Therapeutic Options for the Treatment of Impaired Gut Function

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Abstract. Tissue hypoxia, especially in the splanchnic area, is still considered to be an important cofactor in the pathogenesis of multiple organ failure. Therefore, the specific effects of the various therapeutic interventions on splanchnic perfusion and oxygenation are of particular interest. Restoring and maintaining oxygen transport and tissue oxygenation is the most important step in the supportive treatment of patients with sepsis and impaired gut perfusion. Therefore, supportive treatment should be focused on an adequate volume resuscitation and appropriate use of vasoactive drugs. Adequate volume loading may be the most important step in the treatment of patients with septic shock. An elevated oxygen delivery may be beneficial in some patients, but the increase of oxygen delivery should be guided by the measurement of parameters assessing global and regional oxygenation. Forcing an elevation in oxygen delivery by the use of very high dosages of catecholamines can be harmful. Vasopressors should be used for achieving an adequate perfusion pressure. For norepinephrine, no negative effects on gut perfusion have been demonstrated. Epinephrine and dopamine should be avoided because they seem to redistribute blood flow away from the splanchnic region. There are no convincing data yet to support the routine use of low-dose dopamine or dopexamine to improve an impaired gut perfusion. There is even evidence that low-dose dopamine may reduce the mucosal perfusion in the gut in some patients. It has been suggested that dopexamine can improve splanchnic perfusion, but because these effects remain somewhat controversial, a general recommendation for dopexamine to improve gut perfusion is not justified.

Sepsis is the most frequent cause of death in surgical intensive care, when it advances to the stage of multiple-organ failure. The high incidence of sepsis, and resulting mortality rates ranging from 40 to 70%, have stimulated an increase in research in this field in recent years. Unfortunately, there has not yet been a major breakthrough in sepsis treatment or substantial improvements in the mortality rates. Intestinal failure is one of the most frequent complications among patients with sepsis. The gut can be a target of the infection and can also be responsible for causing or worsening the sepsis. Therefore, the gut has been termed the “motor of sepsis” (1).

The primary mechanism by which the gut contributes to sepsis is through bacterial translocation. Prevention of hypoperfusion or hypoxia of gut tissue has been considered important to reduce the risk of bacterial translocation. Early studies in septic animals by Nelson et al. (2) demonstrated that the critical O$_2$ supply [the point, under diminishing supply conditions, at which O$_2$ consumption (VO$_2$) becomes directly dependent on O$_2$ supply (DO$_2$)] for the small intestine may be significantly greater than the global critical DO$_2$. Accordingly, induction of a high global DO$_2$, which was one earlier approach to treating sepsis, does not rule out a reduced, supply-dependent VO$_2$ in the gut.

However, whether gut blood flow and DO$_2$ are typically decreased under septic conditions is uncertain. Previous findings, by various authors, that splanchnic blood flow may be decreased during sepsis have not been confirmed in more recent clinical trials, perhaps because of differences in the techniques used for flow measurements (3). Animal experiments demonstrated a redistribution of the circulation during sepsis, with relative increases in blood flow to the liver and small intestine. In healthy volunteers, endotoxin infusion doubled splanchnic blood flow (4). In septic patients, splanchnic blood flow was shown to either match an increase in cardiac output or even proportionally exceed the increase in cardiac output (5). Nevertheless, whether elevated splanchnic blood flow can always meet the current demand for oxygen is doubtful, because splanchnic VO$_2$ can be increased to a much greater relative extent than global VO$_2$ (6).

Therefore, it is still unclear to what extent an imbalance between splanchnic DO$_2$ and VO$_2$ during sepsis results in hypoxia and, more importantly, hepatic or gut dysfunction. For instance, a slight supply dependency of VO$_2$ in the splanchnic area in septic patients was reported (7). However, in that study, an increase in splanchnic DO$_2$ was not associated with improved hepatic lactate uptake, indicating that this metabolic dysfunction was not attributable to hypoperfusion. Furthermore, among patients with severe burn injuries who developed
severe systemic inflammatory syndrome, significant reductions in hepatic glucose production and alanine uptake became obvious while hepatic blood flow remained unchanged (6). Consequently, significant metabolic changes under conditions of severe infection are not necessarily proportional to either hepatic blood flow or VO$_2$.

