Review

Bench-to-bedside review: Is there a place for epinephrine in septic shock?

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Abstract

The use of epinephrine in septic shock remains controversial. Nevertheless, epinephrine is widely used around the world and the reported morbidity and mortality rates with it are no different from those observed with other vasopressors. In volunteers, epinephrine increases heart rate, mean arterial pressure and cardiac output. Epinephrine also induces hyperglycemia and hyperlactatemia. In hyperkinetic septic shock, epinephrine consistently increases arterial pressure and cardiac output in a dose dependent manner. Epinephrine transiently increases lactate levels through an increase in aerobic glycolysis. Epinephrine has no effect on splanchnic circulation in dopamine-sensitive septic shock. On the other hand, in dopamine-resistant septic shock, epinephrine has no effect on tonometric parameters but decreases fractional splanchnic blood flow with an increase in the gradient of mixed venous oxygen saturation (SVO_2) and hepatic venous oxygen saturation (SHO_2). In conclusion, epinephrine has predictable effects on systemic hemodynamics and is as efficient as norepinephrine in correcting hemodynamic disturbances of septic shock. Moreover, epinephrine is cheaper than other commonly used catecholamine regimens in septic shock. The clinical impact of the transient hyperlactatemia and of the splanchnic effects are not established.

Introduction

Early goal directed therapy [1] is now considered as a gold standard in the early phase of septic shock. Fluid therapy and vasoactive therapy may be immediately required in order to maintain acceptable blood pressure levels. Invasive or non-invasive assessment of hemodynamic status, although essential to the rational management of septic shock, may take time to establish. In this setting, there is good reason to choose a broad spectrum catecholamine such as epinephrine or dopamine rather than a pure α-adrenergic agonist, which can cause substantial reductions in cardiac output, and as an alternative to a pure β-agonist such as dobutamine, which can exacerbate vasodilation and hypotension through its β_2-adrenergic action [2]. In contrast to norepinephrine-dobutamine, epinephrine when used in septic shock increases lactate level together with a slightly enhanced lactate/pyruvate (L/P) ratio, decreases global splanchnic flow and elevates the tonometric mucosal partial CO_2 tension (PCO_2) gap (tonometer PCO_2 minus arterial PCO_2), a surrogate marker of gastric mucosal metabolism and/or perfusion. Based on these observations, The Task Force of the American College of Critical Care Medicine and the Society of Critical Care Medicine recommends the use of epinephrine only in patients who fail to respond to traditional therapies [3].

The aim of this paper is to provide an alternative point of view regarding the somewhat dark side of epinephrine and to moderate the interpretation of pharmacological data.

Epinephrine effects in volunteers

Hemodynamic effects

In volunteers [4,5], epinephrine increases heart rate as well as mean arterial pressure (MAP), mainly as the result of a rise in systolic blood pressure. Conversely, diastolic blood pressure falls, irrespective of the dosage. Vasodilatation occurs in the calf vascular bed while blood flow in skin capillaries and arteriovenous anastomoses decreases. Concentration-dependent increases in stroke volume and cardiac output occur without any changes in end-diastolic volume, along with decreases in vascular resistances of the systemic circulation, calf and adipose tissue. Coronary blood flow, blood flow to skeletal muscles as well as hepatic blood flow increase while splanchnic vascular resistances decrease. Alternatively, renal blood flow decreases with an increase in the filtration fraction

Metabolic effects

In healthy volunteers [4,5], epinephrine induces hyperglycemia and hyperlactatemia. Because insulin secretion is suppressed by alpha adrenergic stimulation, plasma concentration of insulin remains low. Hyperglycemia is induced by an increase

ICG = indocyanine green; IL = interleukin; L/P = lactate/pyruvate; MAP, mean arterial pressure; PCO_2 = partial CO_2 tension; SHO_2 = hepatic venous oxygen saturation; SVO_2 = venous oxygen saturation.

in glucose production caused by an increase in hepatic glycogenolysis and an increase in gluconeogenesis. There is also a marked increase in oxygen consumption (VO_2). In skeletal muscle, epinephrine increases glycolysis and glycogenolysis, inducing an upsurge in lactate. Muscular lactate serves as a substrate for hepatic neoglucogenesis (Cori cycle). Epinephrine also increases lipolysis and decreases muscular proteolysis.

