Enterocyte Damage in Critically Ill Patients Is Associated With Shock Condition and 28-Day Mortality*

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Objectives: Small bowel dysfunction in critically ill patients is frequent, underdiagnosed, and associated with poor prognosis. Intestinal fatty acid-binding protein is a marker of enterocyte damage, and plasma citrulline concentration is a marker of functional enterocyte mass. Primary objective was to identify factors associated with intestinal fatty acid-binding protein in critically ill patients. Secondary objectives were to study factors associated with plasma citrulline concentration and its correlation with intestinal fatty acid-binding protein.

Design: Prospective observational study.

Setting: ICU in a University Hospital

Patients: Critically ill patients 18 years old or older with an expected length of ICU stay 48 hours or more, without pregnancy, chronic small bowel disease, or chronic renal failure.

Interventions: None.

Measurements and Main Results: Plasma intestinal fatty acid-binding protein and citrulline concentrations, and variables relating to prognosis and treatment, were measured at admission to the ICU. One hundred and three patients were included. Intestinal fatty acid-binding protein elevation at admission to the ICU was associated with catecholamine support, higher lactate concentration, higher Sequential Organ Failure Assessment score, and higher international normalized ratio (all $p \leq 0.001$). Plasma citrulline concentration less than or equal to 10 μmol/L at admission to the ICU was associated with higher intra-abdominal pressure, higher plasma C reactive protein concentration, and more frequent antibiotic use (all $p \leq 0.005$). There was no correlation between plasma levels of intestinal fatty acid-binding protein and citrulline. At ICU admission, Sequential Organ Failure Assessment score ≥12, plasma citrulline ≤ 12.2 μmol/L, and plasma intestinal fatty acid-binding protein concentration ≥355 pg/mL were all independently associated with 28-day mortality (odds ratio, 4.39 [1.48–13.03]; odds ratio, 5.17 [1.59–16.86]; and odds ratio, 4.46 [1.35–14.74], respectively).

Conclusions: In critically ill patients, enterocyte damage is frequent, and it is significantly associated with shock and 28-day mortality. The link between intestinal fatty acid-binding protein and plasma citrulline concentrations in critically ill patients needs to be further evaluated. (*Crit Care Med* 2013; 41:2169–2176)

Key Words: critically ill; intestinal fatty acid-binding protein; plasma citrulline; prognosis; shock

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In critically ill patients, small bowel dysfunction is frequent, underdiagnosed, and associated with poor prognosis (1). Plasma citrulline concentration has previously been recognized as a functional marker of enterocyte mass in various small bowel diseases (2). We recently observed that plasma citrulline concentration was low in a population of medical ICU patients and that low plasma citrulline concentration in this population was associated with a higher mortality rate (3). These results suggest that critically ill patients might have impaired small bowel function defined by a reduction of enterocytic function, but it remains unclear whether this is secondary to enterocyte dysfunction or enterocyte destruction. Intestinal fatty acid-binding protein (I-FABP), a protein specifically localized in small bowel enterocytes, is released into plasma in case of enterocyte destruction, and it is therefore a marker of enterocyte damage (4). Patients

with septic shock have been found to have increased urinary I-FABP concentrations, suggesting that the shock condition is associated with enterocyte damage (5).

However, treatment interventions aimed at improving gastrointestinal perfusion have failed to improve outcome (6). The primary objective of this study was to identify factors associated with plasma I-FABP concentration and its prognostic value in a population of medical ICU patients. The secondary objectives were to study factors associated with plasma citrulline concentration and the correlation between plasma I-FABP and citrulline concentrations.

MATERIALS AND METHODS

Study Population

Adult patients consecutively admitted between April 2010 and July 2010 to a medical ICU in a University Hospital were considered eligible. Inclusion criteria were age, 18 years old or older, and expected length of ICU stay, 48 hours or more. Exclusion criteria were pregnancy, chronic small bowel disease, and chronic renal failure (defined by a documented history of basal serum creatinine concentration > 150 μmol/L).