**Therapeutic Strategies**

The supportive treatment of patients with sepsis begins with achievement of an adequate volume status, titration of an appropriate DO$_2$, and maintenance of a sufficient perfusion pressure (8). However, stabilized global hemodynamics do not guarantee adequate organ perfusion. Therefore, organ perfusion and function parameters should also be considered in the monitoring and guidance of treatment for septic patients. Unfortunately, there is still a dearth of methods suitable for routine clinical assessment of splanchnic perfusion and oxygenation. Techniques such as gastric mucosal PCO$_2$ or indocyanine green clearance monitoring, where available, are potentially useful for the optimization of therapy.

**Preventive Strategies**

The interventions mentioned above can also be used as preventive steps during hemodynamic stabilization. Early adequate treatment of impaired hemodynamics may prevent the development of gastrointestinal hypoperfusion. It has been demonstrated that early initiation of treatment for patients with sepsis can reduce the incidence of organ failure (9). Furthermore, there is evidence that treatment guided by tonometric monitoring of gastric mucosal pH (pHi) may improve outcomes for patients with sepsis (10). It is unclear whether increases in perioperative DO$_2$ should be recommended, in hopes of preventing organ failure. Two clinical studies, each with considerable methodologic limitations, documented a lower incidence of organ failure and a reduction in the mortality rate among patients receiving dopexamine to increase perioperative DO$_2$ (11). However, until comparisons with other catecholamines (e.g., dobutamine) are performed, the use of dopexamine in the perioperative period cannot be justified for high-risk surgical patients.

Enteral nutrition is an important stimulus for a healthy mucosa. Animal experiments demonstrated that enteral nutrition increased bile IgA secretion and reduced bacterial translocation. A recent survey of randomized clinical trials demonstrated that early (within the first 12 h) initiation of enteral feeding could significantly reduce the length of stay and the mortality rate in the intensive care unit, compared with delayed enteral feeding (12). Therefore, enteral nutrition should be initiated as early as possible, i.e., within the first 12 h, according to the surgical status. In addition, prokinetic drugs should be administered to enhance the tolerance to enteral feeding. Other authors have suggested parenteral or enteral administration of glutamine (13), because of its positive effects on intestinal function and the immune system (14). A new treatment involves so-called immune-modulating nutrition mixtures, containing arginine, glutamine, and/or fish oil. These may have positive effects on the incidence and prognosis of infections. However, no clear recommendations can be provided until additional trials confirm the concept of immune-modulating nutrition (12).

**Effects of Catecholamines on Regional Blood Flow**

**General Considerations**

Until better methods to assess the potential imbalance between splanchnic substrate supply and demand become available, most clinicians tend to maintain some degree of hyperdynamic global hemodynamics. After assessment of the extent of myocardial dysfunction and the severity of septic shock, adequate fluid resuscitation is the first and most important therapeutic step, followed by catecholamine infusion (8). Potential side effects, especially on the splanchnic circulation, should be considered in the decision regarding which vasoactive drugs should be used for the treatment of sepsis. In particular, downregulation of $\beta_1$-adrenergic receptors, attributable to long-term (>72-h) inotropic treatment and preexisting heart failure, or less effective stimulation of $\alpha$-adrenergic receptors may occur during sepsis. Furthermore, imbalances in blood pH may contribute to the downregulation of adrenergic receptors. As a result, recommendations regarding the use of specific catecholamines and dosages derived from studies of healthy or nonseptic patients cannot be directly applied to patients in sepsis.

**Dobutamine**

Dobutamine is appropriate for the treatment of septic cardiomyopathy, because of its positive inotropic effect. Increases in splanchnic flow have been associated with increases in cardiac output. However, there are no data on whether dobutamine can selectively increase splanchnic blood flow in patients with sepsis.

