Learning Objectives:
1. To understand the pathophysiology of vasodilatory shock and vasoplegia.
2. To learn the mechanisms of reversal of vasoplegia by methylene blue.
3. To evaluate the evidence for methylene blue therapy in the vasoplegic syndrome.

Pathogenesis of Vasodilatory Shock
The pathogenesis of low systemic vascular resistance (SVR) vasodilatory shock after cardiac surgery has multiple pathways for induction. Contact activation with any foreign surface, e.g. cardiopulmonary bypass (CPB), ECMO or a ventricular assist device (VAD), triggers Hageman (Factor XII) activation and simultaneously activates the intrinsic pathway of coagulation, fibrinolysis and the complement system. The most active components of the complement system are the anaphylotoxins C3a and C5a; their activation culminates in capillary leak and vasodilation.

Severe sepsis or the systemic inflammatory response syndrome (SIRS) invokes massive activation of inducible nitric oxide synthase (iNOS) and release of endogenous nitric oxide (NO). In turn, NO activates the intracellular enzyme soluble guanosine cyclase (sGC) that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), which decreases intracellular calcium and induces intense peripheral vasodilation.

Protracted intracellular acidosis opens potassium-dependent adenosine triphosphate (K\text{ATP}) channels in cell membranes, which allows potassium egress and hyperpolarization of the cell membrane, inactivating calcium channels and inhibiting the vasoconstrictor response to catecholamines such as norepinephrine (NE) or epinephrine (EPI), a syndrome known as vasoplegia.

Endogenous arginine vasopressin (AVP) is an integral component of the endogenous baroreceptor response to arterial hypotension. High plasma levels of AVP (10-100 pg/mL) are released that predominantly activate V\text{1} receptors in vascular smooth muscle and induce compensatory vasoconstriction. In protracted shock, posterior pituitary AVP stores soon become depleted, resulting in an AVP deficiency state with plasma AVP < 3 pg/mL².

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\text{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.

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. Although decreases in endogenous production of NO, interleukins and tumor
necrosis factor (TNF) have not been noted, urinary excretion of NO metabolites is
substantially lower. 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.

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
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.

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, and a
decrease in arterial lactate, thought to be due to the reductive action of MB. However,
pulmonary vascular resistance (PVR) also increases and arterial oxygenation may
decrease, presumably because of ventilation-perfusion mismatch. In susceptible
subjects at high doses, MB may induce haemolytic 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,
oxxygen delivery, but cautioned that high doses of MB increase PVR and may
compromise splanchnic perfusion.

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. The most striking finding was a 40-87% decrease in dose
requirement for NE, EPI 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 NO to prevent this? I will attempt to address some of these questions in this presentation.

**References**