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ORIGINAL

Impact of the route of nutrition on gut mucosa in ventilated adults with shock: an ancillary of the NUTRIREA-2 trial

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Abstract

Purpose: The effects of the route of nutrition on the gut mucosa of patients with shock are unclear. Plasma citrulline concentration is a marker of enterocyte mass, and plasma intestinal fatty acid binding protein (I-FABP) concentration is a marker of enterocyte damage. We aimed to study the effect of the route of nutrition on plasma citrulline concentration measured at day 3 of nutrition.

Materials and methods: Ancillary study of the NUTRIREA-2 trial. Ventilated adults with shock were randomly assigned to receive enteral or parenteral nutrition. Enterocyte biomarkers were measured at baseline, day 3, and day 8 of nutrition.

Result: A total of 165 patients from 13 French ICUs were included in the study: 85 patients in the enteral group and 80 patients in the parenteral group. At baseline, plasma citrulline was low without difference between groups (12.2 µmol L^{-1} vs 13.3 µmol L^{-1}). At day 3, plasma citrulline concentration was higher in the enteral group than in the parenteral group (18.7 µmol L^{-1} vs 15.3 µmol L^{-1}, $p = 0.01$). Plasma I-FABP concentration was increased at baseline, without difference between groups (245 pg mL^{-1} vs 244 pg mL^{-1}). Plasma I-FABP concentration was higher in the enteral group than in the parenteral group at day 3 and day 8 (158 pg mL^{-1} vs 50 pg mL^{-1}, $p = 0.005$ and 225 pg mL^{-1} vs 50 pg mL^{-1}, $p = 0.03$).

Conclusion: Plasma citrulline concentration was higher after 3 days of enteral nutrition than after 3 days of parenteral nutrition. This result raises the question of the possibility that enteral nutrition is associated with a more rapid restoration of enterocyte mass than parenteral nutrition.

Keywords: Plasma citrulline, Plasma intestinal fatty acid binding protein, Enteral nutrition, Parenteral nutrition

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Introduction

There is increasing evidence that critically ill patients are at risk of presenting intestinal failure [1]. Indeed, enterocytes, the main cells involved in absorption and gut barrier functions, are at risk of dysfunction or damage among critically ill patients [2]. Plasma citrulline concentration is a marker of enterocyte mass and could be considered as "the factor V of the gut" [3, 4]. There is increasing evidence that low plasma citrulline concentration is a marker of acute intestinal failure among critically ill patients [5–7]. Intestinal fatty acid binding protein (I-FABP), a small cytosolic protein specific to small bowel enterocytes, is released in case of enterocyte necrosis. Plasma I-FABP concentration could be considered as "the troponin of the gut" [8, 9]. Studying these two biomarkers might help to identify critically ill patients presenting with small bowel mucosal damage or dysfunction by mechanisms of ischemia, hypoxia, or systemic inflammation [2].

The effects of enteral nutrition on the bowel of critically ill patients with shock are unclear. On the one hand, enteral nutrition might have beneficial effects on the bowel with mesenteric arteries vasodilation, and limitation of the phenomenon of small bowel villous atrophy, both mechanisms which could preserve enterocyte mass and barrier function. On the other hand, enteral nutrition might have deleterious effects on the small bowel of patients presenting with shock mainly by increasing the risk of non-occlusive mesenteric ischemia.

The effects of the route of nutrition on enterocyte biomarkers among critically ill patients with shock are unknown. We hypothesized that the enteral route might be associated with a beneficial effect on enterocyte biomarkers of critically ill patients with shock, with a higher concentration of plasma citrulline and a lower elevation of plasma I-FABP concentration, compared to the parenteral route.

The primary objective of this study was to compare plasma citrulline concentration measured after 3 days of nutrition according to the route of nutrition randomly assigned, either enteral or parenteral, among critically ill patients receiving mechanical ventilation and catecholamine therapy. The secondary objectives were to compare the evolution of plasma citrulline and I-FABP concentrations at baseline, at day 3, and at day 8 of nutrition, according to the route of nutrition.

