MINIREVIEW

Enteral Nutrition and Hepatosplanchnic Region in Critically Ill Patients - Friends or Foes?

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Summary

Enteral nutrition (EN) is a preferred way of feeding in critically ill patients unless obvious contraindications such as ileus or active gastrointestinal bleeding are present. Early enteral nutrition as compared to delayed EN or total parenteral nutrition decreases morbidity in postsurgical and trauma patients. The hepatosplanchnic region plays a pivotal role in the pathophysiology of sepsis and multiple organ dysfunction syndrome. The beneficial effects of EN on splanchnic perfusion and energy metabolism have been documented both in healthy volunteers and animal models of sepsis, hemorrhagic shock and burns. By contrast, EN may increase splanchnic metabolic demands, which in turn may lead to oxygen and/or energy demand/supply mismatch, especially when hyperemic response to EN is not preserved. Therefore, the timing of initiation and the dose of EN in patients with circulatory failure requiring vasoactive drugs are a matter of controversy. Interestingly, the results of recent clinical studies suggest that early enteral nutrition may not be harmful even in patients with circulatory compromise. Nevertheless, possible onset of serious complications, the non-occlusive bowel necrosis in particular, have to be kept in mind. Unfortunately, there is only a limited number of clinically applicable monitoring tools for the effects of enteral nutrition in critically ill patients.

Introduction

The hepatosplanchnic region (HSR), i.e. gastrointestinal tract (gut) and the liver, plays a pivotal role in the pathophysiology and pathogenesis of shock, trauma, sepsis and the multiple organ dysfunction syndrome (Fink 1991, Baue *et al*. 1998). The derangement of gut physiological functions is, according to the "gut hypothesis", induced by a variety of local and/or systemic insults, and may result in gut barrier disruption. It has been shown that splanchnic blood flow in septic patients increases in direct proportion to the rise in global cardiac output (Takala 1996). Conversely, fractional splanchnic oxygen consumption (splanchnic VO_2/global VO_2) may increase (Dahn *et al*. 1990). Therefore, the gut becomes a vulnerable organ during any decrease in oxygen delivery in septic patients. Hypoperfusion of gut may have several consequences. Firstly, gut mucosal permeability is increased and immune functions of gut-associated lymphoid tissue are

altered (Zarzaur and Kudsk 2001). Secondly, this leads to the translocation of live bacteria and/or endotoxin across the gut epithelium into mesenteric lymphatic nodes and portal circulation. Finally, a number of cytokines and other pro-inflammatory mediators of gut origin may pass through the mesenteric lymphatic system into portal and systemic circulation. These mechanisms trigger or perpetuate systemic inflammatory response syndrome and presumably the development of multiple organ dysfunction syndrome. Accordingly, HSR has been called „motor" or „undrained abscess" of septic multiple organ dysfunction syndrome (Meakins and Marshall 1986, Deitch 1992, Marshall *et el.* 1993).

Early and intensive resuscitation of HSR is therefore of utmost importance (Marik 1999). The therapeutic strategies aimed at preventing secondary gut injury and/or augmenting gut mucosal cell regeneration in critically ill patients are based on the effort to increase splanchnic oxygen delivery. The cornerstone of such therapy is the early and adequate fluid resuscitation. The second step is the addition of vasoactive drugs. However, even if these therapies are well titrated, they do not provide selective resuscitation of HSR and regional tissue hypoperfusion may persist.

Since it is well known that enteral nutrition (EN) in healthy volunteers increases total hepatosplanchnic blood flow (Qamar *et al.* 1988, Brundin *et al.* 1996, 1998), a particularly attractive concept in critically ill patients would be the selective redistribution of cardiac output in favor of HSR and gut mucosa induced by intraluminally given EN.

However, whether this putative mechanism is preserved in acute stress state, in which the hemodynamic response to EN could be altered, is not known. EN in such circumstances may even be harmful. In this paper, we discuss the benefits and risks of EN (early postpyloric feeding in particular) in critically ill patients focusing on hepatosplanchnic hemodynamic response to EN. The different routes of EN application as well as the immunonutrition are beyond the scope of this article.

