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CLINICAL PERSPECTIVE

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Cardiogenic shock and nutrition: safe?

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Abstract Cardiogenic shock is a common diagnosis in patients in the intensive care unit (ICU), and is characterized by a decreased cardiac output in the presence of adequate intravascular volume associated with an inadequate tissue perfusion including a physiological reduction in the splanchnic territory. It may occur in isolation as a reflection of cardiac pathology, or it may be part of a shock syndrome involving other pathogenic mechanisms. As the use of enteral nutrition (EN) is associated with an increase in mesenteric arterial output, EN could be deleterious by overwhelming the mechanisms of mesenteric adaptation. Accordingly, EN has been suspected to increase the risk of mesenteric ischaemia, bacterial translocation and sepsis in ICU patients with cardiogenic shock. International guidelines recommend a cautious use of EN within 72 h following cardiogenic shock. Recent evidence indicates that mesenteric arterial output may decrease during parenteral nutrition administration, suggesting that parenteral nutrition could have a protective effect on splanchnic organs in ICU patients with cardiogenic shock. Contrary to former beliefs, several meta-analyses have shown that parenteral nutrition is not associated with increased mortality. Exclusive EN is associated with negative energy balance and the combination of EN with supplemental parenteral nutrition during the first days following ICU admission has been proposed to prevent negative energy balance. Such a nutritional strategy could also be beneficial for the mesenteric circulation in cardiogenic shock, and consequently may improve the clinical outcome of patients with cardiogenic shock. Clinical trials are warranted to verify these hypotheses.

Keywords Mesenteric artery · Splanchnic territory · Haemodynamic · Enteral nutrition · Supplemental parenteral nutrition · Undernutrition

Introduction

Early enteral nutrition (EN) is recommended in patients in the intensive care unit (ICU). Cardiogenic shock (CS) is a common pathological state in the ICU and is associated with a mortality rate of around 50% [1]. CS is clinically defined as a decrease in cardiac output and evidence of tissue hypoxia in the presence of an adequate cardiac preload [2]. The European Society of Cardiology has retained some criteria that usually define CS (Table 1) [2]. CS may develop after loss of cardiomyocyte function (e.g. acute myocardial infarction) or as a part of a shock

Table 1 Common haemodynamic monitoring picture of CS according to the 2008 European Society of Cardiology guidelines [2]

Criteria	Threshold defining CS
Heart rate (beats/min)	Usually >100
Systolic blood pressure (mmHg)	Low, usually <90
Cardiac index (l/min/m^2)	<2.2
Pulmonary capillary wedge pressure (mmHg)	>18
Diuresis (ml/kg/h)	<0.5

syndrome initiated by sepsis, anaphylaxis, hypervolaemia, etc. In CS the physiological adaptation secondary to heart damage and insufficiency leads to a decrease in arterial flow to the brain, lungs and kidneys, and, of utmost interest for nutritional management, to the liver and intestine. Severe digestive complications associated with a low mesenteric arterial supply, such as mesenteric ischaemia, bacterial translocation and sepsis, have been reported in patients with CS on EN [3].

The nutritional strategy in ICU patients with CS remains controversial. Early exclusive EN at a low flow rate (continuous EN at a rate of 20 ml/h) has been proposed to reduce the risk of severe intestinal complications, but is associated with negative energy balance and its related complications [4, 5]. Although parenteral nutrition (PN) may be associated with increased metabolic and infectious complications, the use of PN alone could reduce mesenteric arterial output, and its associated risk of mesenteric ischaemia.

This review describes the splanchnic haemodynamic alterations observed in ICU patients with CS and compares the effects of EN and PN on splanchnic haemodynamics in ICU patients with CS and in healthy subjects. It also launches the hypothesis that the combination of EN and supplemental PN in the first days following ICU admission, besides preventing a negative energy balance, may also protect the mesenteric circulation in CS. Therefore, EN with supplemental PN may improve the clinical outcome of patients with CS (Fig. 1). Clinical trials are warranted to verify these hypotheses.