Data Collection

Variables were prospectively collected at admission and after 24 hours in the ICU. The following variables were recorded: age; sex; mean arterial pressure (MAP); gastric residual volume; intra-abdominal pressure measured in the bladder (7); abdominal perfusion pressure calculated as MAP minus intra-abdominal pressure; plasma citrulline concentration as assessed with automated ion-exchange chromatography (Hitachi L-8800, Tokyo, Japan) (8); human I-FABP as assessed with the ELISA kit (Hycult Biotech, Uden, The Netherlands) (9); arterial lactate concentration; serum concentrations of C reactive protein (CRP), creatinine, and bilirubin; international normalized ratio (INR); red-cell transfusion; volume of fluid infusion before admission to the ICU; catecholamine use; mechanical ventilation; continuous venovenous hemofiltration; enteral or parenteral feeding; antibiotic treatment; nosocomial infection; Sequential Organ Failure Assessment (SOFA) score at admission and after 24 hours in the ICU (10); and 28-day mortality. Shock was defined as MAP persisting below 65 mm Hg despite adequate fluid resuscitation, requiring catecholamine support, and associated with arterial lactate concentration greater than or equal to 4 mmol/L.

Statistical Analysis

I-FABP concentrations were divided into two classes, namely, normal concentration (<100 pg/mL) and elevated concentration (≥100 pg/mL). Enterocyte damage was defined as elevated I-FABP concentration. Plasma citrulline concentrations were also divided into two classes, namely, very low concentration (≤10 μmol/L) and moderately low or normal concentration (>10 μmol/L) according to the results of our previous study (3). Differences among qualitative variables were assessed by using Fisher exact test. Differences in quantitative variables were assessed using the Wilcoxon test. Because of the limited number of events in comparison to the number of variables studied, we decided to focus on the prognostic value of plasma I-FABP and citrulline concentrations. Receiver operating characteristic (ROC) curve analysis was performed to calculate the optimal cutoff value for the prediction of 28-day mortality. Logistic regression analysis was performed to evaluate whether plasma I-FABP and citrulline concentrations were independent of the SOFA score to predict 28-day mortality. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Patient Consent and Legal Use of Human Biological Data

Since participation in this study did not in any way affect routine treatment, and no invasive procedures were required (blood samples for study purposes were taken during routine blood tests), the study was approved by the ethics committee of Besançon University Hospital at the session of April 2010 and the need for informed consent was waived. Patients and their families were nonetheless informed about the study.

RESULTS

Study Population

Between April 4, 2010, and July 22, 2010, 132 patients were prospectively evaluated for inclusion in the study. Among these, 29 patients were excluded for the following reasons: 11 for an expected length of ICU stay less than or equal to 48 hours, 2 because of age younger than 18 years, and 16 for chronic renal failure. In total, 103 patients were included in the study. The baseline characteristics of the study population are described in **Table 1**. The 28-day mortality rate was 31% (32 of 103). Nosocomial infection occurred in 27 of 103 patients (26%), and the median duration of ICU stay was 5 (2–13) days.

Variables relating to gastrointestinal dysfunction at ICU admission and at 24 hours are shown in **Tables 2** and **3**. Patients were not given amino acid supplementation. At the time of ICU admission, plasma I-FABP concentration was missing in 13 of 103 patients, and plasma citrulline concentration was missing in 6 of 103 patients. Plasma I-FABP greater than or equal to 100 pg/mL were noted in 48% and 24% of the patients at ICU admission and at 24 hours, respectively. Only 3 of 43 (7%) patients presenting with elevated I-FABP concentration at ICU admission developed mesenteric infarction requiring small bowel or colon resection (Table 3). Plasma citrulline concentrations less than or equal to 10 μmol/L were noted in 27% and 36% of patients, respectively, at ICU admission and at 24 hours.

Univariate Analysis

The results of the univariate analysis according to I-FABP concentration at ICU admission are shown in **Table 4**. Patients with elevated I-FABP concentration at admission to the ICU had higher arterial lactate concentration, higher

TABLE 1. Baseline Characteristics of the Study Population at ICU Admission

Variable	*n* = 103
Age (yr)	66 [53–76]
Sex	
Male	53 (51)
Female	50 (49)
Mean arterial pressure (mm Hg)	80 [69–94]
Creatinine (μmol/L)	123 [80–178]
Arterial lactates (mmol/L)	2.4 [1.8–4.5]
C reactive protein (mg/L)	47 [13–188]
Bilirubin (μmol/L)	13 [9–24]
International normalized ratio	1.39 [1.18–1.78]
Catecholamine support	68 (66)
Continuous venovenous hemodiafiltration	11 (11)
Mechanical ventilation	92 (89)
Red-cell transfusion[a]	18 (17)
Antibiotics	59 (57)
Enteral feeding the first day	17 (17)
Parenteral feeding the first day	7 (7)
Sequential Organ Failure Assessment Score	10 [6–13]
Primary reason for intensive care	
Neurologic disease	8 (8)
Cardiac arrest	21 (20)
Cardiogenic shock	18 (17)
Septic shock	15 (15)
Hemorrhagic shock	3 (3)
Acute lung injury or acute respiratory distress syndrome	21 (20)
Postoperative	6 (6)
Metabolic failure	3 (3)
Intoxication	8 (8)

[a]During ICU stay; *n* (%); median [interquartile range].
Numbers are means ± SD.