Benefits of early enteral nutrition

Early enteral nutrition (EEN) is defined as initiation of enteral feeding within 48 h of admission to the hospital or within 48 h after surgery. The worldwide acceptance of EEN during the last decade of the 20th century was based on the promising results of large clinical studies in surgical and trauma patients (Marik and Zaloga 2001). In these patients, EEN significantly decreased morbidity (the incidence of infectious complication), length of stay and costs as compared to the delayed EN or total parenteral nutrition (TPN) (Moore *et al.* 1992, Minard and Kudsk 1994, Marik and Zaloga 2001).

The principal aim of EEN administration is to maintain functional and structural gut integrity. EEN may optimize the local and systemic immune response not only by means of splanchnic hyperemia, but also by the rise of IgA, trophic and vasoactive hormone secretion, and maintenance of gut microflora. This concept is further supported by studies demonstrating duodenal mucosal atrophy, altered gut permeability, enzymatic dysfunction and the depletion of tissue antioxidant capacity after a few days of EN withdrawal in critically ill patients (Hernandez *et al.* 1999, Tanigawa *et al.* 1999). Though the concept of EEN has been widely accepted, it remains to be determined how to manage patients in acute stress conditions who are hemodynamically unstable and/or require catecholamines. So far, the timing of EN initiation and the dose applied has only been empirical. Moreover, there are only a few studies dealing with the effect of EEN on hepatosplanchnic perfusion and metabolism in patients with acute stress.

Experimental data

Enteral application of glucose improved gastrointestinal perfusion in rats with *E. coli* sepsis (Gosche *et al.* 1990). Similar beneficial effects of EN on splanchnic perfusion were documented in animal models of hemorrhagic shock and burns (Inoue *et al.* 1989, Bortenschlager *et al.* 1994). Kazamias *et al.* (1998) showed a reversal of the lipopolysacharide infusion-induced splanchnic ischemia in a dog model when giving EN *via* jejunostomy. They observed significant improvement in hepatosplanchnic macrocirculation, i.e. significant increase in hepatic arterial, portal venous and superior mesenteric arterial blood flows. Hepatic and intestinal mucosal microcirculation assessed by laser Doppler flowmetry was also positively influenced by EN. Moreover, intestinal mucosal (measured by tonometry) to arterial PCO_2 gradient decreased significantly in the EN-group.

Continuous duodenal feeding in dogs with oleic-acid induced acute lung injury ventilated with positive end-expiratory pressure increased both hepatosplanchnic oxygen delivery (by increasing blood flow) and VO_2 as shown in Figure 1 (Purcell *et al.* 1993). The authors observed a concomitant increase both in gut and liver VO_2. Interestingly, cardiac output did not increase during

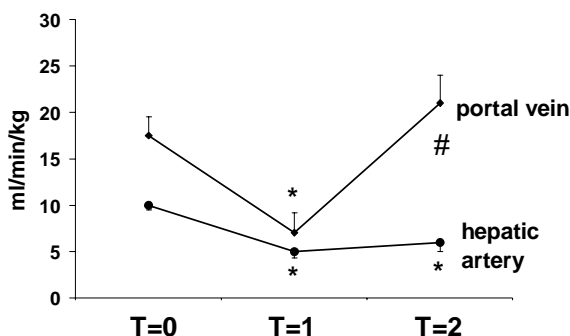EN, suggesting the possible selective redistribution of global blood flow in favor of the splanchnic region.

Fig. 1. *Portal venous and hepatic arterial blood flow. Lung injury and positive end-expiratory pressure (T=1) significantly decreased flows. EN (T=2) returned portal venous flow to baseline levels. * p<0.05 compared to T=0 by t-test, # p<0.05 compared to T=1 by t-test (modified from Purcell et al. 1993)*

Clinical data

Intestinal oxygen tension was measured in patients after upper gastrointestinal elective surgery with an oxygen polarographic microprobe (Braga *et al*. 2001). There were two groups of patients, a jejunal EEN group and a TPN group. After the operation, intestinal oxygen tension dropped in both groups. However, from the 4th postoperative day intestinal oxygen tension recovered faster in the EEN group than in the TPN group.