Haemodynamic changes in the splanchnic (mesenteric and hepatic) area during CS

Changes in splanchnic circulation during CS

The main characteristics of splanchnic haemodynamics in some physiological conditions are summarized in Table 2. Mesenteric blood flow accounts for 10–15% of cardiac output under fasting conditions. The gut mucosa is a tissue particularly sensitive to alterations in perfusion and oxygen status. During feeding, mesenteric organs maintain a prominent functional hyperaemia characterized by a twofold increase in blood flow and metabolic activity. Pathophysiological mechanisms of mesenteric flow regulation are complex and depend on the aetiology of the shock. When the perfusion pressure is reduced in the small intestine, the ischaemia and the EN-related accumulation of local metabolites (pH, adenosine, oxygen tension, etc.) induce a vasodilatation mediated by myogenic and metabolic responses [6]. Moreover, for a mesenteric blood flow lower than 15 ml/min/100 g of tissue, local autoregulation of oxygen consumption is also driven by an increase in tissue oxygen extraction [6]. Unfortunately, this phenomenon may contribute to liver hypoxia by decreasing the oxygen content available for the liver via portal venous inflow as already demonstrated in an animal study [7].

Experimental animal models

In dogs with CS related to cardiac tamponade, the physiological peripheral vascular response induced by catecholamines has been shown to lead to a dramatic decrease in hepatic and portal blood flow [7]. Indeed, the intense visceral vasoconstriction leads to a decrease in visceral blood flow as a consequence of a decline in mean arterial pressure [7]. Conversely, in a nonresuscitated pig model of septic shock, a decrease in cardiac output related to septic cardiomyopathy has been shown to be associated with mesenteric vasoconstriction and hepatic vasodilatation with a well-maintained liver capillary perfusion [8].

ICU patients

In critically ill patients with CS, it is not known whether "increasing intestinal work" through EN could induce such a low flow state and acute mesenteric ischaemia. Nevertheless, some studies have investigated the human mesenteric circulation during CS. Indeed, when systemic blood flow decreases, blood volume is redistributed to increase cardiac preload (partly by venoconstriction) and cardiac output, resulting in decreased peripheral vascular capacitance [9]. As peripheral vascular capacitance is the tissue capillary "afterload", venoconstriction with an increase in venous pressure leads to a decrease in organ perfusion. In this regard, it has been shown that 45% of nonsurvivors of CS die with a satisfactory cardiac index (i.e. >2.2 l/min/m^2), and high SvO_2, indicating that optimization of macrohaemodynamic parameters alone may fail to save the patient [10, 11].

These findings have led to a change in the concept of CS being only a cardiac problem to being an overall microcirculatory disease, related to the systemic inflammatory response syndrome, and, through the release of