TABLE 2. Variables of Digestive Dysfunction in Critically Ill Patients at ICU Admission

Variable of Digestive Dysfunction	+0 hr
Gastric residual volume (mL)	0 [0–50]
Volume ≥ 150 mL	14/102 (14)
IAP (mm Hg)	11.5 [7–16]
IAP ≥ 12 mm Hg	43/86 (50)
APP (mm Hg)	68 [56–83]
APP < 60 mm Hg	25/86 (29)
Citrulline (μmol/L)	16.0 [9.7–24.2]
Citrulline < 20 μmol/L	66/97 (68)
I-FABP (pg/mL)	0 [0–560]
I-FABP > 100 pg/mL	43/90 (48)

IAP = intra-abdominal pressure; APP = abdominal perfusion pressure; I-FABP = intestinal fatty acid-binding protein.
n (%); median [interquartile range].

INR, more frequent catecholamine support, higher SOFA score, and higher 28-day mortality than patients with normal I-FABP levels. Plasma I-FABP concentration at ICU admission was higher among patients with shock than among patients without shock (666 [199–2,414] vs 0 [0–350], respectively, $p < 0.0001$).

A comparison of the study population according to plasma citrulline concentrations at ICU admission is also shown in **Table 4**. Patients with plasma citrulline concentration ≤ 10 μmol/L at admission to the ICU had higher intra-abdominal pressure, higher plasma CRP concentration, and more frequently received antibiotics than patients with plasma citrulline concentration greater than 10 μmol/L. There was no correlation between plasma citrulline and I-FABP at ICU admission ($R = 0.11$, $p = 0.31$).

Figure 1 shows plasma citrulline and I-FABP concentrations at ICU admission according to 28-day mortality. Analysis of the variables according to 28-day mortality is shown in **Table 5**. The median duration (interquartile range) of ICU stay was 5 days (2–16) days in 28-day survivors and 3 days (2–10) in 28-day nonsurvivors. Among the variables relating to gastrointestinal dysfunction measured at ICU admission, higher I-FABP concentration, lower plasma citrulline concentration, and higher intra-abdominal pressure were associated with 28-day mortality. An ROC curve identified that the thresholds of 12.2 μmol/L for plasma citrulline concentration and 355 pg/mL for plasma I-FABP concentration best predicted 28-day mortality (area under the curve of 0.65 and 0.68, respectively).

Logistic Regression Analysis

The results of logistic regression analysis of SOFA score, plasma citrulline, and I-FABP concentrations to predict 28-day mortality are shown in **Table 6**.

In a first model, including SOFA score ≥12, plasma citrulline concentration ≤20 μmol/L, and I-FABP ≥100 pg/mL, only the SOFA score was associated with 28-day mortality. A second model was built using the thresholds of plasma citrulline and I-FABP concentrations determined by ROC curves. In this model, SOFA score ≥12, plasma citrulline ≤12.2 μmol/L, and plasma I-FABP concentration ≥355 pg/mL were all independently associated with 28-day mortality.

TABLE 3. Characteristics of the Critically Ill Patients Presenting With Acute Mesenteric Ischemia Requiring Resection of Bowel Segment

Patient	Intestinal Fatty Acid-Binding Protein[a] (pg/mL)	Citrulline[a] (μmol/L)	Bowel Segment	Pathophysiology	ICU Outcome
1	822	6.7	Small bowel + colon	NOMI	Deceased
2	906	36.9	Colon	NOMI	Deceased
3	345	21.1	Small bowel + colon	NOMI	Deceased

NOMI = nonocclusive mesenteric ischemia.
[a]At ICU admission.

