

Vasoplegic Syndrome

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Abstract

Vasoplegic syndrome is a severe case of vasodilatory shock. It is characterized by severe and persistent hypotension, tachycardia, and normal or increased cardiac output, decrease in systemic vascular resistance, low filling pressure and poor or no response to fluid resuscitation. It is associated with cardiopulmonary bypass, severe sepsis, anaphylaxis, and hemodialysis. It is also described in patients with chronic liver disease. Vasoplegic syndrome is attributed to a combination of endothelial injury, arginine vasopressin system dysfunction and release of nitric oxide and other vasodilatory inflammatory mediators e.g. TNF and interferon gamma IF-gamma. The rationale for use of vasopressin in the management of vasoplegic syndrome cases not responding to other vasopressors, is the low level of vasopressin in these patients. The activation of atrial stretch receptors, higher atrial natriuretic peptide and autonomic dysfunction, leads to inhibition of atrial vasopressin release as seen in patients with heart failure. While methylene blue (another drug used for its management) seems to counteract the effect of nitric oxide (NO) and other vasodilators on vascular endothelium and act competitively with NO.

Introduction

Vasoplegic syndrome is a state of endothelial dysregulation resulting in persistent hypotension and low systemic vascular resistance despite adequate fluid resuscitation and vasopressor administration ¹. It has been observed in different clinical settings. It is associated with cardiopulmonary bypass, severe sepsis, anaphylaxis and hemodialysis ². Episodic and persistent hypotension has been described in chronic liver disease ³. It is observed in all age groups ⁴. Incidence may reach 10 % in post cardiac surgery patients and up to 50% in patients who die from sepsis as well as in association with anaphylaxis and protamine administration for reversal of systemic heparinization ^{5,6}.

Pathophysiology of Vasoplegic Syndrome

Normal physiological response to injurious stimuli is dependent on its magnitude. In severe cases the response progresses to systemic inflammatory response syndrome (SIRS) which may progress to multiple organ failure and death ⁷. The physiological response to SIRS is mediated by different mediators which, in turn, induce a synthesis of two endothelial autocooids: nitric oxide and prostacyclin (PG12) resulting in vasoplegia ⁸.

Vasoplegia due to non septic mechanisms can be thought of as a type of pure form of SIRS, including VS associated with cardiopulmonary bypass, hemodialysis or hepatic failure ⁹. Regardless of the etiology, VS appears to represent dysregulation of NO synthesis and release and vascular smooth muscle cell guanylate cyclase activation, upregulation of inducible NO and increase in NO production leading to the generation of cyclic guanosine 3',5' monophosphate (cGMP) resulting in hypotension. Vasoplegic syndrome is attributed to combination of endothelial injury, arginine-vasopressin system

dysfunction and release of vasodilatory inflammatory mediators including TNFalpha, interferon gamma and IL 1 which promote vasodilation through increase in cGMP 9 10. cGMP causes vasodilation and decrease myocyte contractility with myocardial and vascular smooth muscle relaxation 1 10.

Vasoplegic Syndrome after cardiac surgery.

The VS is a severe systemic inflammatory response syndrome and cardiac surgery provokes a vigorous inflammatory response. Vasoplegic syndrome occurs during the early postoperative period after cardiac surgery with cardiopulmonary bypass 12 in response to the systemic inflammation activated by CPB as well as non specific activation such as surgical trauma, blood loss, blood transfusion and hypothermia. Off pump CABG procedures reduces the inflammatory response, however, despite the reduction of the inflammatory response, VS has been observed as an unusual complication after this technique 14. The occurrence of VS after OPCABG necessitates theorizing a possible cause in the absence of extracorporeal circulation. It is possible that generation of pro-inflammatory mediators secondary to surgical stress, use of re-sterilized disposable devices, neutralization of heparin with protamine, the transfusion of blood products or occurrence of endotoxemia secondary to repeated episodes of hypotension due to displacement and mobilization of the heart 14 may precipitate SIRS and vasoplegic syndrome 15. Additional factors to development of VS include preoperative chronic heart failure with low EF less than 35, preoperative use of angiotensin converting enzyme inhibitors, Betablockers and pre and post operative use of amiodarone and phosphodiesterase inhibitors (milrinone) 16 17.

Management of Vasoplegic Syndrome

Management of VS is controversial. Pressor catecholamines are commonly administered to support the systemic arterial pressure in these cases 19. But their effect is limited by frequent resistance to its action and by severe toxic effects at high doses 19. There are three common mechanisms for the vasodilation and resistance to vasopressors that occur in most types of vasodilatory shock; the activation of ATP-sensitive potassium channels in the plasma membrane of vascular smooth muscles, the activation of inducible form of nitric oxide oxidase and a deficiency of the hormone vasopressin 20.

1- Activation of K-ATP channels in vascular smooth muscle:

Recent work indicates that the membrane potential of vascular smooth muscle cells have a critical role in modulating vascular tone. Positive potential (depolarization) opens the voltage gated calcium channels, increasing the cytosolic calcium concentration and induces vasoconstriction. While hyperpolarization closes these channels, decreasing cytosolic calcium concentration and inducing relaxation 21. The opening of K-ATP channels allow efflux of K, hyperpolarizing the plasma membrane and prevent the entry of calcium into the cell. K-ATP channels are physiologically activated by decrease cellular ATP concentration, increasing intracellular concentration of hydrogen and lactate, a mechanism that links cellular metabolism with vascular tone and blood flow 22.