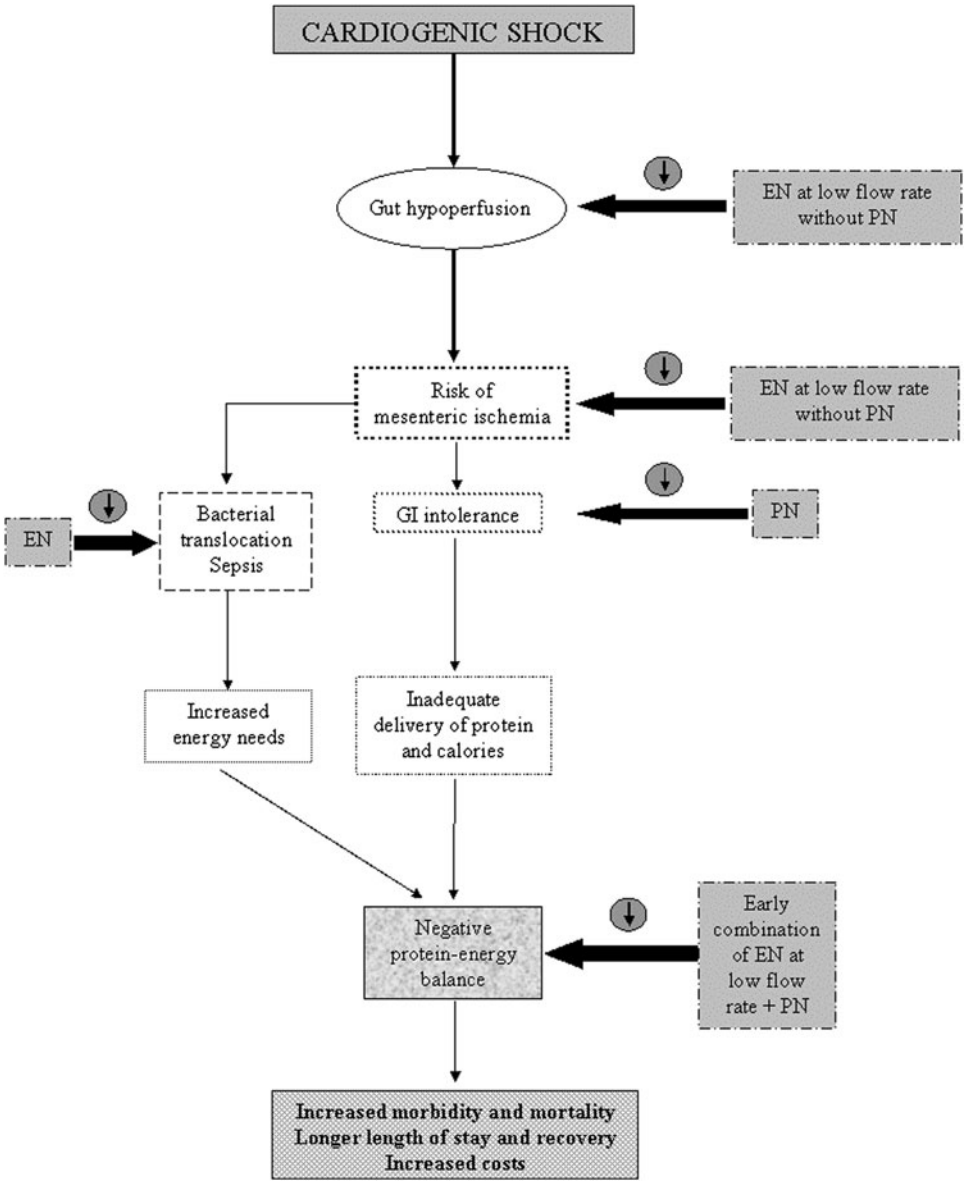


Fig. 1 Hypothetical scheme suggesting an impact of EN and PN on the outcome of CS. CS induces a decrease in splanchnic blood flow, leading to gut hypoperfusion, and in turn, increasing the risk of mesenteric ischaemia. Mesenteric ischaemia is frequently complicated by bacterial translocation and sepsis, increasing energy needs, and by gastrointestinal (*GI*) intolerance, reducing protein-energy delivery. This results in a negative protein-energy balance, increasing morbidity, mortality, length of stay and recovery, and costs. EN at low flow rate and PN, by reducing mesenteric blood flow, could prevent gut hypoperfusion and the risk of mesenteric ischaemia. Simultaneously, PN, by preventing GI intolerance, and EN, by reducing the risk of bacterial translocation and sepsis, have a positive effect on protein-energy balance, by improving the balance between energy needs and protein and calorie delivery. Therefore, early combination of EN at a low flow rate and PN could have a positive impact on the clinical outcome of CS

Table 2 Main characteristics of the splanchnic circulation. The main arteries (and portal vein) of the splanchnic circulation are listed with respect to the organs supplied and their blood flow

Main artery	Organs supplied	Splanchnic blood flow
Coeliac trunk, divided into hepatic, splenic and stomach coronary arteries	Oesophagus, stomach, proximal duodenum, liver, gallbladder, pancreas, spleen	–
Hepatic artery	–	25–30% of total hepatic blood supply (400–500 ml/min)
Splenic and stomach coronary arteries	–	3% of cardiac output under fasting conditions (200 ml/min)
Superior mesenteric artery	Distal duodenum, jejunum, ileum, colon to the spleen flexure	10–15% of cardiac output under fasting conditions (800 ml/min)
Inferior mesenteric artery	Descending colon, sigmoid colon, rectum	
Portal vein	–	70–75% of total hepatic blood supply (1,000–1,100 ml/min)/venous oxygen saturation = 85%

proinflammatory cytokines and neurohormones, leading to multiple organ failure (Fig. 2) [12–14]. Measuring sublingual microcirculation using orthogonal polarization spectral imaging, De Backer et al. [14] reported a decreased proportion of functional capillaries in patients with CS compared to healthy controls. In addition, these alterations in microcirculatory blood flow of the sublingual mucosa (which has a similar embryological origin with the digestive mucosa) were correlated with ICU mortality [14]. As human [15–17] and animal [18] studies have shown similar severities and time courses of microcirculatory changes in the sublingual and in the splanchnic (gut or gastric) areas, the study by De Backer et al. [14] suggests that human splanchnic microcirculation could be altered during CS in some patients.

