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Proper Use of Vasopressors in Septic Shock

Introduction

Several factors contribute to organ dysfunction in septic shock patients, and once the inflammatory response has been activated, many organ systems can be adversely affected. A marked fall in systemic vascular resistance results from arterial and venous dilatation. This is accompanied by leakage of plasma into the extravascular space, leading to relative hypovolemia. The microcirculation is adversely affected, with maldistribution of blood flow. Importantly, oxygen is neither reaching nor being effectively extracted by cells, probably because of arteriovenous shunting or abnormalities in cellular metabolism.

At the organ level, blood flow and perfusion pressure are regulated by two control mechanisms. The first, extrinsic, involves a complex interaction of vasomotor effects between opposing neurohormonal systems. The second, intrinsic, is the organ autoregulation, and depends on changes in afferent arteriolar tone in response to the organ perfusion pressure itself. In healthy subjects below the autoregulatory thresholds, organ blood flow becomes linearly dependent on perfusion pressure. In septic shock patients, the autoregulation system is disturbed resulting in this linear relation between organ blood flow and perfusion pressure. Haemodynamic factors such as volume depletion, low cardiac output or inappropriate vasodilation resulting in systemic hypotension may directly produce organ hypoperfusion through a reduction in organ perfusion pressure. Therefore, one goal of the haemodynamic resuscitation in septic shock should be restoration of adequate organ perfusion pressure without impairing blood flow to the organ.

Objectives in the Initial Resuscitation From Septic Shock

According to the Surviving Sepsis Campaign guidelines, the endpoints of initial resuscitation (first six hours) are: central venous pressure of 8-12 mmHg, mean arterial pressure above 65 mmHg, urine output above 0.5 ml/kg/hour, and central venous (superior vena cava) oxygen saturation (ScvO₂) above 70% (Dellinger et al. 2008).

Several limitations should be underlined about these guidelines on sepsis management:

- Specific endpoints remain undetermined for resuscitation in late septic shock;
- The use of central venous pressure to assess preload responsiveness is controversial because of its poor predictive value; thus, the use of dynamic parameters, as opposed to static parameters, could be preferred when predicting fluid responsiveness in septic patients; and
- The best level of mean arterial pressure is still unknown, although a target goal of 65 mmHg seems equivalent to higher pressures. Abnormalities of oxygen distribution in septic shock can subsist despite normal blood pressure. A normal or elevated ScvO₂ with increased lactataemia surrogates for a defect of peripheral oxygen utilisation. A prominent feature of sepsis is a dysfunction of microcirculation, with impaired perfusion and regional tissue oxygenation causing a deficit in oxygen extraction.

The Use of Vasopressors

Vasopressor agents should be used according to practical considerations in septic shock patients (Table 1). The basic catecholamine structure is a phenylethylamine with three hydroxyl groups. The effects of catecholamines range from pure α -agonist to pure β -agonist. Briefly, the α -agonist stimulation produces a vasoconstriction, whereas the β -agonist stimulation increases cardiac performance. Pure β -agonist will not be considered thereafter.

Dopamine is the immediate precursor of norepinephrine. At low doses D_{1A} receptors are activated causing vasodilatation of the renal and mesenteric circulations. At doses of 2-10 μ g/kg/min, β -adrenergic stimulation has positive inotropic and chronotropic effects, while at higher doses, α -adrenergic stimulation results in peripheral vasoconstriction.

Norepinephrine is the endogenous mediator of the sympathetic nervous system and has both α - and β -adrenergic dose dependent effects. Large doses increase blood pressure via an α -adrenergic mediated vasoconstriction. Norepinephrine induces vasoconstriction visibly in many vascular beds (eg, the skin and muscles), and could therefore alter visceral blood flow and, more notably, renal blood flow, impairing organ function. In experimental rat models, norepinephrine caused ischemia-induced acute renal failure (Cronin et al. 1978). However, it is not clear whether the same scenario of vasopressor-induced visceral hypoperfusion actually occurs in sepsis, which is characterised by marked vasodilation related to muscle α -adrenergic receptor hyporesponsiveness or massive nitric oxide production. When normal haemodynamic status exists, norepinephrine administered to raise mean arterial pressure by 20% does not affect glomerular filtration. In contrast, when severe vasodilation (ie. low systemic vascular resistance and high cardiac index) affects systemic circulation, the infusion of norepinephrine, which is required to restore tissue perfusion pressure, is accompanied by a restoration of urine filtration, a decrease in serum creatinine level, and an increase in clearance of creatinine in septic patients.

The beneficial effect of norepinephrine in septic patients is in agreement with the conclusions of several clinical reports. Epinephrine is synthesised, stored and released from the chromaffin cells of the adrenal medulla. At low doses, stimulation of β_1 - and β_2 -adrenergic receptors is preponderant while at higher doses (0.15-0.3 $\mu\text{g}/\text{kg}/\text{min}$), α -adrenergic receptors are activated with a potent vasoconstriction. Epinephrine increases oxygen delivery in septic shock by increasing cardiac index without having an effect on systemic vascular resistance index or pulmonary artery occlusion pressure. It has been associated with an impaired effect at the level of splanchnic circulation. Actually, in a study by Meier-Hellmann et al., the decrease in splanchnic blood flow with epinephrine occurred in conjunction with three signs of deteriorating tissue oxygenation in this region: a decrease in splanchnic oxygen consumption, a decrease in pHi, and an increase in lactataemia.

