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Advances in vasodilatory shock: a concise review

Abstract

Managing vasodilatory shock remains the most challenging entity for intensivists even today. It is simply because the condition does not respond to high-dose vasopressors and results in high mortality. Currently, catecholamines are the most widely used vasopressors to maintain stable blood pressures in intensive-care settings, but loss of catecholamine-pressor effects is a well-known clinical dilemma. However, studies with newer modalities like angiotensin, arginine vasopressin etc. have pointed favorable outcomes. We briefly discuss the updates in managing vasodilatory shock, with focus on evidence-based recommendations.

Keywords: shock, vasodilatory, angiotensin, vasopressin

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Abbreviations: DB, double blinded; MC, multi-centric; RCT, randomised controlled trial; MAP, mean arterial pressure

Introduction

Background

Shock is the clinical manifestation of a circulatory failure which results in inadequate delivery of oxygenated blood to tissues resulting decreased organ perfusion and cellular dysfunction. Shock is a common clinical condition, specially affecting about one third of patients in the intensive care units.[1] It can be broadly classified into four broad categories namely;[1] (i) Hypovolemic Shock (due to external or internal fluid loss such as haemorrhage etc.), (ii) Cardiogenic shock (due to acute myocardial infarction, cardiomyopathy, arrhythmias, valvular heart diseases etc.), (iii) Obstructive type of shock (due to cardiac tamponade, pulmonary embolism etc.) and (iv) Vasodilatory shock (due to sepsis or anaphylaxis etc.). There is low cardiac output with inadequate oxygen transport in Hypovolemic, cardiogenic and obstructive shock. However, in vasodilatory shock, there is a decreased systemic vascular resistance and altered oxygen delivery to cells.[1]

Septic shock (a form of vasodilatory shock), is the most common form of shock encountered in critical-care settings, followed by cardiogenic and hypovolemic shock.[1] It affects more than 1.5 million americans each year at an annual burden of cost of over $20 billion.[2] It is the leading cause of non-cardiac death in intensive-care units in USA, and has a very high mortality rate (approx. 30% when treated, fatal often in not treated).

Other common causes of shock include systemic inflammatory response syndrome (SIRS), anaphylaxis, pancreatitis, hepatic failure, neurogenic shock due to spinal cord injury, glucocorticoid deficiency and various toxins.[1] Vasodilatory shock can occur solely or in combination with other variants of shock, although it can be the final common pathway in the pathophysiology underlying severe shock of any cause.[3]

Pathophysiology

In vasodilatory shock, plasma catecholamine concentrations are markedly increased and renin-angiotensin system (RAAS) gets activated. However peripheral vasodilatation and hypotension occurs with less oxygen being supplied to the tissues. The most important mechanisms implicated are: (i) activation of ATP-sensitive potassium channels (K+-ATP channels) in the plasma membrane of vascular smooth muscle, (ii) activation of the inducible form of nitric oxide synthase and (iii) deficiency of the hormone vasopressin.[3] K^+-ATP channels are physiologically activated by a decrease in the cellular ATP concentration and a cosequent increase in cellular concentrations of hydrogen ion and lactate. The opening of K^+-ATP channels allows an efflux of potassium, thus hyperpolarizing the plasma membrane. This causes closer of voltage-gated calcium channels which is mostly responsible for catecholamine-induced or angiotensin-II mediated vasoconstriction. Therefore, cytosolic concentration of Ca^{2+} decreases and vasodilatation occur.[3]

Nitric oxide (NO) production is increased due to expression of the 'inducible form' of NO synthase. This increase occurs in various types of cells, including vascular smooth-muscle cells and endothelial cells. Although the underlying mechanism is not fully understood, the role of several cytokines (e.g. interleukin-1β, interleukin-6, tumor necrosis factor-α, interferon-γ and adenosine) has been implicated.[3]

In response to hypotension due to a haemorrhage or sepsis, plasma concentrations of vasopressin released from the neurohypophysis markedly increases which contribute to the maintenance of arterial pressure. However, as shock worsens, vasopressin levels in plasma decrease. The exact underlying mechanism for such a change is still under exploration, but a plausible explanation could be depletion of neurohypophyseal stores of vasopressin after profound osmotic stimulation.[3]