Patients and methods

Study protocol

This was a planned ancillary study (ClinicalTrials.gov NCT03852940) of the large randomized controlled NUTRIREA-2 trial (ClinicalTrials.gov NCT01802099) [10]. This ancillary study was started while the main trial was ongoing. Thirteen participating ICUs included the patients both in the main trial and in this substudy until the number of patients reached 160. Inclusion criteria for this substudy were those of the main study: adult patients, under mechanical ventilation, and receiving catecholamine therapy for shock. Exclusion criteria were contraindication to receive either enteral or parenteral nutrition. The two groups were randomized according to the route of nutrition: one group received early full enteral nutrition for 7 days, whereas the other group received early parenteral nutrition. In both groups, artificial nutrition needed to be started in the 24 h of mechanical ventilation. In the parenteral group, a switch toward enteral nutrition was possible after 72 h among patients who had been weaned off catecholamine for 24 h and plasma lactate concentration was less than 2 mmol.L^{-1}. At day 7, parenteral nutrition was switched to enteral nutrition unless a contraindication to enteral feeding was identified. In the enteral group, parenteral feeding was allowed only after day 8 in case of feeding intolerance and/or insufficient caloric intake.

Take-home message

This study found that among ventilated adults with shock, plasma citrulline concentration was higher after 3 days of enteral nutrition than after 3 days of parenteral nutrition. This result raises the question of a possible beneficial effect of enteral nutrition over parenteral nutrition on the small bowel mucosa of ventilated adults with shock.

Plasma citrulline concentration (norm 20–60 µmol L^{-1}) was assessed with automated ion-exchange chromatography (Hitachi L-8800, Tokyo, Japan) [11]. Low plasma citrulline concentration was defined as a plasma citrulline concentration less than 20 µmol L^{-1}. I-FABP concentration (norm < 100 pg mL^{-1}) was assessed with the ELISA kit (Hycult Biotech, Uden, the Netherlands) [9]. The threshold for I-FABP detection was 100 pg mL^{-1}, and when the concentration was less than 100 pg mL^{-1} (i.e., between 0 and 100), the concentration indicated was 50 pg mL^{-1}. We defined I-FABP detection or elevation as a plasma I-FABP concentration greater than 100 pg mL^{-1}. Plasma citrulline and I-FABP concentrations were measured at inclusion, at day 3, and day 8 of nutrition.

Variables of complication during ICU stay and variables of prognosis were collected: bacteremia; acute mesenteric ischemia confirmed on abdominal computed tomography, at digestive endoscopy, or during laparotomy; 28-day mortality; 90-day mortality.

Statistical analyses

Qualitative variables were expressed as number (percentage) and compared with the Chi-squared test. Quantitative variables were expressed as median [interquartile range] and compared with the Wilcoxon test. The main outcome was plasma citrulline concentration measured after 3 days of nutrition compared by Wilcoxon test according to the route of nutrition. In order to show a significant difference between plasma citrulline of 16 µmol L^{-1} in the enteral group vs and 12 µmol L^{-1} in the parenteral group, with a standard deviation of 8 µmol L^{-1}, with a two-sided test, alpha risk of 5%, and power of 0.9, 85 patients needed to be included in each arm of treatment. For the analysis of the evolution of plasma citrulline and I-FABP according to the route of nutrition at inclusion, day 3, and day 8, the concentrations were compared at each time using the Wilcoxon test. A linear mixed model was performed to analyze the interaction between the groups (route of nutrition) and the time taking into account the data correlation. Statistical analyses were performed with software R (3.4.0).

Results

Description of study population at inclusion

The large randomized controlled NUTRIREA-2 trial included 2410 patients. This ancillary study included 165 patients from 13 French ICUs: 85 patients in the enteral group and 80 patients in the parenteral group (Supplementary Data, Fig. 1).

Demographic characteristics are reported in Table 1. At baseline, there was no difference between the enteral and parenteral groups.

