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# Vasoactive Substances and Their Effects on Nutrition in the Critically Ill Patient

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## Abstract

Critically ill patients often require specialized nutrition via the enteral route. The benefits of enteral feeding, particularly early in the care of the critically ill patient, are well documented. Controversy exists regarding the provision of enteral nutrition (EN) in critically ill patients with hemodynamic instability who require vasopressors or inotropes. Concerns center on the potential for gut ischemia that may develop in the face of an imbalance between oxygen supply and demand. Current guidelines offer some guidance as to when to it is safe to initiate enteral feeding in patients on vasopressors, but the decision on when to start EN in hemodynamically unstable patients requiring vasoactive substances remains a clinical dilemma for most critical care practitioners. This review focuses on the effects of vasoactive substances such as pressors and inotropes on the gastrointestinal tract, as well as their use in combination with EN. (*Nutr Clin Pract.* 2012;27:335-339)

## Keywords

adult, critical care, drug interactions; food-drug interactions; enteral nutrition; vasopressors; inotropes

Critically ill patients often require a number of therapeutic interventions to improve their overall outcome. Among these, early enteral nutrition (EN) is one of the most important yet undervalued and overlooked tools in the armamentarium of the critical care clinician. The benefits of early EN are well documented and include maintenance of the structural integrity of the gastrointestinal (GI) tract, reduced gut permeability, and increased GI blood flow.<sup>1-3</sup> EN has been also been associated with improved clinical outcomes, including reduced infectious complications, reduced hospital length of stay, and costs associated with nutrition therapy, respectively.<sup>4-17</sup> In order for nutrients to be adequately absorbed and used, adequate blood flow to the GI tract is required. Another important component of care in many critically ill patients is the use of inotropes and vasoactive substances in hemodynamically unstable patients. Despite recommendations for early enteral feeding in most critically ill patients, controversy still exists regarding when is the optimal time to safely and effectively deliver EN in patients receiving these important and often life-saving pharmacological therapies. The rationale for withholding EN in patients requiring vasoactive substances for hemodynamic instability is to avoid small bowel necrosis. The most recent joint recommendations from the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) and Society of Critical Care Medicine (SCCM) suggest withholding EN in hemodynamically unstable patients on “high-dose” catecholamine therapy until stable, while advocating for the cautious use of EN in patients on “low-dose” catecholamine therapy.<sup>18</sup> The precise definition of low-dose catecholamine

therapy was not defined in the guidelines, but clinical practice guidelines are available to guide clinicians regarding dosing of vasopressors and inotropes.<sup>19</sup> Table 1 describes the commonly used vasoactive substances in the intensive care unit (ICU). This review focuses on the physiologic effects of inotropes and vasoactive substances on the GI tract, as well as exploring their use in combination with EN.

## Overview of Inotropes and Vasoactive Substances

Hemodynamic instability often requires the use of vasoactive substances to preserve blood flow to vital organs such as the heart and brain, often at the detriment to GI blood flow. The particular choice of vasoactive agent used will depend on the underlying pathophysiology of the hemodynamic instability. Of the various agents that can be used to improve hemodynamic instability, norepinephrine, epinephrine, phenylephrine, dopamine, and dobutamine have been studied with respect to their effects on the GI tract. Norepinephrine and epinephrine both have mixed activity on the  $\alpha$  and  $\beta$  receptors, producing

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**Table 1.** Vasoactive Substances Used in the Intensive Care Unit

Drug/Mechanism of Action	Typical Dosing	Clinical Uses	Gastrointestinal (GI) Effects <sup>28</sup>
Dobutamine β-1 agonist	Dose: 2.5–20 mcg/kg/min Max: 40 mcg/kg/min	Heart failure	Increases GI mucosal blood flow, increases gastric intramucosal pH (pH <sub>i</sub> )
Dopamine Dopa, α, β-1 agonist	Dose: 5–20 mcg/kg/min Max: 50 mcg/kg/min	Septic shock, bradycardia	Decreases pH <sub>i</sub> , increases oxygen delivery (septic shock), precapillary vasoconstriction with diversion of blood away from GI mucosa
Epinephrine α, β-1, β-2 agonist	Dose: 0.05–0.5 mcg/kg/min Max: 1 mcg/kg/min	Shock, cardiac arrest, anaphylaxis, heart block, bradycardia	Decreases splanchnic blood flow
Norepinephrine α, β-1 agonist	Dose: 0.05–1.5 mcg/kg/min Max: 3 mcg/kg/min	Septic shock	Increases gastric pH <sub>i</sub> , increases splanchnic blood flow (septic shock), decreases mucosal blood flow (hypovolemia)
Phenylephrine α agonist	Dose: 0.4–9.1 mcg/kg/min	Septic shock, hypotension	
Vasopressin Antidiuretic hormone analogue	Dose: 0.01–0.04 U/min	Hypotension, septic shock, to decrease pressor requirements, diabetes insipidus, GI bleed, esophageal varices	Increases intestinal vasoconstriction (may cause gastric mucosal acidosis), enhances pressor response

vasoconstriction and increases in systemic vascular resistance and cardiac output. Phenylephrine has only α-1 activity and causes strictly arterial vasoconstriction. Dopamine has different effects based on its dosing, with lower doses (3–5 mcg/kg/min) associated with improved renal and mesenteric blood flow, modest doses (5–10 mcg/kg/min) having inotropic and chronotropic effects, and higher doses (10–20 mcg/kg/min) having vasopressor effects on the arterial circulation. Dobutamine effects primarily are limited to its inotropic effects, making it effective in cardiogenic shock.