Recently, the first clinical study on the physiological effects of postpyloric EN in patients with circulatory compromise has been published (Revelly *et al*. 2001). On the first postoperative day, they. studied patients after cardiac surgery, requiring catecholamines. They found that postpyloric isoenergetic EN increased both cardiac output and the perfusion of HSR. The weak point of this study could be the method used for the assessment of total splanchnic blood flow. The authors used systemic clearance of indocyanine green as a surrogate for HSR perfusion. This value, however, depends not only on the liver perfusion, but also on the indocyanine green extraction in the liver, i.e. on the liver function. Nevertheless, their most important finding was that the balance between splanchnic blood flow and metabolism was maintained during the utilization of enterally given nutrients.

Comparable clinical data on the physiological effects of EN on HSR in sepsis had been lacking. One of the pathophysiological hallmarks in patients with severe

sepsis and/or septic shock is the loss of vasoregulation and micoculatory failure. The pattern of the response of gut vascular bed to EN is unpredictable. EN in such circumstances could further deteriorate oxygen demand/supply mismatch in HSR by means of increased local metabolic demands. This, in turn, may lead to bowel ischemia, bacterial translocation or proinflammatory cascade initiation. Therefore, we have been assessing the influence of hypocaloric postpyloric EEN on hepatosplanchnic perfusion and energy metabolism in critically ill patients with severe sepsis and/or septic shock (Rokyta *et al.* 2001a). The total hepatosplanchnic blood flow was estimated by Fick principle using continuous primed indocyanine green infusion and hepatic vein catheterization (Uusaro *et al*. 1995). We found that postpyloric EN was associated with a mild increase in cardiac output while hepatosplanchnic blood flow significantly increased (Fig. 2) suggesting the maintenance of physiological regional hemodynamic response to EN. Moreover, EEN did not induce any uncoupling between hemodynamics and energy metabolism, since hepatic venous lactate to pyruvate ratio remained unchanged. Moreover, gastric mucosal energy balance, as assessed by a gradient between gastric mucosal PCO_2 (measured by tonometry) and arterial PCO_2, remained unchanged. Our preliminary data therefore suggest that the initiation of hypocaloric postpyloric EN in septic patients requiring low dose of norepinephrine might not compromise HSR.
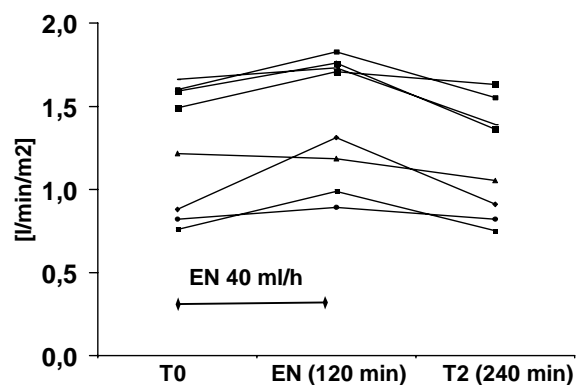

Fig. 2. *Hepatosplanchnic blood flow. T0 – baseline; EN – enteral nutrition ; T2 – 120 min after cessation of EN (Rokyta et al. 2001b)*

Risks of early enteral nutrition

The intolerance of EN in critically ill patients is more frequent during gastric than postpyloric feeding due to persistent gastroparesis. Enteral feeding, regardless of

application site, may generate functional disturbances resulting in diarrhea or gut distension. The risks of EEN in septic patients have already been mentioned (see above). The most severe complication related to EN is bowel necrosis (see below).