Duration of ICU stay was 8 [5; 16] days and 11.5 [6.5; 18.5] days for enteral and parenteral groups, respectively ($p = 0.09$). The 28-day mortality was higher in

Table 1 Demographic characteristics at baseline in both groups

Variables	Missing values		Enteral nutrition ($n = 85$)	Parenteral nutrition ($n = 80$)	p
	Enteral nutrition (n)	Parenteral nutrition (n)			
Sex (male)	0	0	65 (76%)	57 (71%)	0.45
Age (years)	0	0	66.1 [56.3; 74.7]	64.3 [56.6; 75.3]	0.93
IGS2 score at inclusion	0	0	56 [47; 69]	60 [44; 72]	0.68
SOFA score at inclusion	0	0	10 [9; 13]	11 [9; 13]	0.47
SOFA—ventilation	0	0	3 [2; 3]	3 [2; 3]	0.96
SOFA—platelet	0	0	0 [0; 1]	0 [0; 2]	0.35
SOFA—liver	0	0	0 [0; 1]	0 [0; 1]	0.87
SOFA—circulation	0	0	4 [4; 4]	4 [4; 4]	0.77
SOFA—neurology	0	0	1 [0; 4]	1 [0; 4]	0.58
SOFA—kidney	0	0	1 [0; 3]	1 [0; 3]	0.85
Cause of shock					0.95
Septic	0	0	59 (69%)	57 (71%)	
Cardiogenic	0	0	15 (18%)	15 (19%)	
Non-infectious SIRS	0	0	3 (4%)	2 (3%)	
Other	0	0	8 (9%)	6 (8%)	
Renal replacement therapy	0	0	18 (21%)	16 (20%)	0.85
Type of catecholamine					
Norepinephrine	0	0	80 (94%)	75 (94%)	0.92
Epinephrine	0	0	3 (4%)	2 (2%)	0.70
Dobutamine	0	0	12 (14%)	7 (9%)	0.28
Catecholamine dose					
Norepinephrine (mg/h)	0	0	2.52 [1.02; 5.26]	1.83 [0.99; 4.30]	0.21
Biology at inclusion					
Creatinine (µmol L^{-1})	1	0	155 [89; 238]	140 [94; 242]	0.68
CRP (mg L^{-1})	19	14	147 [73; 260]	147 [57; 282]	0.93
Citrulline (µmol L^{-1})	3	3	12.2 [8.6; 18.0]	13.3 [10.2; 20.3]	0.49
I-FABP (pg mL^{-1})	3	3	245 [50; 815]	244 [50; 896]	0.92

Numbers are median [interquartile range]

the enteral group than in the parenteral group (44% vs 29%, $p = 0.049$), but 90-day mortality was not different between groups (48% vs 39%, $p = 0.25$). No case of acute mesenteric ischemia occurred in this substudy. Only one case of bacteremia positive for *Staphyloccocus epidermidis* of cutaneous origin occurred in the enteral group.

Plasma citrulline kinetics according to route of nutrition

Evolution of plasma citrulline concentration during the first week according to the route of nutrition is shown in Table 2 and Fig. 1. At baseline, plasma citrulline concentration was low (norm 20–60 µmol L^{-1}), without difference between enteral and parenteral groups (12.2 [8.6; 18.0] µmol L^{-1} vs 13.3 [10.2; 20.3] µmol L^{-1}, $p = 0.49$). At day 3, plasma citrulline concentration was higher in the

Table 2 Plasma citrulline levels at baseline, day 3, and day 8, according to the route of nutrition

Citrulline (µmol L^{-1})	Missing values		Enteral nutrition ($n = 85$)	Parenteral nutrition ($n = 80$)	p
	Enteral nutrition (n)	Parenteral nutrition (n)			
At day 0	3	3	12.2 [8.6; 18.0]	13.3 [10.2; 20.3]	0.49
At day 3	16	10	18.7 [13.4; 29.2]	15.3 [9.8; 21.2]	0.01
At day 8	32	25	20.1 [14.2; 31.6]	16.9 [13.4; 22.7]	0.07