Clearly, epinephrine is the most potent natural β-agonist, which explains the fact that in volunteers or in patients with septic shock, epinephrine increased glucose and lactate levels more than norepinephrine.

Epinephrine effects in septic shock

Epinephrine is effective in restoring global hemodynamics

In patients unresponsive to volume expansion or other catecholamine infusions, epinephrine can increase MAP, primarily by increasing cardiac index and stroke volume together with more modest increases in systemic vascular resistance and heart rate. This is an important advantage, especially in patients with altered cardiac function. The effects of epinephrine in hyperdynamic or normodynamic septic shock are highly predictable, correlating an increase in MAP with an increase in cardiac index [6]. Using epinephrine as a first line agent, Moran *et al*. [7] reported a linear relationship between epinephrine dosage and heart rate, MAP, cardiac index, left ventricular stroke work index, and oxygen delivery and consumption. Despite an increase in oxygen consumption, no adverse cardiac side effects have been described in septic shock. Electrocardiographic changes indicating ischemia or arrhythmias have not been reported in septic patients. In patients with right ventricular failure, epinephrine increases right ventricular function by improving contractility [8]. Considering global hemodynamics, epinephrine is more effective than dopamine and is just as efficient as norepinephrine [9].

Epinephrine increases lactate concentration

In human septic shock, epinephrine increases lactate levels and decreases arterial pH [10]. From the equation $L/P = K.NADH/NAD.[H^+]$, where K is the dissociation constant, it may be seen that a change in H^+ could result in a proportional change in the L/P ratio. Thus, interpretation of the L/P ratio should be done while accounting for arterial pH. In the same study, we found that epinephrine increased lactate level without any increase in the L/P ratio when the latter was normalized to pH ($H^+ = 10^{-pH}$). This rise in lactate is transient, however, as levels return to baseline values after 12 hours [9]. The fact that β-receptor density is down-regulated during sepsis [11] likely explains the transient character of epinephrine increased lactate.

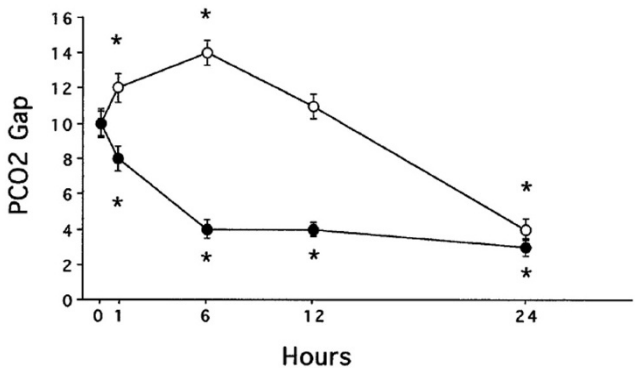
Epinephrine infusion is associated with an increase in lactate concentration not only in septic conditions but also under fully aerobic conditions, such as in healthy volunteers at rest and during exercise. In a model of endotoxinic shock, we demonstrated that the infusion of epinephrine was associated with a significant increase in lactate without any change in L/P ratio [12]. Moreover, epinephrine use was not associated with a decrease in tissue ATP [12], demonstrating that epinephrine-induced hyperlactatemia is probably related to direct effects of epinephrine on carbohydrate metabolism and not to cellular hypoxia. Indeed, elevated blood lactate concentrations during shock states are often viewed as evidence of tissue hypoxia, with lactate levels being proportional to the defect in oxidative metabolism [1]. However, many tissues generate pyruvate and lactate under aerobic conditions (so-called aerobic glycolysis) in a process linking glycolytic ATP supply to activity of membrane ion pumps such as Na^+,K^+-ATPase [13]. Stimulation of aerobic glycolysis (glycolysis not attributable to oxygen deficiency or glycogenolysis) occurs not only in resting, well-oxygenated skeletal muscles but also during experimental hemorrhagic shock and experimental sepsis, and is closely linked to stimulation of active sarcolemmal Na^+,K^+-ATPase transport under epinephrine stimulation. Epinephrine stimulates the release of lactate from skeletal muscle through stimulation of Na^+,K^+-ATPase for oxidation purposes or gluconeogenesis (Cori cycle). Thus, increased lactate production is the result of aerobic glycolysis rather than the result of anaerobic glycolysis. Although this is an ATP-consuming process, the source of energy in the liver ultimately comes from fatty acids. Thus, lactate provides glycolytic ATP to several peripheral cells, this ATP being derived from energy-producing lipid oxidation. This hypothesis was recently demonstrated in human septic shock [14].