The Clinical Studies

Martin and colleagues compared the ability of dopamine and norepinephrine to reverse haemodynamic and metabolic abnormalities in human hyperdynamic septic shock. Norepinephrine was found, at the doses tested, to be more effective and reliable than dopamine in reversing the abnormalities of hyperdynamic septic shock. In the great majority of the patients, norepinephrine was able to increase mean perfusing pressure without apparent adverse effects on peripheral blood flow or on renal blood flow. At the same time, oxygen uptake was increased. In a non-randomised study, the same group found better survival in patients treated with norepinephrine than in those treated with dopamine or epinephrine (Martin et al. 2000).

Two studies seem to confirm that administration of dopamine can be associated with increased mortality in septic shock patients (Levy et al. 2005; Sakr et al. 2006). In a population of 110 septic shock patients, resistance to dopamine was associated with an increased risk of death (odds ratio: 9.5; 95% confidence interval: 3-25) (Levy et al. 2005). The dopamine group of an observational study which included 1,058 patients with shock had a higher hospital mortality rate than patients given other vasopressor agents (42.9% versus 35.7%, a statistical significance of $P=0.02$) (Sakr et al. 2006).

The stimulation of α -adrenoreceptors, by inducing contraction of mesenteric vascular smooth muscle, can result in gut ischemia. The effects of dopamine, norepinephrine and epinephrine on splanchnic circulation have been compared in patients with septic shock (De Backer et al. 2003). Dopamine was progressively withdrawn and replaced successively by norepinephrine and then epinephrine to maintain constant mean arterial pressure (moderate shock) or to increase mean arterial pressure above 65 mmHg (severe shock). This study showed that dopamine and norepinephrine have similar haemodynamic effects, while epinephrine can impair splanchnic circulation in severe septic shock.

Recent randomised studies showed that this splanchnic effect does not impact on patient outcome. In a French study which aimed to compare the efficacy and safety of administering norepinephrine plus dobutamine with those of epinephrine alone in 330 randomised septic shock patients, there was no significant difference between the two groups with regard to mortality rate (Annane et al. 2007). Some years later, a large randomised trial compared dopamine and norepinephrine in 1,679 patients. Among these patients, 1,044 had a septic shock (De Backer, 2010). Although there was no significant difference in deaths from the two groups, the use of dopamine was associated with a greater number of adverse events. De Backer and his team later conducted a meta-analysis in septic shock patients treated with either dopamine or norepinephrine. Six randomised studies were retrieved, totalling 2,769 patients (De Backer et al, 2012). The conclusion was clear: dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events, making norepinephrine the first choice for the treatment of septic shock.

A Role for Vasopressin

Over time, vascular responsiveness to catecholamines diminishes. This vascular hyporeactivity to catecholamines is most likely due to excessive nitric oxide formation associated with an activation of ATP sensitive potassium channels and a reduction in calcium entry through voltage-gated calcium channels. Thus, the search for alternative vasopressors, used alone or in combination with standard therapies, is of great interest. Vasopressin mediates vasoconstriction via V1-receptors, which are coupled to phospholipase C, and increases intracellular calcium concentration. The plasma vasopressin levels of septic shock patients are almost always increased at the initial phase of septic shock, and subsequently decreased.

A large randomised clinical trial entitled VASST study aimed to compare the survival of 778 septic shock patients treated with vasopressin (up to 0.03 IU/min) or norepinephrine (Russel et al. 2008). The inclusion criterion was septic shock requiring at least 5 $\mu\text{g}/\text{min}$ of norepinephrine for six hours during the last 12 hours. Target mean arterial pressure was 65-75 mmHg. Lactatemia and renal function were unaffected by the two treatments and mortality was similar in both groups (35.4% versus 39.3%, $P=0.26$). The survival of patients with less severe forms of shock, defined by an entry dosage of norepinephrine ranging from 5 to 14 $\mu\text{g}/\text{min}$, was higher in the group treated with vasopressin (26.5% versus 35.7%, $P=0.05$). Three hypotheses may explain this result. First, the significance could be due the 5% probability of a mistake in the statistical test. Second, vasopressin may have beneficial hormonal actions, independent of its vasopressor effect. Third, the addition of vasopressin may be inefficient in the patients treated with high doses of norepinephrine. In a recent metaanalysis, the potential role of vasopressin or terlipressin was evaluated. Overall, it was concluded that these drugs do not provide any survival benefit (Polito et al. 2012); they have a sparing effect on norepinephrine requirement. They can be considered as rescue therapy when catecholamines fail to improve blood pressure.

Conclusion

Vasopressor agents are required to maintain a minimal level of blood pressure in septic shock patients. Recent evidence suggests that norepinephrine should probably be the first choice in these cases. In several studies, dopamine is associated with a poor outcome and more negative side-effects.

Vasopressin improves the norepinephrinemediated vessel smooth muscle contraction and its use is associated with a cardiac output decrease, which can be detrimental in selected patients. However, its use does not impact on the outcome of septic shock patients. Early combination of

norepinephrine and vasopressin in cases of septic shock should be tested in future studies.

Key Learning Points

- 1) Fluid resuscitation is always the first step in haemodynamic management.
- 2) The use of norepinephrine or epinephrine can be left at the discretion of the treating physician, but norepinephrine should probably be the first choice.
- 3) Low-dose vasopressin administration remains an option for catecholaminerefractory septic shock.
- 4) The potential benefit of early vasopressin use in combination with a moderate dose of norepinephrine remains to be determined.
- 5) The status for dopamine remains to be determined.

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