Model of evolution of plasma citrulline concentration[a] between day 0, day 3, and day 8, according to route of nutrition	Parameter [CI 95%]	p
Intercept	2.597 [2.451; 2.743]	< 0.0001
Time	0.042 [0.024; 0.060]	< 0.0001
Route of nutrition	0.028 [− 0.175; 0.232]	0.78
Interaction between time and route of nutrition	0.030 [− 0.003; 0.048]	0.09

Numbers are n (%) and median [interquartile range]

[a] Plasma citrulline concentration was log transformed because of non-normal distribution

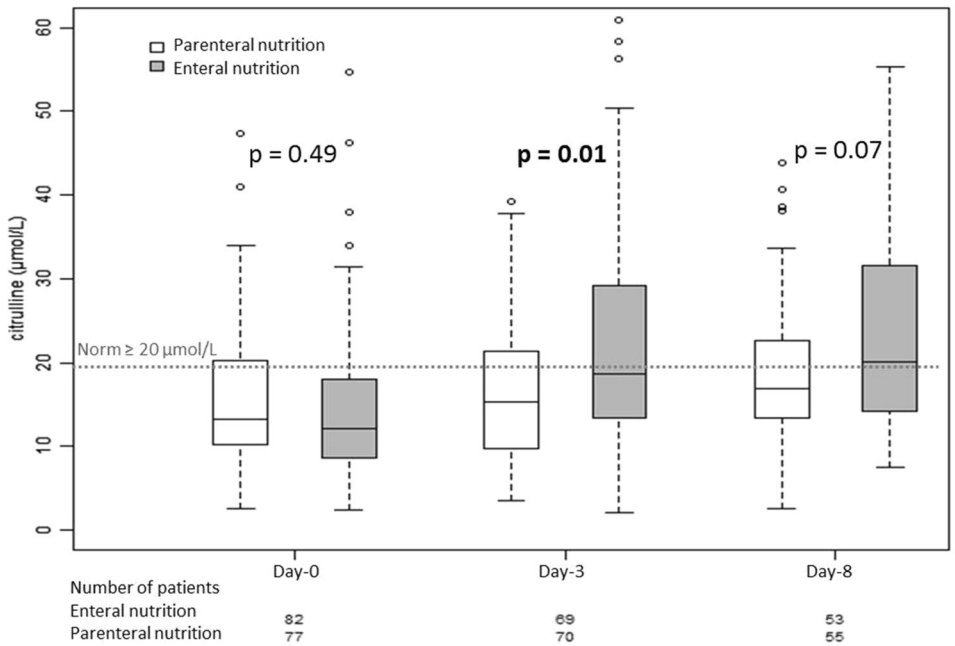

Fig. 1 Plasma citrulline concentration at inclusion, day 3, and day 8, according to the route of nutrition among ventilated adults with shock. Plasma citrulline was low (norm ≥ 20 µmol L^{-1}) at inclusion and not different between the two groups. After 3 days of nutrition, plasma citrulline concentration was higher in the enteral group than in the parenteral group. There was a trend toward a higher plasma citrulline concentration in the enteral group than in the parenteral group at day 8 of nutrition

enteral group than in the parenteral group (18.7 [13.4; 29.2] µmol L^{-1} vs 15.3 [9.8; 21.2] µmol L^{-1}, $p=0.01$). A plasma citrulline concentration of 10 µmol L^{-1} or less at day 3 was less frequent in the enteral group than in the parenteral group (13% vs 27%, $p=0.04$). Plasma citrulline concentration at day 8 was not different between groups (20.1 [14.2; 31.6] µmol L^{-1} vs 16.9 [13.4; 22.7] µmol L^{-1}, $p=0.07$). A sensitivity analysis excluding the six patients in whom a switch between parenteral and enteral nutrition had been performed found that plasma citrulline concentration at day 8 was higher in the enteral group than in the parenteral group (20.9 [14.6; 32.7] µmol L^{-1} vs 16.8 [13.2; 22.5] µmol L^{-1}, $p=0.04$). According to the linear mixed model, the evolution of plasma citrulline concentration during the overall week of nutrition was not statistically different between groups ($p=0.09$) (Table 2). At baseline, there was a negative correlation between plasma citrulline and CRP concentrations ($R=-0.33$, $p=0.0001$).

