constriction that could ultimately result in visceral ischemia.

Arginine Vasopressin (AVP)

Actions, benefits and limitations of AVP infusion in vasodilatory shock:

Low dose AVP infusion (1-4 u/hr, or 0.015-0.067 u/min) has a number of potentially beneficial effects in vasodilatory shock\textsuperscript{13}. AVP appears to inhibit activation of inducible nitric oxide. It binds to and closes K\textsubscript{ATP} channels, restores membrane polarity and the vasoconstrictor response to catecholamines. Depleted endogenous AVP levels are restored: infusion of 1-4 u/hr achieves plasma AVP levels of 20-30 pg/mL.
These actions consistently result in increased blood pressure and decreased catecholamine requirement. Diminution of high-dose NE decreases pulmonary vascular resistance (PVR) and cardiac arrhythmias. Compared to NE, AVP preferentially induces efferent arteriolar constriction and thereby may enhance glomerular filtration rate (GFR) and renal function.

The 2008 Surviving Sepsis Campaign recommends that AVP infusion (0.03 u/min) may be added to NE (still recommended for initial therapy) if the mean arterial pressure (MAP) cannot be maintained above 65 mmHg. In our current clinical practice we administer AVP 1-4 u/hr (maximum 6 u/hr) in all forms of vasoplegia where hypotension is refractory to increasing doses of NE (> 3 mcg/min), where the PVR is increased, or when oliguria occurs. This includes sepsis, contact activation states and high-dose milrinone therapy for severe right ventricular failure. The goal is to decrease (but not eliminate) the NE infusion rate.

AVP is not beneficial in doses > 6 U/h and is contraindicated in the presence of hypotension secondary to hypovolemia or low cardiac output, and should not be used to “make blood pressure”. Excessive dosing or inappropriate usage can induce severe acral cyanosis (and even cutaneous gangrene), splanchic and coronary constriction. AVP should always be infused via a central catheter, because extravasation from a peripheral catheter can cause severe cutaneous necrosis.

Evidence basis for use of AVP and its analogues in vasodilatory shock

The most definitive randomized controlled study (RCT) performed on AVP thus far is the Vasopressin and Septic Shock Trial (VASST). It was designed to test the hypothesis that low-dose AVP infusion (0.01-0.03 u/min or 0.6-1.8 u/hr) would decrease 28-day mortality among patients with septic shock who were being treated with NE 5-15 mcg/min. In the 778 patients studied, there was no significant difference in mortality between the AVP and NE (35.4% vs. 39.3%). However, in patients with less severe septic shock (prospectively defined as requiring NE 5-14 mcg/min), there was a significant improvement in mortality with AVP over NE (26.5% vs. 35.7%, p < 0.05). It is possible that the lack of benefit in more severe septic shock (NE > 14 mcg/min) was due to an inadequate dose of AVP or late intervention.

Role of corticosteroids in vasodilatory shock

An retrospective analysis of the VASST study by its authors demonstrated that the concomitant administration of corticosteroids with AVP significantly decreased mortality (35.9% vs. 44.7%, p = 0.03), and increased plasma AVP levels by one to two thirds. This further implicates the relationship between AVP and steroid metabolism, considering that V3 receptor activation increases ACTH release and cortisol levels. It also warrants future prospective studies.

Indeed, the role of steroids in septic shock remains in flux. The use of ACTH-stimulation tests to evoke adrenal hyporesponsiveness as an indication for hydrocortisone therapy has been discredited by subsequent equivocal outcomes, intra-study use of etomidate (which impairs cortisol synthesis), and the observation that these studies were based upon total rather than free cortisol levels. The 2008 Surviving Sepsis Campaign recommends the administration of hydrocortisone (300 mg/day) when hypotension responds poorly to adequate fluid resuscitation and vasopressors, and that it should be weaned once vasopressors are no longer required.
Terlipressin

Terlipressin (tricyl-lysine vasopressin) is an AVP analogue used in Europe but not currently available in the US or Canada. It is twice as potent at the V₁ receptor than AVP, but has a much more prolonged half-life (4-6 hr), which makes it more difficult to titrate.²⁰ A small European RCT (TERLIVAP) compared continuous infusion of AVP (0.03 u/min) and terlipressin (1.3 mcg/kg/hr) with NE (15 mcg/min) as first-line therapy in septic shock in 45 patients. Terlipressin appeared superior to AVP in decreasing NE requirements, with lower bilirubin levels and less rebound hypotension, but had a greater effect in lowering platelet count.