### Effects of Critical Illness and Enteral Nutrients on GI Blood Flow

A plethora of assorted etiologies associated with critical illness can cause decreases in GI blood flow, including sepsis, hemorrhage, hypovolemia, polytrauma, and cardiogenic shock.<sup>20</sup> This decrease in GI blood flow is as a consequence of redistribution of blood to vital organs and can be due to a number of different mechanisms, including elevated nitric oxide (NO), which acts as vasodilator shunting blood to other vital organs and as a free radical causing cellular damage.<sup>21–23</sup> In the setting of decreased GI blood flow, there is alteration in the microcirculation of the small intestine. The effects of disrupted microcirculation can lead to villi dysfunction. Clinically, villi dysfunction usually manifests as malabsorption and decreased intestinal absorption of nutrients delivered via the intestine. Furthermore, reperfusion to the gut can lead

to an ischemic reperfusion injury that also will increase villi dysfunction and atrophy. This phenomenon is related to enzyme systems that convert newly available oxygen to oxygen free radicals, which can increase oxidative stress in tissues and induce further cellular injury.<sup>24</sup> Splanchnic blood flow is known to increase after meals with greater increases shown after high-fat meals. In addition, complex feedings of proteins, carbohydrates, and fats often elicit an increased hyperemic response compared with meals with equal amounts of each macronutrient.<sup>25,26</sup> Critically ill patients often require complex feeding, including high-protein formulas, to promote wound healing.<sup>26</sup> The hyperemic response that occurs with enteral feedings is associated with shunting of blood to the splanchnic circulation, rather than increases in cardiac output.<sup>27,28</sup>

### Effects of Vasoactive Substances on GI Blood Flow

Specific effects of vasoactive substances on the GI tract are mixed. The effect of norepinephrine on the GI tract varies with the underlying pathophysiology associated with the hemodynamic instability. Krejci et al<sup>29</sup> examined the effects of norepinephrine, epinephrine, and phenylephrine on GI blood flow in sepsis. Norepinephrine, epinephrine, and phenylephrine were all shown to increase mean arterial pressure. Norepinephrine and epinephrine also increased cardiac output. However, norepinephrine and epinephrine also caused a decrease in

intestinal blood flow and the overall fraction of cardiac output to the GI tract. Meier-Hellman et al<sup>30</sup> investigated the effects of a combined regimen of norepinephrine and dobutamine compared with epinephrine in sepsis. Epinephrine lowered splanchnic blood flow, whereas the combination of norepinephrine and dobutamine had no effect on GI blood flow. In the setting of hypovolemic shock, norepinephrine decreases mucosal blood flow. The effects of vasopressors on the GI tract and splanchnic blood flow would appear to be dose related (ie, increasing doses lead to escalating effects), but this has not been fully investigated. In addition, alterations in GI blood flow can persist, even when adequate volume resuscitation and improved systemic hemodynamics due to reperfusion injury discussed earlier. Prior to initiating vasopressors, clinicians must ensure adequate fluid resuscitation to avoid these potentially deleterious complications.

### EN and Vasoactive Substances

In clinical practice, EN is often withheld in patients on vasoactive substances. Reasons for this practice are varied, but the most often quoted rationale is that specifically in patients with low-flow states (ie, hemodynamically unstable), EN will increase splanchnic oxygen demand. If and when the body is not able to meet this demand, splanchnic ischemia ensues. In addition, although a rare complication, small bowel necrosis is a feared complication of enteral feeding and highly associated with mortality.<sup>31-36</sup> Signs of small bowel necrosis include non-specific symptoms such as abdominal pain and distention, high nasogastric output, and signs of intestinal ileus,<sup>36</sup> which may be misinterpreted as GI intolerance. Small bowel necrosis is often accompanied by hypotension and hypovolemic shock. Fear of splanchnic ischemia and ultimately small bowel necrosis is a feared complication, and for this reason, many clinicians will avoid enteral feeding in patients requiring vasoactive substances. The medical literature evaluating the use of EN and vasoactive substances in hemodynamically unstable patients is lacking.