Plasma I-FABP kinetics according to route of nutrition

Plasma I-FABP levels during the first week are shown in Table 3 and Fig. 2. Plasma I-FABP concentration (norm < 100 pg mL^{-1}) was increased at baseline, without difference between enteral and parenteral groups (245 [50; 815] pg mL^{-1} vs 244 [50; 896] pg mL^{-1}). Plasma I-FABP concentration was higher in the enteral group than in the parenteral group at day 3 and day 8 (158 [50; 334] pg mL^{-1} vs 50 [50; 250] pg mL^{-1}, $p=0.005$ and 225 [50; 531] pg mL^{-1} vs 50 [50; 294] pg mL^{-1}, $p=0.03$). A plasma I-FABP concentration greater than 100 pg mL^{-1} at day 3 was more frequent in the enteral group than in the parenteral group (65% vs 39%, $p=0.002$). According to the linear mixed model, the evolution of plasma I-FABP concentration during the overall week of nutrition was not statistically different between groups ($p=0.13$) (Table 3).

Evolution of biological variables, caloric and protein intake, norepinephrine use, and SOFA score

Evolution of plasma glutamine, creatinine, and lactate concentrations, caloric and protein intakes, norepinephrine use, and SOFA score according to the route of nutrition is shown in Supplementary Data (Table 4). Globally, compared to the patients in the parenteral group, patients in the enteral group had more frequently norepinephrine use at day 3 (56% vs 35%, $p=0.01$), a lower caloric intake at day 3 (1476 [1079; 1740] kcal vs 1672 [1379; 1882] kcal, $p=0.04$), a lower protein intake at day 3 (58 [43; 68] g/day vs 72 [58; 81] g/day, $p=0.002$), and a lower mean protein intake during the first week (0.65 [0.55; 0.80] g/kg/day vs 0.79 [0.65; 0.92] g/kg/day, $p=0.003$). On the contrary, there were no differences in the evolution of glutamine, creatinine, and lactate plasma concentrations, and for the SOFA score, between enteral and parenteral groups.

Discussion

The main results of this study were that plasma citrulline concentration was higher after 3 days of enteral nutrition than after 3 days of parenteral nutrition among adult patients with shock, and that enteral nutrition was associated with a higher I-FABP concentration at day 3 and day 8 than parenteral nutrition.

Plasma citrulline concentration at day 3 of nutrition was higher in the enteral group than in the parenteral group. This result was concordant with our primary hypothesis. Citrulline is an amino acid mainly produced by enterocytes from glutamine, is then released into the

Table 3 Plasma intestinal fatty acid binding protein levels at baseline, day 3 and day 8, according to the route of nutrition

I-FABP (pg mL^{-1})	Missing values		Enteral nutrition ($n=85$)	Parenteral nutrition ($n=80$)	p
	Enteral nutrition (n)	Parenteral nutrition (n)			
At day 0	3	3	245 [50; 815]	244 [50; 896]	0.92
At day 3	16	9	158 [50; 334]	50 [50; 250]	0.005
At day 8	33	23	225 [50; 531]	50 [50; 294]	0.03

Model of evolution of plasma I-FABP[a] between day 0, day 3, and day 8, according to route of nutrition	Parameter [CI 95%]	p
Intercept	5.511 [5.161; 5.861]	< 0.0001
Time	−0.095 [−0.150; −0.040]	< 0.0001
Route of nutrition	0.117 [−0.373; 0.607]	0.64
Interaction between time and route of nutrition	0.061 [−0.017; 0.139]	0.13

Numbers are median [interquartile range]