TABLE 4. Univariate Analysis of the Variables According to Plasma Concentrations of Intestinal Fatty Acid-Binding Protein and Citrulline at ICU Admission

Variables	I-FABP (< 100 pg/mL)	I-FABP (≥ 100 pg/mL)	*p*	Citrulline (≤ 10 μmol/L)	Citrulline (> 10 μmol/L)	*p*
n	47	43		26	71	
Mean arterial pressure (mm Hg)	83 [71–96]	80 [66–93]	0.44	84 [70–94]	77 [69–92]	0.52
Intra-abdominal pressure (mm Hg)	10 [7–16]	13 [8–16]	0.30	18 [12–21]	10 [7–15]	0.0009
Abdominal perfusion pressure (mm Hg)	68 [59–84]	70 [63–82]	0.67	65 [56–84]	68 [59–83]	0.93
Gastric residual volume (mL)	0 [0–100]	0 [0–0]	0.25	0 [0–0]	0 [0–90]	0.15
Citrulline (μmol/L)	13.1 [9.7–19.8]	17.2 [12.2–29.5]	0.20			
Intestinal fatty acid-binding protein (pg/mL)				0 [0–666]	0 [0–524]	0.77
Creatinine (μmol/L)	106 [69–157]	136 [92–197]	0.07	130 [106–195]	117 [75–171]	0.37
Arterial lactates (mmol/L)	2.2 [1.6–2.7]	2.9 [2.1–5.9]	0.0009	2.6 [1.9–4.6]	2.4 [1.8–4.4]	0.64
C reactive protein (mg/L)	125 [14–223]	37 [10–127]	0.14	173 [25–268]	40 [8–145]	0.005
Bilirubin (μmol/L)	12 [9–20]	14 [8–29]	0.66	12 [7–23]	14 [9–25]	0.48
International normalized ratio	1.27 [1.14–1.45]	1.59 [1.30–2.12]	0.001	1.47 [1.31–1.78]	1.34 [1.17–1.78]	0.22
Fluid infusion before admission (mL)	1,000 [500–1,500]	1,000 [500–1,500]	0.89	1,125 [500–1,500]	750 [500–1,500]	0.11
Catecholamine support	23/47 (49)	37/43 (86)	0.0002	19/26 (73)	46/71 (65)	0.48
Continuous venovenous hemodiafiltration	3/47 (6)	7/43 (16)	0.18	4/26 (15)	7/71 (10)	0.48
Mechanical ventilation	40/47 (85)	41/43 (95)	0.16	22/26 (85)	66/71 (93)	0.24
Red-cell transfusion	5/47 (11)	11/43 (26)	0.10	3/26 (12)	14/71 (20)	0.55
Antibiotics	28/47 (60)	25/43 (58)	1	22/26 (85)	36/71 (51)	0.003
Sequential Organ Failure Assessment score	6 [5–10]	11 [10–14]	< 0.0001	10 [6–13]	10 [6–13]	0.72
Nosocomial infection	10/47 (21)	14/43 (33)	0.24	8/26 (31)	18/71 (25)	0.61
28-day mortality	9/47 (19)	18/43 (42)	0.02	12/26 (46)	18/71 (25)	0.08
ICU stay (d)	5 [2–13]	5 [2–16]	0.65	5 [2–11]	5 [2–15]	0.86
Hospitalization stay (d)	14 [6–26]	15 [3–27]	0.66	14 [2–31]	14 [5–26]	0.70

n (%), median [interquartile range].