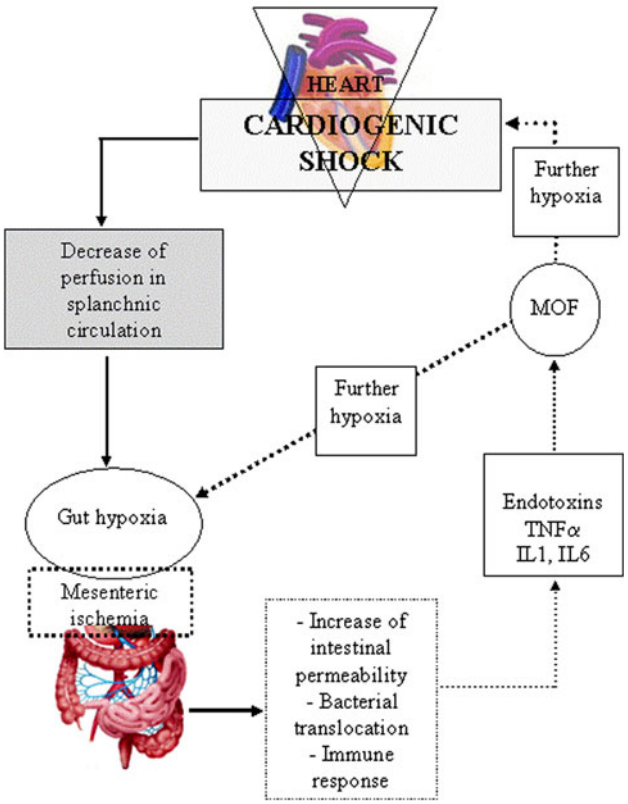


Fig. 2 Gut ischaemia as a motor of multiple organ failure (*MOF*) in ICU patients. Cardiogenic shock induces a decrease in splanchnic blood flow, leading to gut hypoxia and the risk of mesenteric ischaemia. Gut hypoxia increases intestinal permeability and bacterial translocation. The bacterial endotoxins are responsible for a major gut immune response, inducing the secretion of proinflammatory cytokines, such as tumour necrosis factor α (*TNFα*) and interleukins (*IL1* and *IL6*). These cytokines further exacerbate the inflammatory process in body tissues, leading to the onset of MOF. MOF aggravates splanchnic hypoxia and leads to the persistence of cardiogenic shock

Intestinal ischaemia in the course of critical illness

The microvasculature of the villus exhibits a countercurrent arrangement of blood flow in the arterioles and venules. Thus, much of the blood oxygen diffuses out of the arterioles directly into the adjacent venules without ever being carried in the blood to the tips of the villi. In this system, 80% of the oxygen may take this short-circuit route and therefore not be available for the metabolic exchanges in the gut mucosa. Under normal conditions, this oxygen shunting is not detrimental to the villi. In contrast, it becomes deleterious under low-flow conditions since blood arrival at the gut mucosa becomes greatly reduced. During CS, the low cardiac output induces hypotension through an increased total systemic vascular resistance and the action of the renin angiotensin system. Of this response, which aims to maintain central arterial blood pressure, 40% is mediated through mesenteric vascular vasoconstriction [6]. The latter is the primary mechanism underlying mesenteric ischaemia following CS.

Early identification of mesenteric ischaemia is of great importance, since the gastrointestinal tract is identified as the "motor" of multiple organ failure [17] (Fig. 2). Indeed, the most severe complications of mesenteric ischaemia, i.e. mesenteric infarction and peritonitis, frequently occur with the development of septic shock and multiple organ failure. In the setting of the ICU, intense abdominal pain, which is often a symptom of mesenteric ischaemia, is less reliable, since patients are deeply sedated and are frequently receiving high doses of analgesics. Intestinal malabsorption is also present but it is a nonspecific and late sign of intestinal ischaemia. Therefore, it is necessary to have other criteria to detect the early onset of mesenteric ischaemia in critically ill patients with CS. Several methods for the measurement of regional splanchnic blood flow have been evaluated in the ICU setting, but their validation is questionable since no gold standard exists. These methods include:

1. Fick principle using the measurement of indocyanine green clearance which depends on liver dye extraction (altered in hepatic dysfunction).
2. Monitoring the oxygen saturation of subhepatic veins.
3. Gastric tonometry, as microcirculation in the gastric mucosa is compromised early during blood flow redistribution [19, 20]. (This technique coupled with measurement of intramucosal pH in critically ill patients could be related to erroneous measurements if hydrogen ions are secreted by parietal cells [22]).
4. Duplex ultrasound [23, 24].
5. Sublingual capnometry.
6. Measuring sublingual microcirculation using orthogonal polarization spectral imaging which is a promising method for monitoring the gut microcirculation [14–18]. However, in the absence of clinical trials, its routine use cannot be recommended in ICU patients.