Methylene Blue

Mechanisms of Action

Methylene blue (MB) is an industrial dye and redox indicator that has been found to be effective in reversing vasoplegia. The vasoconstrictor activity of MB appears to be mediated by selective inhibition of the action of iNOS and sGC and also by scavenging NO.²²,²³ Although decreases in endogenous production of NO, interleukins and tumor necrosis factor (TNF) have not been noted,²⁴ urinary excretion of NO metabolites is substantially lower.²⁵ Attenuation of the urinary excretion of renal tubular injury markers has also been noted. MB may also have other beneficial effects such as improved myocardial performance by depressing effects of molecules such as TNF-alpha. MB also inhibits superoxide radical formation by competing with oxygen for the transfer of electrons by xanthine oxidase.²⁶

Methylene Blue: Evidence Basis

There have been numerous clinical reports of a favorable response to MB in refractory vasoplegia associated with septic shock, anaphylaxis, CPB and transplantation.²⁷⁻³² MB has been administered prophylactically during CPB in a patient with vasoplegia due to bacterial endocarditis, and to treat a protamine reaction and vasoplegia after CPB.³³

A favorable response is characterized by an increase in mean arterial pressure (MAP) and decreased requirement for inotropic and vasopressor agents. Some early non-randomized studies noted an improvement in cardiac indices and oxygen balance,³⁵ and a decrease in arterial lactate, thought to be due to the reductive action of MB.³⁶ However, PVR also increases and arterial oxygenation may decrease, presumably because of ventilation-perfusion mismatch.³⁸,³⁹ In susceptible subjects at high doses, MB may induce hemolytic anemia, and the pigment interferes with pulse oximetry.

There have been very few randomized controlled trials (RCTs) with MB. Most have utilized a loading infusion of MB of 1–3 mg/kg over 10–30 min, followed by a continuous infusion of 0.25–1 mg/kg/hr.

A small dose-ranging RCT on 15 patients evaluated MB at 1 mg/kg, 3 mg/kg or 7 mg/kg over 20 min. The authors noted a dose-dependent enhancement of hemodynamic function even at the lowest dose, with improved left ventricular filling, cardiac index, oxygen delivery, but cautioned that high doses of MB increase PVR and may compromise splanchnic perfusion.⁴⁰

In another small RCT of 20 patients with septic shock, patients were randomized to placebo or MB 2 mg/kg, followed 2 hrs later by increasing infusion rates between 0.25 and 2 mg/hr over 4 hrs.⁴¹ The most striking finding was a 40-87% decrease in dose requirement for NE, epinephrine and dopamine.
In the largest postoperative RCT performed to date, the vasoplegic syndrome was defined as a combination of hypotension due to low SVR, low cardiac filling pressures, normal or high cardiac index, and high vasopressor requirement. 56 of 638 consecutive cardiac surgery patients met criteria and were randomized to MB 1.5 mg/kg or placebo. Patients who received MB had a striking decrease in mortality (0% vs. 21.4%, p = 0.01) and shorter duration of vasoplegia (6 vs. > 48 hrs, p = 0.0007).

Perhaps the most enterprising RCT is that performed by Ozal et al., who administered MB 2 mg/kg over 30 min or placebo 1 hr preoperatively to 100 CABG patients at high risk for vasoplegic syndrome because they were on ACE inhibitors, calcium channel blockers or heparin. Patients who received MB before surgery had a significant reduction in postoperative vasoplegic syndrome (0% vs. 26%, p < 0.001), ICU length of stay (1.2 ± 0.5 d vs. 2.1 ± 1.2 d, p < 0.001) and hospital length of stay (6.1 ± 1.7 d vs. 8.4 ± 2.0 d; p < 0.001).

**Methylene Blue: Unanswered Questions**

There are many as yet unanswered questions about the use of MB. What are its specific indications? Should it be administered early – even preoperatively - or as a rescue drug, in which case, are we waiting too long? What is the most beneficial dosing regimen? What is the potential for adverse effects? What is the potential for unwanted pulmonary vasoconstriction? Should we always administer it with inhaled nitric oxide to prevent this? I will attempt to address some of these questions in this presentation.

**References**

guanylate cyclase decreases mortality in a rat sepsis model. J Pharmacol Exp Ther 2009; 328: 991-9