Epinephrine increases the PCO_2 gap

In a clinical setting of dopamine-resistant septic shock, we compared the effects of norepinephrine-dobutamine versus epinephrine alone on gastric tonometry using saline tonometry [8]. Despite similar increases in arterial pressure and oxygen delivery in both groups, the PCO_2 gap increased in epinephrine-treated patients. This increase was transient, however, as both groups had the same normal PCO_2 gap after 24 hours (Fig. 1). Moreover, the amplitude of the PCO_2 gap increase was moderate and consistently below 18 mmHg [15]. This suggests one of two possibilities [16]. First, that epinephrine increases splanchnic oxygen utilization and CO_2 production through a thermogenic effect, especially if gastric blood flow does not increase to the same extent, inducing a mismatch between splanchnic oxygen delivery and splanchnic oxygen consumption. Second, that epinephrine decreases mucosal blood flow with a decrease in CO_2 efflux, the net result being an increase in CO_2 gap. The latter hypothesis is not supported by Duranteau *et al*. [17], however, who demonstrated, using laser Doppler flow, that epinephrine induces higher gastric mucosal blood flow than norepinephrine and dopamine without significant change in the PCO_2 gap.

Moreover, De Backer *et al*. [18] did not observe any variation in the PCO_2 gap during epinephrine infusion using air

Figure 1



Evolution of the partial CO_2 tension (PCO_2) gap (tonometer PCO_2 – arterial PCO_2) during infusion of epinephrine (open circles) or norepinephrine-dobutamine (closed circles). Asterisks indicate $p < 0.01$ versus baseline. (Reproduced from [8] with permission.)

tonometry. Conversely, also using air tonometry, we have frequently observed a decrease in the PCO_2 gap in the early phase of septic shock when using epinephrine as a first line agent (unpublished data). It is our hypothesis that the improvement in arterial pressure and oxygen delivery induced by epinephrine in severely hypotensive patients may offset the putative deleterious effects on mucosal oxygen adequation.

Epinephrine decreases splanchnic blood flow and increases the SVO_2-SHO_2 gradient