Undoubtedly, future research focusing on more precise methods of mesenteric arterial flow measurements is warranted.

Impact of starvation, oral or EN, on mesenteric arterial output

Healthy subjects

In healthy subjects, oral intake induces physiological adaptive haemodynamic changes, consisting of an increase in both cardiac output and mesenteric flow [25, 26] together with an increase in splanchnic oxygen consumption [27]. After a meal, the superior mesenteric artery (SMA) blood flow increases reaching a value higher than 40% of total cardiac output [28]. In healthy subjects, the mesenteric response to oral intake depends on the energy [29] and on the macronutrient content of the meal [23, 25, 26, 30]. In one study [25], the increase was higher after fat administration, and, in another [26], the increase was higher after protein administration. Conversely, the osmolarity of oral intake did not affect mesenteric blood flow [26]. Therefore, the response to feeding via healthy gut is associated with an increased blood flow to the splanchnic circulation and enhanced gastric acid secretion [31]. Thus, it has been anticipated that EN alone may modify the haemodynamic adaptive response to CS. Through the increase in mesenteric arterial blood flow and the ATP consumption related to nutrient absorption [24, 32], EN may induce gut hypoperfusion and mesenteric ischaemia.

ICU patients

Several studies have shown that the administration of EN in haemodynamically stable individuals with circulatory shock is associated with an increase in splanchnic blood flow and oxygen delivery [32, 33]. However, none of these studies was performed in ICU patients with CS. In patients undergoing cardiopulmonary bypass and requiring dobutamine and/or norepinephrine [32] or in mechanically ventilated patients with severe sepsis [34], the postpyloric administration of EN solution induces an increase in splanchnic blood flow related to splanchnic vasodilatation. This results in an increase in cardiac output and a decrease in systemic vascular resistance [31, 34]. However, conflicting results have been found regarding the impact of EN on hepatic arterial blood flow. Increased [34] as well as normal values [32, 35] have been reported, together with hypoperfusion of the gastric mucosa [32]. All these parameters returned to within normal ranges after cessation of EN. In parallel, there was no change in splanchnic oxygen consumption or in gastric mucosal energy balance, and an increased cardiac output was observed even in patients requiring norepinephrine. Thus, with an increase in mesenteric blood flow, intestinal perfusion remains adequate during EN in patients with normal cardiac function.

Recently, using semiquantitative estimates of the blood flow in the SMA determined by duplex ultrasonography, Gatt et al. [24] studied the changes in SMA blood flow in 14 healthy volunteers and 20 haemodynamically stable ICU patients, 3 h after the initiation of EN or PN. Patients fed enterally showed increased postprandial SMA blood flow from 7.3 ml/s (range 2.9–12.1 ml/s) to 11.2 ml/s (range 8.2–26.0 ml/s; $P = 0.007$), while patients on PN showed decreased postprandial SMA blood flow from 14.5 ml/s (range 4.8–24.8 ml/s) to 6.1 ml/s (range 2.4–9.2 ml/s; $P = 0.013$). The increased splanchnic blood flow induced by EN may be related to hormonal regulation, since Parker et al. [29] have shown that there is a positive correlation between the meal energy content and postprandial increases in N-terminal neurotensin and noradrenaline concentrations. In addition, Brundin and Wahren [36] have shown that intravenous glucose administration induces an increased oxygen demand and blood flow in extra-splanchnic tissue, while splanchnic energy expenditure and perfusion decrease. It therefore could be hypothesized that glucose administered parenterally shunts blood away from the gut that, in turn, decreases splanchnic blood flow. From these observations, possible advantages and disadvantages of EN and PN in ICU patients with CS are depicted in Table 3.

However, the main question remains: what are the effects of EN support on splanchnic haemodynamics in patients with CS? Some clinical reports suggest that early EN could be associated with gut ischaemia in relation to alterations in splanchnic blood flow in patients with severe circulatory failure [37–39]. ICU patients with CS may be vulnerable to gut haemodynamic alterations related to EN administration. Indeed, in CS, the heart is unable to respond to an increase in splanchnic blood flow, increasing the risk of mesenteric ischaemia.

It has been hypothesized that low flow states in relation to alterations of splanchnic perfusion may limit the effectiveness of intestinal nutrient absorption [40]. Berger et al. [39] analysed paracetamol kinetics in 16 patients who had undergone cardiac surgery with adequate haemodynamic status and 23 patients with haemodynamic failure, and found no abnormalities in intestinal absorption in either group. Therefore, haemodynamic failure is not a contraindication to the use of EN in ICU patients with CS on the basis that circulatory failure could affect the intestinal absorptive function.