That is to say; conditions that compromise tissue oxygenation and result in lactic acidosis, activate K-ATP channels in vascular smooth muscle and thereby cause vasodilatory shock.

2- Increased synthesis of Nitric Oxide

Nitric oxide production is increased as a result of increased expression of inducible NO synthase (iNOS). The mechanisms responsible for increased iNOS expression may be due to several cytokines (IL-1B, IL-6, TNF alpha, IF gamma and adenosine) ²³. The vasodilatory effect of NO is mediated by the activation of myosin-light chain phosphatase and potassium channels in the plasma membrane of vascular smooth muscles ²² especially those channels sensitive to cytosolic calcium (K-Ca channels). These channels blunt the effect of vasoconstrictors ²⁴. Nitric oxide can activate K-ca channels by two mechanisms; direct nitrosylation of the channel and activation of cGMP dependent protein kinase; this activation contributes to vasodilation and vasopressor-resistance in vasodilatory shock ²⁵.

3- Deficiency of vasopressin

Normally, vasopressin plays a minor role in arterial pressure regulation, but in response to hypotension e.g. septic or hemorrhagic shock, it is released from the neurohypophyseal gland with marked increase in its plasma concentration ²⁶. As Shock worsens its plasma levels decrease ²⁷. The exact mechanism responsible for this low concentration may be due to depletion of neurohypophyseal stores of vasopressin after profound osmotic stimulation and after sustained baroreflex stimulation ²⁸. Correction of low plasma concentration of vasopressin by administration of the hormone increases arterial pressure by 25-50 mmHg in patients with vasodilatory shock not responding to volume replacement and catecholamine administration ²⁷.

What are the reasons for marked sensitivity to exogenous vasopressin administration in vasodilatory shock?

Several possibilities are likely: 1- As plasma concentrations of vasopressin are relatively low, its vascular receptors are available for occupancy by the exogenous hormone, whilst norepinephrine and angiotensin II concentrations are high in vasodilatory shock; these high concentrations cause desensitization of the receptors.

2- The vasopressor effect of vasopressin is increased in patients with autonomic dysfunction and patients with vasodilatory shock are usually comatosed or sedated. Also, patients with sepsis have impaired sympathetic nervous systems. 3-Vasopressin potentiates the vasoconstrictor effect of norepinephrine which is present in high concentrations ³⁰. 4-Vasopressin directly inactivates K-ATP channels in vascular smooth muscle. 5-Vasopressin blunts the increase in cGMP induced by nitric oxide and atrial natriuretic peptide and decreases the synthesis of iNOS that is stimulated by lipopolysaccharide ³¹.

Dose of vasopressin in vasodilatory shock:

Different doses of vasopressin have been used but a dose of 6u/h provide a steady plasma concentration of 150pg/ml, increasing the dose has no additional effect ³².

N.B. It must be stressed that there are limitations regarding the widespread use of vasopressin for management of refractory vasodilatory shock after cardiac surgery. These limitations include the lack of a dose response investigation and the risk of complications such as decrease coronary blood flow, cardiac output and gut perfusion at high doses.

Methylene blue (MB)

It is approved for oral and intravenous administration in the setting of methemoglobinemia, hemolysis and as a surgical tracer dye for detection of fluid leak. It is available as a solution 10mg/ml; its oral absorption ranges from 53-97%³³, intra-tracheal administration has been described experimentally. It is eliminated in bile, feces and urine as leucomethylene blue. It is used in all age groups ⁴.

Mode of action on vascular smooth muscle:

Methylene blue counteracts the effect of NO and other nitrovasodilators in the endothelium and vascular smooth muscle and it is believed to act competitively with NO, by binding to iron heme-moiety of soluble guanylyl cyclase (sGC) and blocking sGC action in vascular smooth muscle. NO decreases the level of cGMP and alleviates the vasorelaxant effect seen in VS ³⁴. Dose: Single dose of i.v. MB 1-2mg/Kg over 20 minutes infusion time as a rescue treatment in the setting of vasoplegia of anaphylaxis and cardiac surgery. Continuous MB infusion is described in the patient who is not responding to a single dose of MB and is administered for a variable length of time: 120mg MB diluted in D5W given over 1-6 hours ³⁵. Methylene blue has been used in the setting of vasoplegia related to cardiac surgery, sepsis ³⁵, anaphylaxis, liver failure and hemodialysis ³⁶. At higher doses than that described above, MB becomes an oxidant which oxidizes hemoglobin, resulting in methemoglobinemia and hyperbilirubinemia ³⁷.

Contraindications and side effects of MB:

Methylene blue must not be used in patients who are hypersensitive to the drug. Although contraindicated in patients with severe renal insufficiency, it can be used in hemodialysis-dependent patients ³⁷. MB must be used cautiously in patients with either Glucose-6- Phosphate dehydrogenase deficiency or those who have a low level of NADPH because of the risk of hemolytic anemia³⁸. Rare side effects are associated with MB use and include cardiac arrhythmias (nodal rhythm or ventricular ectopy), coronary vasoconstriction, and angina, decreased COP, decreased renal and mesenteric blood flow, increase pulmonary vascular resistance and worsening gas exchange ³⁹.

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