**Norepinephrine**

Because of its strong vasoconstricting effects, norepinephrine is used as a “last resort” vasopressor, i.e., when hemodynamic stabilization cannot be achieved with other drugs. Several studies of patients with sepsis demonstrated that diuresis and serum creatinine clearance increased during norepinephrine infusion (15–18). However, patients in those studies exhibited marked arterial hypotension before the norepinephrine treatment. Therefore, the fundamental mechanism for the improved renal function was probably the reestablishment of an adequate perfusion pressure. In other words, an inadequate perfusion pressure should not be tolerated just because of the fear of potential side effects of norepinephrine. Furthermore, it has been shown that the negative effects of norepinephrine attributable to peripheral vasoconstriction and splanchnic hypoperfusion are less during sepsis, presumably because of the reduced response of $\alpha$-adrenergic receptors to stimulation, as well as preexisting vasodilation.

**Epinephrine**

Epinephrine has been recommended in severe septic shock for $\beta$-adrenergic stimulation, to increase cardiac output, and
α-adrenergic stimulation, to maintain perfusion pressure. Although some groups stabilized patients with septic shock with epinephrine when high-dose dopamine or norepinephrine treatment was unsuccessful (19,20), our group found that a serious side effect is a reduction in splanchnic blood flow (21). Therefore, epinephrine should not be the drug of first choice.

**Dopamine**

Currently, dopamine is most commonly used in low doses (1 to 3 μg/kg per min) to improve renal function and splanchnic oxygenation. However, no clear evidence exists for a reduction in the incidence of renal failure with this approach, and the potential positive effects of low-dose dopamine treatment could not be confirmed in patients with sepsis (22). Moreover, a redistribution of nutritive blood flow and impairment of splanchnic oxygenation, especially in the mucosa, which is most prone to hypoxia, may occur. In comparison with norepinephrine, dopamine in vasopressor dosages was found to increase BP in patients with sepsis; however, norepinephrine also increased pH, whereas dopamine decreased it (23). Dopamine in a dose of 5 μg/kg per min was equally effective, compared with dobutamine; however, dopamine produced a decrease in intestinal mucosal perfusion (24). Low-dose dopamine treatment increased splanchnic blood flow in patients with sepsis who exhibited normal fractional splanchnic blood flow, but it did not further increase, and in some cases it decreased, splanchnic blood flow in patients with already elevated fractional perfusion (25). Furthermore, dopamine has been shown to negatively affect endocrine function, e.g., by inducing hyperprolactinemia, which is known to inhibit lymphocyte and macrophage function. Dopamine may also inhibit several growth hormones, which is considered to be one reason for the development of often-intractable catabolism. Furthermore, dopamine has been shown to influence thyroid hormones, which may result in impaired myocardial and vascular function (26). Because of these negative effects on various hormones and the lack of evidence for the prevention of renal failure with low-dose dopamine treatment, routine clinical application of low-dose dopamine treatment is being increasingly questioned. Even in high doses, dopamine seems to have more disadvantages than dobutamine or norepinephrine.

**Dopexamine**

A few studies have supported the concept that β2-adrenergic stimulation by dopexamine would result in a redistribution of blood flow from the muscularis layer to the mucosa, with an increase in total splanchnic blood flow (27,28). However, the increase in splanchnic blood flow seems to be only a passive reaction to the increase in cardiac output; to date, no studies have been able to verify a selective effect of dopexamine on splanchnic blood flow. One histologic study in pigs, using liver biopsy specimens, showed that dopexamine reduced the extent of cell damage and endothelial swelling, compared with dobutamine (29). However, decreases in pH with dopexamine were found in septic patients (30) and patients who had undergone cardiac surgery (31). It remains unclear to what extent a redistribution of blood flow on the microcirculatory level, as has been described for dopamine, may be the reason for this finding. The effects of dopexamine on the regional circulation, especially the splanchnic system, are still relatively controversial. No studies that would justify dopexamine administration to selectively improve splanchnic blood flow are currently available. Because dopexamine may, like dopamine, negatively affect the gastrointestinal mucosa, its routine use for patients with sepsis cannot be recommended here.