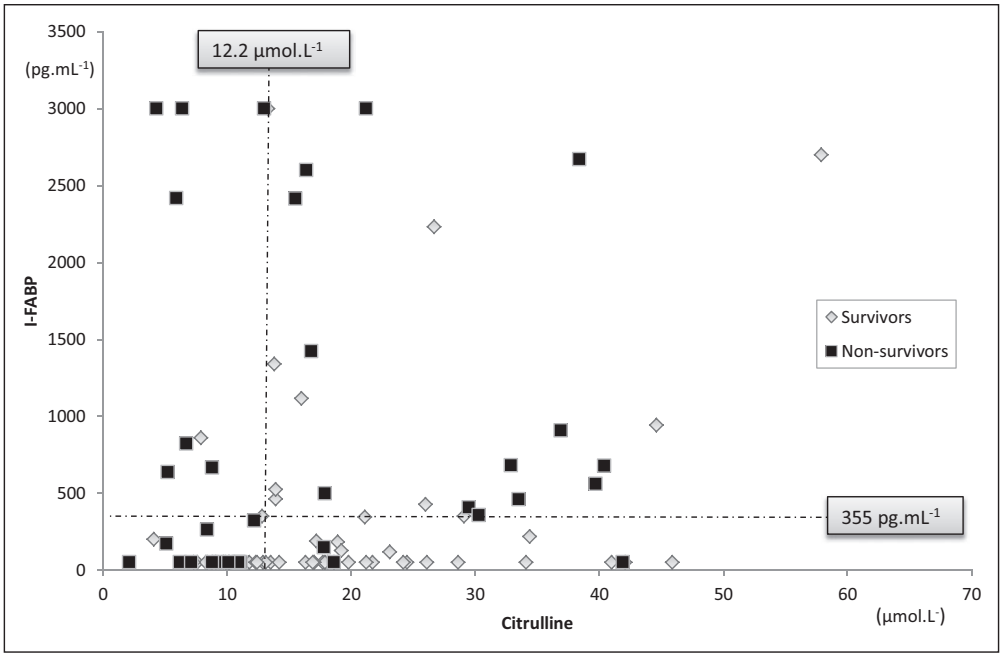

Figure 1. Plasma citrulline and intestinal fatty acid-binding protein (I-FABP) concentrations at ICU admission according to 28-day mortality. Thresholds of 12.2 µmol/L for plasma citrulline concentration and 355 pg/mL for plasma I-FABP concentration are represented as *dotted lines*.

DISCUSSION

The main finding of this study is that in critically ill patients, enterocyte damage as reflected by an increased I-FABP concentration was associated with presence of shock. The link between shock and I-FABP concentration has been poorly studied. In a previous study evaluating gastric tonometry in patients with septic shock, urinary I-FABP concentration was found to be increased in this population, suggesting that the shock condition was associated with enterocyte damage (5). In the context of severe trauma, de Haan et al (11) have shown that plasma I-FABP was associated with shock state: patients with elevated shock index had a significantly

TABLE 5. Univariate Analysis of the Variables at ICU Admission According to the 28-Day Mortality

Variables	Survivors d-28 *n* = 71	Nonsurvivors d-28 *n* = 32	*p*
Mean arterial pressure (mm Hg)	78 [70–93]	82 [62–97]	0.69
Intra-abdominal pressure (mm Hg)	10 [7–15]	15 [10–19]	0.008
Abdominal perfusion pressure (mm Hg)	68 [56–84]	69 [58–78]	0.85
Gastric residual volume (mL)	0 [0–90]	0 [0–25]	0.56
Intestinal fatty acid-binding protein (pg/mL)	0 [0–351]	458 [0–2415]	0.004
Citrulline (µmol/L)	17.0 [11.6–26.0]	11.1 [6.4–18.6]	0.02
Creatinine (µmol/L)	113 [72–158]	154 [119–212]	0.002
Arterial lactates (mmol/L)	2.2 [1.6–3.1]	3.4 [2.1–8.1]	0.006
C reactive protein (mg/L)	42 [8–184]	61 [28–206]	0.13
Bilirubin (µmol/L)	12 [8–20]	14 [9–32]	0.14
International normalized ratio	1.31 [1.14–1.59]	1.68 [1.39–2.67]	0.0008
Fluid infusion before admission (mL)	750 [500–1,500]	1,000 [500–1,375]	0.72
Catecholamine support (*n*)	42/71 (59)	26/32 (81)	0.04
Continuous venovenous hemodiafiltration	4/71 (6)	7/32 (22)	0.03
Mechanical ventilation	65/71 (92)	27/32 (84)	0.31
Antibiotics	37/71 (52)	22/32 (69)	0.14
Sequential Organ Failure Assessment score	7 [6–11]	12 [9–14]	0.0004

n (%), median [interquartile range].

TABLE 6. Logistic Regression Analysis of the Sequential Organ Failure Assessment Score, Plasma Citrulline, and Intestinal Fatty Acid-Binding Protein Concentrations to Predict the 28-Day Mortality