Experimental data

Raina *et al.* (1997) compared EN to total parenteral nutrition (TPN) in rats infused with tumor necrosis factor α (TNF-α). They found increased vascular permeability as well as more profound macroscopic changes in the stomach and small and large intestines in the EN + TNF-α rats as compared to EN and TPN + TNF-α rats.

These functional and structural detrimental effects of EN contrast with positive results of other experiments in septic animals (see benefits of EEN). How to explain these differences? Firstly, different animal species and models of sepsis were investigated. Secondly, different variables were studied (functional and structural changes versus hemodynamics and energy metabolism). One could only speculate so far that the adequate early hemodynamic response to EN might not guarantee the absence of functional and possibly also structural gut disturbances. During sepsis, the derangement of gut cellular mitochondrial functions may occur despite an adequate regional blood flow (cytopathic hypoxia) (Fink 2001). Under these conditions, the application of EN may further compromise enterocyte´s functions. Obviously, more experiments comprising hemodynamic, metabolic, functional and structural response of HSR to EN are needed before providing a definite answer.

The administration of EN in flow-limited conditions may be detrimental due to "intramesenteric steal effect". This phenomenon was disclosed in a dog model (Larson *et al.* 1994). Intrajejunal EN was administered during unrestricted or restricted superior mesenteric arterial (SMA) blood flow. EN during unrestricted SMA blood flow induced diffuse small bowel hyperemia, both in a segment with direct contact with EN (proximal jejunum) and in an isolated segment without contact with EN (distal ileum). By contrast, EN during restricted SMA blood flow induced a hyperemic response in the proximal jejunum only, whilst perfusion in the distal ileum decreased. This redistribution of blood within SMA bed is called intramesenteric steal phenomenon and may have clinical relevance in patients with abdominal artery diseases. In a similar "flow-limited" rat model, Kles *et al.* (2001) investigated the impact of postpyloric EN on jejunal oxygen kinetics and

energy metabolism (ATP to ADP ratio, lactate to pyruvate ratio etc.). EN in a group with SMA occlusion was associated with the deterioration of hepatosplanchnic oxygen kinetics and energy metabolism and with jejunal mucosal damage as documented by histology.

Nonocclusive bowel necrosis

Nonocclusive bowel necrosis (NOBN) is a rare, but potentially fatal complication, related to EEN in acutely stressed patients. NOBN was described in the course of various modes of enteral feeding, including EN *via* a jejunostomy (Schunn and Daly 1995, Jorba *et al.* 2000, Marvin *et al.* 2000, Frey *et al.* 2001). Diagnostic criteria for NOBN include a patent mesenteric vascular bed as well as the absence of bowel obstruction (Schunn *et al.* 1995). The pathophysiology of NOBN is shown in Figure 3. (Marvin *et al.* 2000). This scenario clearly shows that gut homeostasis during EN could be altered by several mechanisms.
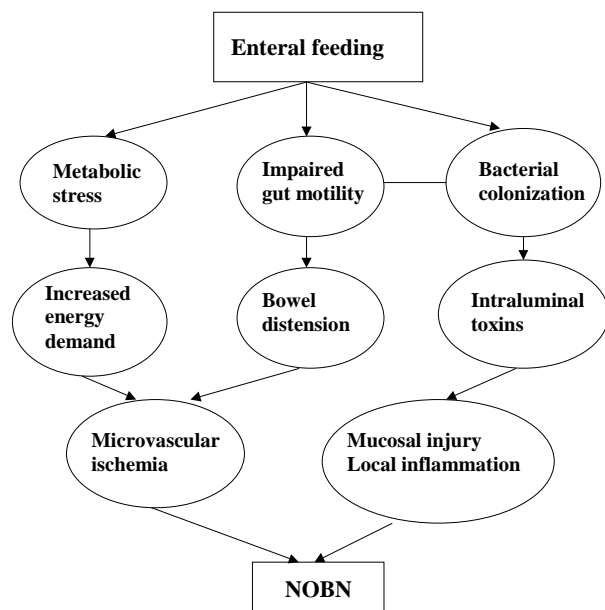
Fig. 3. *Proposed pathophysiology of nonocclusive bowel necrosis (NOBN) (modified from Marvin et al. 2000).*

