Effects of Vasoactive Agents on the Gastrointestinal Microcirculation in Septic Shock

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Introduction

Recent studies have demonstrated the importance of microcirculatory alterations in the early stage of sepsis [1–3]. The gastrointestinal tract, particularly perfusion of the splanchnic bed and the integrity of the gut mucosa, occupies a key position in the pathogenesis of multiple organ failure (MOF) in sepsis.

The mechanisms of alterations in microvascular hemodynamics during sepsis are particularly complex since they involve not only systemic changes such as increase in cardiac output and decrease in systemic pressure but also changes in regional blood flow distribution and alterations in local microvascular regulatory mechanisms due to the effects of inflammatory mediators on endothelial or vascular smooth muscle cells. This complexity is particularly evident regarding changes in the intestinal microcirculation for which the decrease in systemic pressure cannot alone explain the intestinal microvascular disturbances associated with endotoxemia. Indeed, our group has previously demonstrated by intravital videomicroscopy that the hemodynamics in the intestinal microcirculation during endotoxic and hemorrhagic shock were completely different for the same amount of pressure decrease [1]. Factors that can possibly affect the microcirculatory response to shock or the redistribution of blood flow toward the mucosa have been identified by others. The involvement of inflammatory mechanisms mediated by leukocyte activation and cytokine release is possibly more important in sepsis than in hemorrhagic shock (even if also present in the latter situation). Moreover, hemorheological factors, such as alterations of red blood cell (RBC) shape, can also contribute to deleterious changes in villus perfusion during sepsis [4, 5].

In the early phase of septic shock, when fluid administration fails to restore adequate arterial pressure and organ perfusion, it is recommended that therapy with vasopressor agents should be initiated [6]. Vasopressor therapy may also be required transiently, to maintain perfusion in the face of life-threatening hypotension, even when adequate cardiac filling pressures have not yet been reached. Potential agents include dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin. Martin et al. [7] reported the superiority of norepinephrine over other vasopressors in treating septic patients. Other studies have reported the potential value of the use of vasopressin in septic patients [8, 9], which allowed the withdrawal of other catecholamines and improved systemic circulation.

However, the microvascular effects of these vasopressor agents on the splanchnic circulation are still largely unknown and may play a role in their selection for a given patient. Thus, the ideal vasopressor for the first-line agent in the early phase of septic shock is highly debated. Another question is whether vasodilatory agents

may have a place in the treatment of the microcirculatory dysfunction. Indeed, more and more data in the literature suggest that vasodilator agents are capable of "opening the microcirculation" and restoring it after septic shock [10].

Effects of Vasopressor Agents

In mice submitted to endotoxic shock, we investigated the effects of norepinephrine and vasopressin on intestinal microcirculation by intravital microscopy [11]. We measured RBC flux and velocity in villus tip arterioles and the density of perfused villi. One hour after endotoxin injection, the mean arterial pressure (MAP) decreased significantly to 46 ± 4 mmHg. The density of perfused villi, RBC velocity, and flux in the villus tip arterioles were dramatically decreased in hypotensive sepsis. The doses of vasopressors were titrated to restore MAP to its baseline level. Neither norepinephrine nor vasopressin administered at doses sufficient to restore MAP was able to restore RBC velocity and flux to their preshock baseline values. However, norepinephrine and vasopressin prevented additional decreases in RBC flux and velocity (Fig. 1). These findings are in line with a study by Levy et al. [12], which reported that the mesenteric blood flow was not restored either by norepinephrine or by vasopressin administered at doses that restored MAP. This clearly showed that restoring MAP, which is usually the first end-point during resuscitation in septic

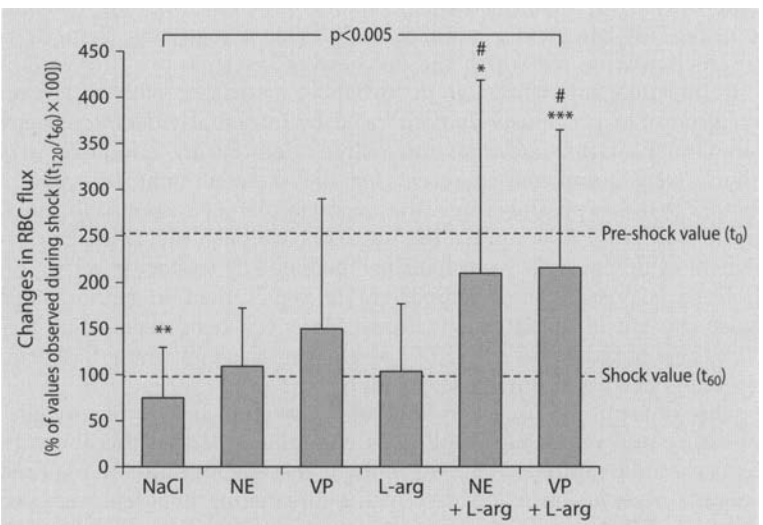

Fig. 1. Changes in erythrocyte (RBC) flux in villus tip arterioles. Anesthetized and ventilated mice received *Escherichia coli* endotoxin (2 mg/kg bolus i.v.) at t_0, which induced after 1 hr (t_{60}) a decrease in mean arterial blood pressure (MAP) to 40–50 mmHg associated with a significant decrease in RBC flux. The mice were randomly allocated to different treatment groups (n=6 in each group): continuous i.v. infusion for 1 hr with saline (NaCl, control group), norepinephrine (NE), vasopressin (VP), L-arginine (L-arg), NE+L-arg, or VP+L-arg. The doses of vasopressors (used alone or combined with L-arginine) were titrated to restore MAP to the baseline level. Changes in RBC flux between pre- and post-treatment were expressed as a percentage of the pre-treatment value and were significantly different among groups ($p<.001$). Values are expressed as mean ± SD. *$p<.05$, **$p<.01$, and ***$p<.001$ for t_{120} vs. T_{60}. #$p<.05$ treatments vs. control at t_{120}. From [11] with permission.