In summary, nutritional support affects SMA blood flow in haemodynamically stable ICU patients. However, it is not possible to draw any conclusions about the clinical impact of these changes on ICU patients with CS

Table 3 Advantages and disadvantages of EN and PN in ICU patients with CS (advantages of one route are often considered as disadvantages of the other)

Enteral nutrition	Parenteral nutrition
Advantages	Disadvantages
Maintenance of intestinal trophicity	Gut mucosal atrophy (not proven in humans)
Decreased risk of bacterial translocation and infections	Increased risk of bacterial translocation and infections
Better regulation of insulin secretion and glycaemia	Hyperglycaemia and insulin resistance
No dysfunction in lipid metabolism	Risk of hypertriglyceridaemia
No risk of hepatic dysfunction	Risk of hepatic dysfunction
Lower risk of complications with overfeeding	More serious consequences of overfeeding
Lower risk of refeeding syndrome	Higher risk of refeeding syndrome
Better bile clearance, reduced risk of hydrocholecystis	Higher risk of hydrocholecystis
Disadvantages	Advantages
Increased SMA and hepatic blood flow	Reduced SMA blood flow
Risk of mesenteric ischaemia	Decreased risk of mesenteric ischaemia
Risk of gastrointestinal intolerance (vomiting, aspiration, diarrhoea, etc.)	No risk of aspiration and of gastrointestinal intolerance
Delayed achievement of the energy target	Immediate achievement of the energy target
Frequently associated with negative protein-energy balance	Improvement of the protein-energy balance

since: (1) no study has been performed in this subgroup of patients; (2) haemodynamic measurements have never been correlated with clinical events; and (3) it cannot be excluded that the increase in splanchnic blood flow related to EN could be beneficial in patients with CS, by reinforcing the intestinal epithelial barrier. However, although data are somewhat conflicting, it can be stated that haemodynamic response to enteral feeding may or may not be adequate in critically ill patients with low flow states, indicating the need for careful monitoring [41]. Clearly, clinical trials are warranted to answer these questions. The aim of these studies will be to investigate the effects of nutritional support on splanchnic blood flow continuously monitored by noninvasive techniques, such as duplex ultrasonography, in different subgroups of patients. They should determine whether other intrinsic factors could be involved and elucidate the mechanisms underlying the haemodynamic changes in the splanchnic area in the context of the nutritional support.

Relevance of nutritional support in the management of critically ill patients with CS

Impact of undernutrition and protein-energy deficits in patients with CS

Undernutrition is found in around 50% of patients with severe chronic congestive heart insufficiency [42], and in 9% of patients undergoing cardiac surgery [43]. Cardiac cachexia and undernutrition are independent predictive factors of mortality, prolonged length of stay and increased incidence of postoperative complications in patients with chronic heart failure [43, 44]. Independent of the nutritional status, a state of negative energy balance is also associated with increased morbidity in ICU patients. In a recent prospective study in 48 critically ill patients, including 13 patients undergoing cardiac surgery, Villet et al. [5] reported that EN alone led to insufficient energy and protein coverage 1 week after ICU admission, and that this energy deficit correlated with both total and infectious complications. In another study of 50 critically ill patients, a strong positive relationship between the cumulated energy debt and the frequency of complications, including adult respiratory distress syndrome, renal failure, need for surgery, and pressure sores, has been reported [4]. In ICU patients with CS, EN is frequently insufficient to obtain sufficient optimal energy delivery [21]. A Swedish study in cardiothoracic ICU patients has confirmed that it is usually not possible to meet the entire nutritional requirement by EN [45]. This observation may be related to the fact that vasoactive drugs (dopamine, dobutamine and norepinephrine) are independent risk factors for a high gastric aspirate volume and digestive intolerance [46]. Moreover, the use of vasoactive drugs is positively correlated with muscle catabolism and negatively correlated with enteral energy intakes [21].

The increased incidence of complications resulting from undernutrition and energy deficit translates into a prolonged hospital stay and increased health-care costs [47–50]. Therefore, it is mandatory to provide ICU patients, including those with CS, with minimum amounts of energy and nutrients to improve their clinical outcome [51].