Firstly, the absorption of intraluminal nutrients may deleteriously increase energy demands in stressed enterocytes. This metabolic stress of enterocytes (or colonocytes) may occur for a variety of reasons, including an imbalance between energy demand and supply, shunting of blood away from mucosa, and a primary defect in enterocyte mitochondrial function. Failure in normal compensatory mechanisms with abnormal redistribution of flow away from the mucosa

could lead to selective mucosal ischemia and possible necrosis. The potential increase of intraluminal intestinal pressure generated by EN may become of importance in this context, taking into account following experimental data. Gore and Bohlen (1977) demonstrated in a rat model that every sustained intraluminal pressure increase above 10 mm Hg may significantly diminish intestinal mucosal villi perfusion, since capillary pressures in rat mucosal villi are significantly lower as compared to capillary pressures in the intestinal muscle layer. Subsequently, Kvietys *et al.* (1986) studied the effects of intraluminal pressure changes on gut blood flow and oxygen uptake in isolated loops of canine ileum. They found that intraluminal pressures above 18 mm Hg (achieved by intraluminally infused silicone fluid in the absence of gut motility) led to a significant decrease of ileal oxygen uptake, presumably due to a compression of mucosal blood vessels. Although no such data are available during EN, one may speculate that the increased gut intraluminal pressure induced by continuous postpyloric EN could impair gut mucosal perfusion.

Furthermore, EN in the setting of ileus allowed bacterial overgrowth, thereby further deteriorates bowel distension and mucosal perfusion. Generated intraluminal toxins during EN may cause direct mucosal injury or initiate destructive bowel wall inflammation.

Monitoring of the tolerance of enteral nutrition

Continuous monitoring of EN tolerance in critically ill patients is a challenging task. To date, however, the only available monitoring tool has been a careful and repeated clinical examination. Special attention should be paid to peristalsis (although this might not be present even when the bowel function is maintained), abdominal distension, gastric rests and diarrhea. The onset of hemodynamic instability and/or systemic inflammatory response syndrome without clear etiology may represent the signs of NOBN development. Unfortunately, the early marker for detecting incipient NOBN has not been discovered yet.

Gastric tonometry measurement might help to detect the incipient NOBN. At present, gastric tonometry is the only clinically feasible monitoring tool for the adequacy of gut perfusion (Brinkmann *et al.* 1998). A few clinical studies have investigated the effects of postpyloric EN on gastric mucosal (measured by tonometry) to arterial PCO_2 gradient (PCO_2 gap). Continuous postpyloric EN in healthy volunteers as well as in stable critically ill patients does not significantly influence PCO_2 gap (Levy *et al.* 1998, Rokyta *et al.* 2001b). Moreover, Andel *et al.* (2001) observed gradual PCO_2 gap decrease during postpyloric high-energetic EN in burned patients. Nevertheless, even normal PCO_2 gap values may not entirely exclude inadequate perfusion, oxygenation and/or energy metabolism in more distant parts of the gastrointestinal tract.

Hepatic vein catheterization is another monitoring tool enabling the assessment of hepatic venous hemoglobin oxygen saturation and other regional metabolic parameters. The drawbacks of this method include invasivity, restricted time for keeping the hepatic venous catheter in place, and the lack of direct access into portal circulation (De Backer 1999).

Conclusions

Early enteral nutrition in critically ill patients forms an integral part of "hepatosplanchnic resuscitation". Although the results of recent clinical studies suggest that EEN is not harmful even in patients with circulatory compromise, the initiation of EEN in patients at risk for splanchnic hypoperfusion (sepsis, cardiogenic shock, hemodynamic instability) may lead to functional and structural gut derangement and therefore requires careful clinical monitoring. Further studies are needed to clarify the optimal timing, dose and composition of EEN in critically ill patients.

Acknowledgements

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