Epinephrine decreases splanchnic blood flow, with transient increases in arterial, splanchnic and hepatic venous lactate concentrations. The reduction in splanchnic blood flow has been associated with a decrease in oxygen delivery and a reduction in oxygen consumption [19]. These effects may be due to a reduction in splanchnic oxygen delivery to a level that impairs nutrient blood flow, likely resulting in a reduction in global tissue oxygenation, but may be potentially reversed by the concomitant administration of dobutamine. The addition of dobutamine to epinephrine-treated patients has been shown to improve gastric mucosal perfusion, as assessed by improvements in intramucosal pH, arterial lactate concentration and the PCO_2 gap [20]. It is not clear whether a transient decrease in hepatosplanchnic blood flow in septic shock is deleterious [20]. The mucosa and the submucosa are known to receive most of the splanchnic blood flow. Indocyanine green (ICG) clearance explores both splanchnic blood flow and liver function. De Backer and colleagues [18] compared epinephrine, norepinephrine and dopamine titrated for the same mean arterial pressure using three different tools to evaluate splanchnic perfusion and splanchnic metabolism. Splanchnic perfusion was assessed using: ICG clearance as a reflection of global hepatosplanchnic blood flow; hepatic venous saturation and the gradient of mixed venous oxygen saturation (SVO_2) and hepatic venous oxygen saturation (SHO_2) as a reflection of the balance between splanchnic oxygen delivery and oxygen consumption; and the gastric PCO_2 gap as a reflection of gastric mucosa perfusion/metabolism adequacy. The authors concluded that in patients who responded to dopamine, no differences were found with regard to splanchnic effects. On the other hand, in nine of ten cases of dopamine-resistant septic shock, epinephrine, when associated with dobutamine, decreased hepatosplanchnic blood flow, increased the SVO_2-SHO_2 gradient and increased arterial lactate and hepatic lactate consumption without any net effect on the PCO_2 gap, which may also indicate a constant blood flow in the mucosa. Moreover, the absence of variation in the PCO_2 gap argues against a deleterious effect of epinephrine on splanchnic circulation because gut mucosa is probably the area of the body most sensitive to a decrease in blood flow. In various animal models, a decrease in splanchnic blood flow is associated with an increase in the PCO_2 gap. The more likely explanation is that the energetic cost of metabolic processes induced by epinephrine such as neoglucogenesis and lactate consumption decreases the ability of the liver to metabolize ICG. Nevertheless, metabolizing ICG is not a natural process. Because epinephrine does not decrease liver lactate consumption, liver energy equilibrium is likely to remain stable.

In contrast, Seguin *et al*. [21] demonstrated in patients with septic shock that epinephrine at doses that induced the same mean arterial pressure did not modify ICG clearance and enhanced more gastric mucosal blood flow than the combination of dobutamine at 5 µg/kg per minute and norepinephrine.

Moreover, the effects of epinephrine may be different according to the studied area. Duranteau *et al*. [10] demonstrated using laser Doppler flow that epinephrine induced higher gastric mucosal blood flow than norepinephrine without any significant changes in intramucosal pH. Thus, it is likely that despite a relative decrease in splanchnic blood flow in the epinephrine-treated patient, gut mucosa receives sufficient blood flow to meet its metabolic needs. In fact, epinephrine exerts both sides of its β-2 properties: a redistribution of blood flow from the splanchnic bed to the muscular bed, and a redistribution of splanchnic flow towards the mucosa.

Limitation of splanchnic blood flow estimation

The clarification of the role of epinephrine in septic patients is somewhat limited by the few techniques currently available for estimating splanchnic tissue oxygenation, in addition to each of these techniques having its own limitations. The ICG method used by De Backer *et al*. [18] and other teams for splanchnic blood flow determination actually measures liver venous blood flow, which fails to distinguish supply from the portal vein and the hepatic artery. Consequently, changes in distribution of blood flow between the muscularis and the mucosa of the gut are not detectable by this method. The tonometric measurement raises the same types of concern

because it only represents flow conditions in the gastric region. It has been shown, at least in an animal model, that changes in blood flow to the various organs in the splanchnic region are quite variable following induction of sepsis. An increase in SVO_2-SHO_2 gradient signifies that the splanchnic area consumes more O_2 than the rest of the body. It does not mean that the splanchnic area is hypoxic.