[a] Plasma I-FABP was log transformed because of the non-normal distribution

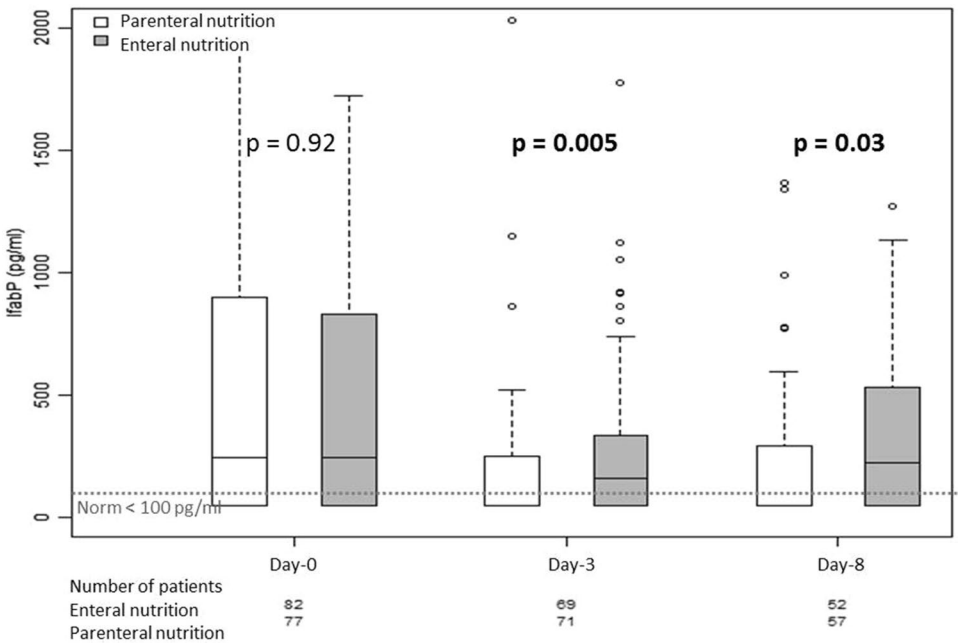

Fig. 2 Plasma intestinal fatty acid binding protein (I-FABP) concentration at inclusion, day 3, and day 8, according to the route of nutrition among ventilated adults with shock. Plasma I-FABP concentration was increased (norm < 100 pg mL^{-1}) at inclusion and not different between the two groups. Plasma I-FABP was higher in the enteral group than in the parenteral group at day 3 and day 8 of nutrition

portal circulation, reaches the systemic circulation, and is taken up by kidneys for arginine synthesis [12]. Indeed, citrulline could be a masked form of arginine not sensitive to arginase activity. Plasma citrulline concentration is considered to be a marker of enterocyte mass because it is well correlated with the small bowel length and with the villi length [13]. Several results of this study suggest that the enteral route might induce a better restoration of the enterocyte mass than parenteral nutrition among critically ill patients with shock. First, there was no difference in the evolution of glutamine concentration, which is the main precursor of citrulline [12]. Therefore, the difference in plasma citrulline concentration at day 3 between groups was not explained by a difference in citrulline precursor bioavailability. Second, the evolution of the kidney function was similar between groups. This makes a difference of citrulline clearance unlikely to explain the difference of plasma citrulline concentration between groups. Third, despite a lower caloric and protein intake in the enteral group at day 3, plasma citrulline concentration was higher after 3 days of enteral nutrition than after 3 days of parenteral nutrition. All in all, these results strongly support the beneficial effect of early enteral nutrition on the enterocyte mass of critically ill patients with shock.

Whereas plasma I-FABP globally decreased between inclusion and day 3, the comparison of I-FABP at day 3 and day 8 according to the route of nutrition suggests that there was a delay in the normalization of plasma I-FABP in the enteral group compared to the parenteral group. Indeed, plasma I-FABP concentration was higher in the enteral group than in the parenteral group after 3 days and after 8 days of nutrition. This result was not expected. I-FABP is a small cytosolic protein specific to small bowel enterocytes [8]. I-FABP is involved in the transport of fatty acids in the enterocyte during absorption. Normally, this protein is low or undetectable in plasma (norm < 100 pg mL^{-1}). In case of enterocyte necrosis, I-FABP is released into the extracellular space and becomes detectable in urine or plasma. I-FABP is considered to be a promising biomarker of acute mesenteric ischemia [14]. Three hypotheses might be proposed in the present study. First, norepinephrine was more frequently used at day 3 in the enteral group than in the parenteral group (56% vs 35%, $p = 0.01$). It is well established that plasma I-FABP elevation is strongly related to the shock state and to the catecholamine dose [15, 16]. Second, enteral nutrition per se might be responsible for a subclinical mucosal ischemia. Indeed, the NUTRIREA-2 study found that full enteral nutrition was associated with a higher risk of acute mesenteric ischemia than parenteral nutrition among ventilated adults with shock [10]. However, one can notice that no case of obvious acute mesenteric ischemia was observed in this substudy.