Hemodynamic changes

In vasodilatory shock, cardiac output and heart rate increases initially to compensate for reduced oxygen supply to tissues. Subsequently, a hyperdynamic left ventricular systolic contraction propels blood further into the tissues. However, despite such inotropic and chronotropic stimulation, systemic vascular resistance (SVR) decreases due to vasodilatation.[3] This results in increase of venous capacitance and pooling of blood in venous system, decreasing preload and cardiac output. As a result, several counter regulatory systems such as sympathetic nervous system, RAAS gets activated, thus restoring the cardiac output and blood pressure.[1,3] However, since counter-regulatory measures may result in adequate even increased cardiac output, tissue oxygenation still remains deficient due to decreased SVR and peripheral vasodilatation.[3]

Management

Objective: The goal of treatment in vasodilatory shock is primarily reversal of the underlying cause. In septic shock, removal of focus

of infection can dramatically improve survival. This should be followed by hemodynamic stabilization with fluids and vasopressors. Finally, prevention of renal and myocardial injury and subsequently preventing associated complications such as thromboembolism, deep vein thrombosis etc is crucial.

Initial resuscitation

The Surviving Sepsis Campaign 2016 (SSC-2016)[4] guidelines have been updated with a focus on vasodilatory shock. Since septic shock is the most common variant of vasodilatory shock, it is recommended that treatment and resuscitation should begin as early as possible.[4] At least 30mL/kg of intravenous crystalloid fluid must be given within the first 3 hour of presentation. Following initial fluid resuscitation, additional fluids must be guided by frequent reassessment of hemodynamic status. Reassessment should include a thorough clinical examination and evaluation of heart rate, blood pressure, arterial oxygen saturation, respiratory rate, body temperature, urine output along with other non-invasive or invasive monitoring parameters, as available.[4] Assessing cardiac function becomes imperative to determine type of shock, if clinical examination does not lead to a clear diagnosis.[4]

Dynamic variables such as stroke volume (SV), pulse pressure variation (PPV), SV variation with passive leg raise (PLR) or fluid challenge are better predictors of fluid responsiveness compared to static variables such as central venous pressure (CVP) etc.[4,5] In patients requiring vasopressors, the target mean arterial pressure (MAP) must be 65mm Hg.[4,5] Elevated lactate levels can be used as a marker of tissue hypo-perfusion.

Fluid therapy

It is recommended to continue fluid challenge as long as hemodynamic parameters continue to improve.[4,5] According to SSC-2016, balanced crystalloids or saline are the fluid of choice for initial resuscitation and subsequent volume replacement in patients with septic shock patients.[4,5]

Albumin (4-5%) has been recommended in SSC-2016 in addition to crystalloids for resuscitation and subsequent volume replacement, if substantial amounts of crystalloids needed. In the SAFE trial (n=6997, DB, MC, RCT) there was no significant difference in survival between two treatment arms (one receiving 4% albumin and one group normal saline in initial ICU resuscitation).[6] In the ALBIOS trial (n=1818, MC, RCT) where patients received 20% albumin/crystalloid or crystalloid during, resuscitation and through Day 28 in the ICU, albumin/crystalloid group had an improved hemodynamic profile compared to crystalloid group, however there was no increase in survivability.[7]

The SSC-2016 recommendations discourage using hydroxyethyl starche (HES) or gelatin for volume replacement in patients with sepsis or septic shock.[4,5,8] Meta-analysis, of 16 RCTs evaluating gelatin versus crystalloids and albumin showed gelatin solutions increased the risk of anaphylaxis and could be harmful by increasing mortality, renal failure, and bleeding possibly due to extravascular uptake and coagulation impairment colloid resuscitation fluid which warrants its use with caution.[8,9]