Choice of nutritional support in patients with CS

Recent evidence-based European and American nutritional guidelines advocate an early initiation of EN (within 24 or 48 h of admission to the ICU, respectively) as the preferred route of nutritional support in ICU patients [42, 52–55]. Early initiation of EN is associated with a reduced risk of infections, lower ICU mortality,

lower hospital mortality and shorter length of ICU stay in mechanically ventilated ICU patients [56–60], and with a decreased rate of infectious complications, a shorter total length of hospital stay, and lower overall costs of management of postsurgical patients [61, 62]. However, EN is frequently insufficient to cover the energy expenditure even in the hands of a well-trained and experienced nutrition team.

Based on the hypothesis that EN alone could be harmful in ICU patients with CS, the nutritional management of these patients remains controversial and essentially based on expert opinion. Indeed, randomized studies comparing the use of PN and EN and evaluating the clinical outcome are lacking. As a result, recent ICU guidelines provide no specific recommendation for nutritional support in ICU patients with CS, except the necessity for haemodynamic stability before initiating the nutritional support [63]. The few clinical studies performed in patients with haemodynamic instability demonstrate that EN could be well tolerated. In the study by Berger et al. [39] in 16 ICU patients with adequate haemodynamic status and 23 patients with severe haemodynamic instability following open-heart surgery, postpyloric or gastric EN initiated at the rate of 20 ml/h between days 2 and 5 after admission was well tolerated. Berger et al. [21] have also reported that 70 patients with haemodynamic failure after cardiopulmonary bypass could receive EN with a minimum mean daily energy deficit (-255 ± 370 kcal/day) without experiencing serious gastrointestinal complications. Moreover, in patients with the most severe cardiac failure needing the insertion of an intraaortic balloon pump, the 7-day energy deficit was lower (270 vs. 1,920 kcal). Thus, EN may be possible in most patients with severe haemodynamic failure [21], but usually results in hypocaloric feeding.

The choice of enteral solution does not appear to be critical for digestive tolerance. Indeed, polymeric, protein-enriched or not [21, 32], and semi-elemental diets [21, 34, 39] are both well tolerated at a flow rate of 20–40 ml/h. No randomized controlled study has compared the tolerability of EN in patients with CS according to the fibre content of the solution. In two studies [32, 34], the tolerability of EN has been evaluated only after a 2 or 3 h infusion. The putative effects of pharmaconutrients, such as glutamine, omega 3, short-chain fatty acids, vitamins E and C, selenium, or combination of them, on the clinical outcome in ICU patients with CS have only been discussed in relation to animal models (for review, see reference [64]). Thus, their use in ICU patients with CS is not recommended.

In specific situations, such as worsening GI intolerance and ventilatory parameters, mean arterial pressure below 70 mmHg, and an increase in the doses of pressor agents, some authors have advised the use of total PN [64]. However, clinical studies supporting this strategy are lacking. We think that, in these situations, the tolerability of low flow-rate EN should be evaluated before deciding to initiate total PN.

In summary, although no clinical data have demonstrated harmful effects of EN in patients with CS, a cautious use of EN is advocated during the first 72 h following ICU admission. The impact of EN on the splanchnic circulation may depend on the modalities of administration, i.e. bolus feeding versus continuous administration. As a minimal flow rate of 20 ml/h seems to be well tolerated, we suggest that early EN should be initiated but should not exceed 250–500 ml/day during the 72 h following ICU admission. The recommendations concerning the delivery of EN and PN in ICU patients with CS are summarized in Table 4.

Combined nutritional support: a new combination to improve the clinical outcome in patients with CS

EN is frequently associated with protein-energy deficit in ICU patients, a condition associated with increased morbidity. In ICU patients with CS, EN is expected to be insufficient to meet energy requirements as a low flow rate is recommended and the use of vasoactive drugs is associated with gastrointestinal intolerance [46] and protein-energy deficit [21]. A recent observational study in 1,209 ICU patients demonstrated that early EN or PN, achieving the energy target in the three first days of the ICU stay is associated with a decrease in morbidity and mortality [65]. Thus, supplemental PN together with insufficient EN could optimize nutritional therapy by preventing the onset of early energy deficiency. In the study by Villet et al. [5], the patients receiving combined EN and PN achieved a higher mean calorie intake (2,160 kcal/day) than did patients receiving EN alone (1,365 kcal/day; $P < 0.0001$). Other studies have demonstrated that PN could allow a higher proportion of the energy needs to be met than EN [66, 67]. Recently, we presented the preliminary results of a prospective, controlled, randomized study [68] which was initiated to investigate if the delivery of 100% of the energy target in ICU patients from day 4 by EN and supplemental PN could optimize their clinical outcome (http://www.clinicaltrials.gov, study protocol #NCT00802503). We showed that the mean energy delivery from day 4 to day 8 was higher with EN and supplemental PN than with EN alone ($98.0 \pm 19.0\%$ vs. $80.0 \pm 31.7\%$, $P < 0{,}001$) [68]. Therefore, the combination of EN and PN could be an efficient way to increase mean calorie intake in ICU patients and to match energy requirements with delivery. In a study of 49 mechanically ventilated, malnourished critically ill patients, the combined nutrition group experienced an improvement in nutritional status [69].