Berger et al<sup>37</sup> investigated intestinal absorption and clinical tolerance of EN in 2 groups of patients according to hemodynamic stability. Hemodynamically stable patients were defined as without circulatory failure on clinical grounds and on intraoperative transesophageal echocardiographic evaluation. Hemodynamically unstable cardiac surgery patients were defined as requiring high-dose vasopressors, with or without the need for intra-aortic balloon pumps. The aim of the study was 2-fold: to investigate intestinal absorption in patients with and without hemodynamic instability and to investigate the feasibility of EN in patients with hemodynamic instability who required vasoactive substances. Of the 23 patients in the unstable group, 23 were on vasoactive substances on postoperative day 1, and 22 remained on vasoactive substances on postoperative day 3. The mean dosage of vasoactive drug used

in the unstable group was as follows: dopamine, 4 mcg/kg/min; dobutamine, 12 mcg/kg/min; and norepinephrine, 11 mcg/min. Most patients were on dopamine/dobutamine or the combination of dobutamine and norepinephrine. EN was initiated at 20 mL/h and titrated as tolerated to provide 25 kcal/kg/d, however most patients in the unstable group achieved only about half of their calculated caloric requirements. Patients were randomized to receive EN through a nasogastric tube placed postpylorically on postoperative day 1 or nasogastric feeds on postoperative days 2-4, according to the decision of the attending physician. Gastric residuals were assessed every 6 hours in all patients. Intestinal absorption was assessed using the acetaminophen absorption test, which is similar in nature to peptide absorption, and has been previously described as a means to evaluate gastric emptying in critically ill patients.<sup>37-41</sup> The investigation noted that gastric acetaminophen absorption was delayed on postoperative day 1, but when administered postpylorically, acetaminophen absorption was not different from control participants. The investigators attributed this difference to the use of postoperative opioids, which have well-described effects on pylorus closing. However, on postoperative day 3, there were no differences noted among gastric or postpyloric acetaminophen absorption. The dosing of vasoactive substances used in patients with hemodynamic compromise did not significantly differ from postoperative days 1-3. Among tolerance to EN, there were no reported cases of elevated gastric residuals (>300 mL), bowel distention, or other signs of intolerance. The authors concluded that the use of hypocaloric EN was feasible in cardiac surgery patients with hemodynamic instability. The study does show that the use of early EN in patients requiring vasoactive substances was generally well tolerated, albeit in a small study population. In addition, the descriptive nature of the study limits its ability to prove whether early EN in cardiac surgery patients requiring vasoactive substances improves clinical outcomes. A larger, controlled trial is necessary to better answer these questions.

Revelly et al<sup>42</sup> investigated the effects of early EN on metabolic processes and splanchnic circulation among cardiac surgery patients receiving hemodynamic support. The study included a total of 9 patients who underwent cardiac surgery under cardiopulmonary bypass. All patients required dobutamine (range, 200-800 mcg/min), with 4 patients also requiring norepinephrine (range, 6-25 mcg/min), respectively. EN was delivered using a standard formulation and administered for 3 hours. Energy requirements were assessed using indirect calorimetry. Gastric tonometry was used to assess gastric intramucosal pH (pH<sub>i</sub>). All patients were assessed at baseline (2 hours) and at completion of the study period (total of 5 hours). Indocyanine green clearance (ICG) was assessed prior to and after EN to assess for splanchnic blood flow. The use of ICG clearance to assess for splanchnic blood flow, particularly hepatic blood flow, has been described elsewhere.<sup>43,44</sup> EN was not associated

with a decrease in  $pH_i$ , suggesting of a lack of splanchnic ischemia. In addition,  $EN_i$  was associated with an increase in ICG clearance, suggesting increased splanchnic blood flow. The results of this study, however, may not be generalizable to other patient populations, such as those with cardiogenic or septic shock or organ failure. Also, the small sample size and descriptive nature make applying these results difficult.

## Conclusion

Based on the evidence, cautionary use of EN with vasoactive substances is warranted. However, the use of vasoactive substances should not entirely preclude clinicians from using the enteral route to supply nutrition. The evidence suggests that EN may be safely delivered to patients requiring vasoactive substances for hemodynamic support, but more study is required as most of the evidence is in cardiac surgery patients, which may not be entirely generalizable to patients with hemodynamic instability due to noncardiac causes (ie, sepsis). Clinicians may consider low-dose "trophic" feeds in patients with hemodynamic instability requiring vasoactive substances, but this too needs further investigation. In addition, studies are needed to investigate whether the use of specialized enteral formulas may be beneficial as "trophic" feeds in the hemodynamically unstable patient. Caution is advised in patients with signs of feeding intolerance, increasing vasoactive requirements, increased ventilator support, and hypotension. If signs of intolerance persist, clinicians should consider withholding EN until patients are more hemodynamically stable, with decreasing vasoactive requirements. Although rare, clinicians should also consider the diagnosis of splanchnic ischemia and small bowel necrosis in enterally fed patients who are exhibiting signs of GI intolerance and who are hypotensive.

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