	Simple Logistic Regression		Multiple Logistic Regression			
			Model 1		Model 2	
Variables	OR [CI 95%]	*p*	OR [CI 95%]	*p*	OR [CI 95%]	*p*
Citrulline		0.23		0.28		
≥ 20 μmol/L	1		1			
< 20 μmol/L	1.83 [0.69–4.90]		1.90 [0.60–6.03]			
Citrulline		0.009				0.006
> 12.2 μmol/L	1				1	
≤ 12.2 μmol/L	3.36 [1.36–8.30]				5.17 [1.59–16.86]	
I-FABP		0.02		0.18		
< 100 pg/mL	1		1			
≥ 100 pg/mL	3.04 [1.18–7.83]		2.12 [0.72–6.27]			
I-FABP		0.004				0.014
< 355 pg/mL	1				1	
≥ 355 pg/mL	4.00 [1.54–10.40]				4.46 [1.35–14.74]	
Sequential Organ Failure Assessment score		0.0004		0.003		0.008
< 12	1		1		1	
≥ 12	5.24 [2.11–13.02]		4.98 [1.74–14.25]		4.39 [1.48–13.03]	

OR = odds ratio [CI 95%]; I-FABP = intestinal fatty acid-binding protein.

higher level of I-FABP concentration than those with low shock index or controls. Working recently on the definition of acute intestinal failure, we highlighted that, theoretically, acute dysfunction of enterocytes should be associated with low citrulline and normal I-FABP plasma concentrations, whereas acute reduction of enterocyte mass should be associated with low citrulline and elevated I-FABP plasma concentrations (12). The present study conducted mainly in medical ICU patients clearly establishes that enterocyte damage is significantly more frequent in critically ill patients with shock than in those without shock.

The pathophysiology of enterocyte damage in critically ill patients may be mediated by nonocclusive mesenteric ischemia (NOMI). Acute mesenteric ischemia (AMI) is defined by a recent and rapid inadequation between the demand and the delivery of oxygen and nutriments in the splanchnic area (13). In the overall population, arterial embolism, arterial thrombosis, venous thrombosis, and NOMI account for, respectively, 25%, 25%, 10%, and 20% of the causes of AMI. However, in critically ill patients, the high prevalence of shock makes NOMI the leading cause of AMI.

I-FABP, a small cytoplasmic protein specifically localized in small bowel enterocytes, involved in fatty acid transport, is normally undetectable in plasma (4). In case of enterocyte damage, I-FABP is released into the extracellular space, leading to a rise in its plasma and urinary concentrations. Recently, it has been shown that I-FABP may be of interest in case of NOMI. Indeed, severe acute pancreatitis is associated with elevated levels of I-FABP, which correlate in turn with a clinical score of gastrointestinal dysfunction (14). In healthy adults, small bowel hypoperfusion during submaximal effort was recently shown to cause acute reduction of enterocyte mass (15).

In the present study, we found that shock, a cause of NOMI, was associated with increased I-FABP concentration. Shock is responsible for widespread tissue hypoperfusion, associating NOMI and ischemia of other organs, such as the liver or kidneys. Indeed, we found that elevated concentrations of I-FABP were associated with increased concentrations of plasma creatinine, higher INR, and high lactate concentration, suggesting that shock was the common pathway to different organ failures. However, an adverse effect of catecholamines on mesenteric blood flow is also possible.

Whereas about one-half of the patients presented with elevated I-FABP concentration at ICU admission, none of them had occlusive mesenteric ischemia. The fact that only 7% of the patients presenting with enterocyte damage at admission developed mesenteric infarction requiring small bowel

or colon resection suggests that an increase in plasma I-FABP may be an early marker of occult ischemia of the small bowel, before irreversible lesions have been established.

A major finding of this study is that enterocyte damage in critically ill patients is associated with poor prognosis. Indeed, we found that I-FABP concentration measured at admission to the ICU was higher among 28-day nonsurvivors. The prognostic value of I-FABP concentration in terms of morbidity has been widely studied. During acute pancreatitis, Besselink et al (16) found that I-FABP concentrations in the first 72 hours were higher in patients who developed bacteremia, infected necrosis, and organ failure. In a population of 100 surgical ICU patients, Lieberman et al (17) found that elevated concentrations of I-FABP were correlated with development of clinical systemic inflammatory response syndrome. In patients undergoing extracorporeal circulation during aortic surgery, Hanssen et al (18) found that plasma I-FABP was positively correlated with plasma interleukin (IL)-6 and IL-8, suggesting a link between gut damage and systemic inflammation. On the contrary, the prognostic value of I-FABP in terms of mortality has rarely been reported. In a population of 19 critically ill patients with postoperative abdominal sepsis and nine patients with pneumonia-induced sepsis, Derikx et al (19) found that nonsurvivors had higher levels of I-FABP than survivors. The present study is the first report of the prognostic value of I-FABP as regards mortality in such a large general population of medical ICU patients.