However, until recently, PN has been restricted in ICU patients, since it has been suggested that it is associated

Table 4 Recommendations for the management of nutritional support in ICU patients with CS

	Enteral nutrition	Parenteral nutrition	Combination enteral/parenteral
Indications	All patients unable to meet their energy needs by oral intake in the 72 h following ICU admission (C)	All patients with the indications for EN but complicated by GI intolerance or intestinal ischaemia (C)	All patients whose protein-energy needs are not met after 48 h of EN
Recommendations	Early EN should be initiated in the first 24 h in patients fully resuscitated and/or stable (C)	Strict glycaemic control should be obtained to avoid the deleterious effects of hyperglycaemia and overfeeding (C)	The same recommendations as for EN and PN alone are applicable
	EN should be begun at a low flow rate (20 ml/h) during the first 48 h to evaluate GI tolerance (E)		Consider de-escalation of PN together with an increase in EN energy delivery (E)
	EN should be stopped in hypotensive patients (mean arterial blood pressure <60 mmHg) or if the doses catecholamine agents[a] need to be escalated (E)		
	Strict monitoring for early signs of intestinal ischaemia (abdominal distension, high residual gastric volumes, hypoactive bowel sounds, metabolic acidosis) is mandatory (E)		
Choice of solution	Polymeric (E) Fibre-free (E) No pharmaconutrients (E)	'All-in-one' solution (E) No pharmaconutrients (E)	See beside

The grade of recommendation is indicated in parentheses (from references [52, 55, 63])
[a] Norepinephrine, phenylephrine, epinephrine, dopamine.

with bacterial translocation from the gut to the bloodstream. However, the actual observed incidence of bacterial infections is similar in patients receiving PN and those receiving EN [70]. Recent meta-analyses have shown no increased mortality for PN in comparison to EN [53, 57, 71–74]. The benefit of PN is even higher when trials comparing early PN with delayed EN (>24 h) are taken into account [71].

Today, PN can be successfully and safely administered providing the nutritional needs are adequately met by the prescription with the objective of avoiding protein-energy deficit, overfeeding and hyperglycaemia [75]. With respect to these conclusions, the recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend the use of PN in combination with EN when EN does not meet 60% of the energy target within 72 h following ICU admission [63]. From a pathophysiological point of view, the combination of EN and PN may represent an appropriate way to feed ICU patients with CS. A partial EN may contribute to maintaining the integrity of the intestinal epithelial barrier, thereby reducing the risks of mesenteric ischaemia and bacterial translocation. As PN reduces splanchnic arterial blood flow, it may be protective against the risk of intestinal ischaemia. Thus, we suggest supplemental PN to be started within 24 h following ICU admission, and then further adapted according to enteral intake. PN should be maintained as long as the CS is present, together with careful cardiac preload monitoring. PN should gradually be weaned over time as EN approaches nutritional goal. Clinical trials are now necessary to demonstrate whether combined nutritional support could improve the clinical outcome in ICU patients with or without CS as compared with EN or PN alone.

Conclusion

Physiological adaptation to CS leads to a reduction in splanchnic perfusion. The increase in splanchnic blood flow needed when EN is given may not be possible during CS, introducing the risk of splanchnic underperfusion, intestinal ischaemia and/or vital organ–mesenteric blood steal. From the few studies available, the use of EN does not seem to be contraindicated, but must be initiated at a low flow rate. Total PN is indicated in patients with severe gastrointestinal intolerance or mesenteric ischaemia. Minimal EN would lead to a protein-energy deficit, in turn associated with a worse clinical outcome. As a recent meta-analysis suggests that early PN is safe, supplemental PN together with EN could limit nutritional deficiencies when EN is insufficient to cover energy requirements during the first days after ICU admission. Clinical trials are warranted to verify the hypothesis that

combined EN and PN could improve clinical outcome in ICU patients with CS.

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