**Therapeutic Options**

Several interventions to improve splanchnic perfusion and oxygenation have been discussed in recent years. In general, it is difficult to assess the effectiveness of these approaches and to develop clear recommendations for the treatment of regional perfusion abnormalities. This difficulty is explained by the fact that clinical studies of patient outcomes are not available and by the lack of appropriate methods to unambiguously assess different therapeutic interventions. Nevertheless, some recommendations for the treatment of impaired regional perfusion can be provided. Most of the recommendations have not been absolutely proven but can be regarded as appropriate on the basis of their evidence.

One of the most important steps in the treatment of critically ill patients is the establishment of adequate volume status, as has been recommended by most expert commissions (32,33). In particular, fluid resuscitation should be guided not only by global hemodynamic parameters but also by regional perfusion parameters (lactate levels, diuresis, and regional CO2 tension). It must be emphasized that most guidelines emphasize the adequacy of fluid resuscitation and that the type of infusion solution, i.e., crystalloid versus colloid, is less important.

The concept of maximizing DO2 in critically ill patients to prevent regional hypoxia must be questioned (34–36). Achievement of hyperdynamic global hemodynamics with fluid resuscitation and thus optimization of cardiac preload seems to be appropriate. However, it seems to be not indicated and probably deleterious to challenge hyperdynamic circulation with high doses of catecholamines (35). Therefore, the decision to use positive inotropic and vasoactive drugs to increase cardiac output must be made individually, and the effectiveness of such strategies should be assessed using parameters of regional perfusion, e.g., lactate levels, diuresis, and regional CO2 tension. Currently, dobutamine can be regarded as the catecholamine of choice for positive inotropic support.

Maintaining sufficient perfusion pressure is an additional important step in the treatment of critically ill patients, to prevent regional hypoperfusion. In deciding what arterial perfusion pressures might be considered appropriate for different organs, preexisting morbidities (such as hypertension or arterial occlusive disease) must be taken into account. Data from multicenter studies of septic patients revealed that, in the clinical setting, hemodynamic management in such patients is characterized by mean arterial pressures between 70 and 90 mmHg. Mean arterial pressures of >75 mmHg are currently considered adequate. It is worth noting that the potential negative effects of vasopressors should not limit their use in cases of inadequate perfusion pressure. In particular, patients with
preexisting diseases of the vascular system and developing organ dysfunction (as assessed using diuresis, regional CO₂ tension, and serum lactate levels) should always undergo evaluation to determine whether organ function could be improved by increasing arterial BP. Norepinephrine can be regarded as the vasopressor of choice.

It remains unclear whether there are additional interventions that may have selective positive effects on regional perfusion (including perfusion of the splanchnic system). Low-dose dopamine treatment seems to be ineffective and may even be harmful because of redistribution of blood flow. In contrast to several studies that suggested potentially positive effects of doxepamine, other studies demonstrated that doxepamine might also increase regional CO₂ tension (an indicator of impaired perfusion). Newer approaches, e.g., the use of prostacyclins, have yielded interesting and promising experimental results, which must be confirmed in appropriate clinical studies (37).

The major interventions for the treatment of regional perfusion abnormalities can be regarded as those that are used for the reestablishment and maintenance of global hemodynamics. However, the observation of stable global hemodynamics does not automatically exclude the possibility of hypoperfusion of single organs or organ systems. Therefore, parameters that allow assessment of regional perfusion and oxygenation should be monitored during stabilization of global circulatory conditions. Furthermore, optimization of volume status, cardiac output, and organ perfusion pressure seems to be the most effective strategy for the prevention and treatment of impaired regional perfusion.

Conclusion

Although it is now widely accepted that the gut plays a major role in the pathogenesis of sepsis, clinical interventions to monitor and treat this organ system, with respect to perfusion and oxygenation, remain very limited.

However, early and subsequent treatments of disturbed hemodynamics, especially with consideration of regional perfusion parameters, are most important as preventive and therapeutic steps. Unfortunately, we do not have clear evidence that more extended pharmacologic interventions for selective effects on gastrointestinal perfusion, i.e., low-dose dopamine, doxepamine, or prostacyclin treatments, are actually effective. In contrast, current data support the concept of early enteral nutrition as a preventive strategy. Whether special immune-modulating nutrition solutions have more advantages cannot be definitively answered at this time.

References