In addition, the level of I-FABP was only moderate, 200 pg mL^{-1}, suggesting a limited ischemic damage. There is still uncertainty on the appropriate threshold of I-FABP for identification of acute mesenteric ischemia [2, 14]. Third, it cannot be excluded that parenteral nutrition is associated with less reperfusion of villi than enteral nutrition, with slower release of I-FABP in the circulation, and therefore lower plasma I-FABP concentration [17]. All in all, this study raises the question of the possibility that early initiation of full enteral nutrition, at 20 kcal/kg/day, among critically ill patients with shock, is associated with concomitant subclinical ischemic damage to the mucosa. Further studies should assess whether trophic enteral nutrition, with lower caloric intake, is associated with lower I-FABP concentration.

Despite this higher level of I-FABP in the enteral group, plasma citrulline concentration increased more rapidly in the enteral group than in the parenteral group. This result suggests that despite a subclinical ischemic damage associated with full enteral nutrition, enteral nutrition might have beneficial effects which largely counterbalance the subclinical ischemic effect. Several hypotheses could be made. First, early enteral nutrition might limit the phenomenon of small bowel mucosa atrophy. It is well established that the villi length is closely related to plasma citrulline concentration among patients presenting with small bowel villous atrophy diseases [4]. Second, enteral nutrition might be associated with a reduced risk of septic enteropathy. Indeed, about 70% of the patients of this substudy presented with septic shock, and plasma CRP concentration was very high at inclusion. There is strong evidence that sepsis, even of extradigestive origin, can induce villi reduction [18, 19] and therefore could induce subsequent plasma citrulline reduction. In addition, it is now well established that plasma citrulline concentration is inversely correlated with plasma CRP concentration [2]. This result was also observed in this study. On the one hand, the inverse relation between plasma CRP and citrulline concentration is possibly linked to the effect of systemic inflammation on villi length and enterocyte mass, but on the other hand, it could be the marker of a systemic inflammation originating from gut damage. Systemic inflammation and pro-inflammatory cytokines can directly alter enterocyte proliferation in crypts, reduce the speed of enterocyte migration along the villus axis, and increase enterocyte apoptosis, all these phenomena leading to reduced villi length and enterocyte mass during sepsis [18–21]. It has been postulated that, compared to parenteral nutrition, enteral nutrition might decrease systemic and local inflammation [22–24]. By limiting this phenomenon of septic enteropathy, enteral nutrition might allow a more rapid restoration of the villi length, increasing the functional enterocyte mass, and subsequently inducing a more rapid increase of plasma citrulline concentration.

To the best of our knowledge, this study reports the highest number of critically ill patients in whom plasma citrulline and I-FABP concentrations have been measured. In addition, this is the only multicentric and randomized study dealing with the impact of the route of nutrition on enterocyte biomarkers. Literature is scarce on this topic. It has been described that critically ill children with SIRS or septic shock have a progressive increase of plasma citrulline under enteral nutrition between admission and day 5, suggesting an increase of the enterocyte mass under enteral nutrition [25]. In a recent study, Parent et al. compared the evolution of plasma amino acid among 10 critically ill patients receiving enteral nutrition, 10 critically ill patients receiving parenteral nutrition, and 10 controls [26]. They observed that plasma citrulline concentration was low at ICU admission compared with controls; plasma citrulline progressively increased in the enteral group during the first 7 days of nutrition; on the contrary, plasma citrulline concentration stayed low in the parenteral group during the first week of nutrition. These results reinforce our hypothesis: compared to parenteral nutrition, enteral nutrition is associated with a more rapid increase of plasma citrulline concentration suggesting a more rapid restoration of the enterocyte mass.