Vasoactive medications

Norepinephrine is now regarded as the first-choice vasopressors in treatment of vasodilatory shock.[4,5,10] Addition of either vasopressin (up to 0.03U/min) or epinephrine to norepinephrine has been recommended, when there is intent to raise MAP to target or decrease norepinephrine dosage.[4,10] Dopamine is indicated as an alternative vasopressor to norepinephrine, but only in highly selected patients (e.g. those with low risk of tachyarrhythmias and absolute or relative bradycardia). SSC-2016 do not recommend using low-dose dopamine for renal protection,[4,9] although dobutamine has been indicated in patients who show evidence of persistent hypo-perfusion despite adequate fluid loading and the use of vasopressor agents.[4]

In 1953, *Arterenol* (norepinephrine) was used in a small clinical study (n=32) in patients with shock, with excellent results in 72% patients. Overwhelmed by its response several clinical trials were to follow over the years. In Dopamine *versus* Norepinephrine trial (MC, RTC) no significant difference in 28 day, 6 month or 12 month mortality was recorded.[9] In meta-analysis of 32 trials of vasopressors in septic shock, norepinephrine was the most favoured agent (RR 0.89, 95% CI: 0.81, 0.98).[10] In an Epinephrine *versus* Norepinephrine trial (n=277, DB, MC, RCT) there was no difference in MAP achieved, max daily dose, mean CVP or net fluid balance during infusion.[11] However, Epinephrine was associated with significant development ($p< 0.001$) of tachycardia and lactic acidosis in first 4 to 24 hours period.[11] In Vasopressin *versus* Norepinephrine trial (n=778, MC, DB, RCT), the severity of septic shock was reported to be lower with vasopressin ($p=0.05$), however, no significant differences were found in other hemodynamic parameters.[12] Meta-analysis of Vasopressin/Terlipressin treatment in vasodilatory shock revealed a lower short-term mortality of 40.2% in vasopressin/terlipressin group *versus* 42.9% in control group (RR=0.91, 95% CI: 0.79, 1.05, $p=0.21$).[13] Although, use of vasopressin or terlipressin did not produce any short-term survival benefit, its property of reducing norepinephrine requirement in vasodilatory shock may be valued by physicians.

Refractory cases

Refractory vasodilatory shock is a state of persistent hypotension despite the use of high doses of vasopressors. It is a very critical condition with 30-day all-cause mortality in treatment-refractory septic shock is more than 50%.

A clinical study published in JAMA[14] was the first to use angiotensin in a cohort of 21 patients, and reported favourable effect on blood pressure in 15 out of 21(72%) critically ill patients.[14] Later such findings were corroborated in the ATHOS trial, which was a 'proof of concept' study (n=20) pointing that human Angiotensin-II could effectively increase mean arterial pressure (MAP).[15] Subsequently, ATHOS 3 trial, which was an international, double-blind, placebo controlled trial involving a larger cohort (n=344) in 75 intensive-care units, also showed that Angiotensin-II effectively increased blood pressure in patients with vasodilatory shock that did not respond to high doses of conventional vasopressors.[16]

On 21st December 2017, US-FDA finally approved *Giapreza* (angiotensin II) injection for intravenous infusion to increase blood pressure in adults with septic or other distributive shock. Currently, two other drugs are under late stage development: *Vasopressin* and *Selepressin* (V1a selective agonist). In a trial of Selepressin 2.5ng/kg/min infusion in early septic shock (n=53, DB, PC, MC, RCT) revealed promising results, with a higher proportion of patients maintaining MAP without norepinephrine, decreased mean cumulative dose of norepinephrine, shorter duration of shock with mortality benefits.[17]

Conclusion

Vasodilatory shock is the leading cause of death in intensive care set-ups with its most common form being septic shock. The SSC-2016 guidelines have delineated major aspects in managing vasodilatory shock, and focused on fluid therapy and vasoactive medications other than definitive therapy, which are most important supporting care to increase survival benefits. Fluid resuscitation (crystalloids) qualifies as an important determinant maintaining stable hemodynamic parameters, along with vasopressors (norepinephrine preferred; dopamine/dobutamine in certain patients) to achieve the target of MAP ≥65mm Hg in patients with septic or vasodilatory shock. Despite optimal treatment with well-defined protocols, mortality rate remains high. However, there have been some promising clinical studies to indicate that the future drug pipeline looks robust and feasible.

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Conflicts of interest

The author declares that there is no conflicts of interest.

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