Immunological and anticoagulant effects of epinephrine during sepsis

An immunomodulatory effect of epinephrine has been reported to supposedly be mediated via beta-adrenergic receptors. In whole blood *in vitro*, Van Der Poll *et al*. [22] demonstrated that epinephrine inhibits endotoxin-induced IL-1β production through an inhibition of tumor necrosis factor and an enhancement of IL-10. They concluded that endogenous or exogenous epinephrine may attenuate excessive activity of inflammatory cytokines during infection. Oberbeck *et al*. [23] investigated in mice submitted to cecal ligation and puncture the effects of epinephrine and/or beta-adrenergic blockade on cellular immune functions. They found that epinephrine infusion did not affect the lethality of septic shock in mice but induced alterations in splenocyte apoptosis, splenocyte proliferation and IL-2 release and was associated with profound changes in circulating immune cell subpopulations. Treatment with propranolol augmented the epinephrine-induced increase of splenocyte apoptosis, did not affect the decrease of splenocyte proliferation and IL-2 release, augmented the release of IL-6 and antagonized the mobilization of natural killer cells observed in epinephrine-treated animals. Furthermore, these immunological alterations were accompanied by a significant increase of sepsis-induced mortality. Co-administration of propranolol and epinephrine augmented the propranolol-induced changes of splenocyte apoptosis and IL-6 release and was associated with the highest mortality of septic mice. These data clearly indicate that adrenergic mechanisms modulate cellular immune functions during sepsis, with these effects being mediated via alpha- and beta-adrenergic pathways. The conclusions on survival are not truly proven as epinephrine and propranolol also act on hemodynamics. Therefore, alterations in the serum concentrations of catecholamine may affect the immunocompetence of the organism and may thereby affect the clinical course of critically ill patients [24].

It is also interesting to note that epinephrine exerts anti-thrombotic effects during endotoxemia by concurrent inhibition of coagulation and stimulation of fibrinolysis. Thus, epinephrine, whether endogenously produced or administered as a component of treatment, may limit the development of disseminated intravascular coagulation during systemic infection [25].

In summary, although the clinical impact remains to be demonstrated during septic conditions, epinephrine modulates the inflammatory state and decreases the hypercoagulation state.

Other properties of epinephrine

Unlike with norepinephrine, the hemodynamic effects of epinephrine (MAP and cardiac index increase) were obtained without the adjunction of dobutamine. This may prove to be important from a practical standpoint in situations such as transportation. Arrhythmia has not been described in the setting of septic shock. Morever, epinephrine when used alone is cheaper than vasopressin or the combination norepinephrine-dobutamine.

Does the choice of catecholamine influence patient evolution and prognosis?

Currently, there is no prospective randomized clinical study indicating that one catecholamine is superior to the other during septic shock. A recent meta-analysis by the Cochrane group [26] failed to demonstrate any difference between tested vasopressors. Furthermore, no study has demonstrated a relationship between improvement in PCO_2 gap or ICG clearance after pharmacological intervention and an improvement in prognosis. Thus, all current data regarding the splanchnic effects of catecholamine should be considered as pharmacological investigations of a vasoactive agent evaluated by a particular monitoring device. The discrepancy observed between all of these measurements further highlights the absence of clinical relevance.

Catecholamine use is not only limited to specialized intensive care units

The initial choice of catecholamine in the intensive care unit is relatively well standardized, at least for hyperkinetic septic shock. Hemodynamic evaluation is easy and accessible (even if the type of monitoring remains debatable), with the choice of catecholamine based on rational evaluation. This is not the case for many situations in other clinical settings. For example, catecholamines are used on the ward, during transportation, in the emergency room and even in patients' homes. Physicians are often young and/or have little experience in intensive care treatment. Diagnosis is not always straightforward and, in some cases, it may be difficult to distinguish between cardiogenic, hypovolemic or septic shock. In these particular circumstances, it seems more appropriate to use a catecholamine with predictable effects, such as epinephrine, rather than a strong vasoconstrictor such as norepinephrine.

Conclusion

Two opposite points of view are proposed. First, why should we use epinephrine, a drug with such potential negative effects, when there are other alternatives for the treatment of septic patients. On the other hand, epinephrine is commonly used worldwide and the reported morbidity and mortality rates with it are no different from those observed with other vasopressors. The French study comparing epinephrine and norepinephrine-dobutamine has been presented only in an abstract form [27]. These preliminary results seem to demonstrate that there is no evidence for the superiority of

norepinephrine plus dobutamine over epinephrine alone for the management of adults with septic shock. Thus, we have to wait for the definitive publication to decide whether Dr Jekyll or Mr Hyde is the true nature of epinephrine in the treatment of septic shock [28].

Competing interests

The author(s) declare that they have no competing interests.

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