From a pragmatic point of view, this study suggests that early and full enteral nutrition could have complex effects on the small bowel mucosa of critically ill patients with shock, in particular septic shock patients. Several studies have suggested the beneficial effect of enteral nutrition among patients with controlled shock [27, 28]. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend withholding enteral nutrition in case of uncontrolled shock, whereas low dose enteral nutrition can be started as soon as the shock is controlled [29]. The risk of small bowel mucosal ischemia could be counterbalanced by other beneficial effects of enteral nutrition. Further studies should evaluate whether trophic enteral nutrition has only beneficial effects on villi, by reducing the phenomenon of inflammatory and septic enteropathy, without deleterious effects of small bowel ischemia.

The main limitation of this study is that the absorptive function of the patients was not evaluated, and plasma citrulline concentration was not correlated with histological modifications of the small bowel mucosa under nutrition. However, it is not easy and possibly dangerous to perform systematic digestive endoscopy with duodenal biopsies among critically ill patients with shock. In the context of short bowel syndrome patients receiving teduglutide, a glucagon-like peptide

2 analog, it has been described that the increase in villous length is associated with an increase in plasma citrulline concentration [30]. This suggests that the variation of plasma citrulline concentration reflects the variation of enterocyte mass [30]. However, there was a poor correlation between plasma citrulline concentration and absorption. Similarly, Poole et al. found no correlation between plasma citrulline concentration and absorption of glucose among critically ill patients, even if plasma citrulline concentration was lower in patients than in controls [31]. Therefore, plasma citrulline concentration appears to be a marker of enterocyte mass but the question of its accuracy for the evaluation of the absorptive function is still unclear, in particular in the context of ICU [32]. Another limitation of this study is the number of missing values at day 8 which limits the interpretation of biomarkers kinetics during the first week of nutrition according to the route of nutrition. A last limitation of this study is linked to the fact that the interpretation of plasma I-FABP concentration is still debated. In this study, the cutoff of 100 pg mL^{-1} was considered to define detectable I-FABP. However the appropriate cutoff for the analysis of I-FABP is still unknown. First, the cutoff used probably depends of the population studied, and could be different between a general population of critically ill patients without particular digestive sign, and among patients presenting to the emergency department with acute abdomen and high suspicion of acute mesenteric ischemia. Cutoff values reported in the literature for the diagnosis of acute mesenteric ischemia among patients presenting with acute abdomen, using the same kit as us, vary between 90 and 815 pg mL^{-1} [14]. Second, the cutoff depends of the kit of I-FABP used [14]. Third, the signification of I-FABP increase could depend of the criteria studied, with different cutoffs for reversible mesenteric hypoperfusion and for transmural bowel infarction [33]. Fourth, increase plasma concentrations of I-FABP have been described among healthy patients at rest, and after intense exercise [34, 35]. Actually, isolated increase of plasma I-FABP concentration does not equal acute mesenteric ischemia, and the interpretation of plasma I-FABP concentration should take into account the context, and clinical and biological examination of the patient.

In conclusion, plasma citrulline concentration was higher after 3 days of enteral nutrition than after 3 days of parenteral nutrition despite a lower caloric and protein intake in the enteral group. While the higher I-FABP concentration observed in the enteral group at day 3 could be related to a more frequent use of norepinephrine or to the subclinical phenomenon of mucosal ischemia, the increase in plasma citrulline concentration raises the question of the possibility that enteral nutrition could be associated with a more rapid restoration of enterocyte mass than parenteral nutrition.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflict of interest.

Ethical approval
The study protocol was approved by the ethics committee of the French Intensive Care Society and appropriate French authorities.

Informed consent
According to French law, because the treatments and strategies used in the study were classified as standard care, there was no requirement for signed consent, but the patients or next of kin were informed about the study before enrolment and confirmed this fact in writing.

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