In addition, we found that plasma I-FABP concentration, plasma citrulline concentration, and SOFA score were all independently associated with 28-day mortality (Table 6). Whereas the SOFA score is largely validated to assess the prognosis of ICU patients, it is possible that integrating acute intestinal failure as a new item in this score might improve its overall prognostic value. Interestingly, using the threshold of 20 μmol/L, which is the lower limit of the normal range for plasma citrulline concentration (20–40 μmol/L), was not associated with 28-day mortality. Indeed, only a very low plasma citrulline concentration appears to be associated with a poor prognosis. To the best of our knowledge, there is no validated threshold for the prognostic value of plasma I-FABP concentration. Detection of I-FABP in the plasma corresponding to the threshold of 100 pg/mL was associated with 28-day mortality, but use of a higher threshold, 355 pg/mL, was associated with a higher odds ratio. The optimal cutoff value of plasma I-FABP concentration found by ROC curve analysis for determining its prognostic value in critically ill patients needs to be confirmed by further studies.

The lower limit of normal plasma citrulline concentration is 20 μmol/L, but we believe that using a threshold of 10 μmol/L is more relevant in critically ill patients. First, it has been shown in patients with villous atrophic diseases that only a plasma citrulline concentration ≤ 10 μmol/L was associated with severe villous atrophy (20). Second, in human immunodeficiency virus-infected patients, it has been shown that the threshold of 10 μmol/L was accurate to discriminate patients requiring parenteral nutrition because of enteropathy and those in which the enteral route was possible (21). Third, we have found that there is a high prevalence of low plasma citrulline concentration in critically ill patients due to various mechanisms, and using the usual threshold of 20 μmol/L may not be discriminant in these patients (3). Indeed, in the present study, 68% of patients had a plasma citrulline concentration less than 20 μmol/L at ICU admission and 80% at 24 hours. Fourth, only a very low plasma citrulline concentration was found to be associated with poor prognosis in critically ill patients in our previous study (3). This result is confirmed in the present study: plasma citrulline concentration < 20 μmol/L at ICU admission was not associated with 28-day mortality, whereas a threshold of 12.2 μmol/L as identified by ROC curve analysis was associated with 28-day mortality (Table 6). To summarize, we believe that using a threshold of 10 μmol/L is more relevant for the identification of small bowel dysfunction in critically ill patients.

In the present study, we observed both a high prevalence of enterocyte damage at ICU admission (48%) and a rapid reduction of plasma citrulline concentration during the first day in the ICU (–6.3 ± 11.9 μmol/L). However, contrary to two other studies, no correlation was observed in our study between plasma concentrations of citrulline and I-FABP. First, during acute pancreatitis, Pan et al (14) found that I-FABP concentrations reached higher levels during severe attacks, were positively correlated with a clinical score of gastrointestinal dysfunction, and were negatively correlated with plasma citrulline concentration. Second, after successful cardiopulmonary resuscitation for cardiac arrest in 21 adults, Grimaldi et al (22) found that urinary I-FABP concentration was correlated with a decrease in plasma citrulline concentration. Whereas these previous studies were conducted in relatively homogenous groups of patients with a delineated pathology, the present study involves a heterogenous population reflecting the overall admissions in a medical ICU.

The present study has several limitations. First, since I-FABP is eliminated by the kidney, it is likely that acute renal failure is associated with decreased clearance of I-FABP. However, even if AMI is often associated with acute renal failure by various mechanisms, such as hypovolemia or renal embolism, I-FABP has been found to be an accurate biomarker of small bowel ischemia.

Second, the interpretation of plasma citrulline concentration in critically ill patients, which depends on renal function and also the level of systemic inflammation, deserves some caution. Indeed, in the present study, plasma citrulline concentration was likely overestimated in case of acute renal failure due to renal accumulation of citrulline. In addition, plasma citrulline concentration decreased during the first day in the ICU among patients with enterocyte damage at admission, but also among patients without enterocyte damage, suggesting that different mechanisms might coexist to explain plasma citrulline reduction. It is likely that the rapid reduction of plasma citrulline concentration on the first day in the ICU was partly explained by the high prevalence of enterocyte damage at admission. In addition, a lower plasma citrulline

concentration was associated with a higher CRP concentration and more frequent antibiotic therapy, suggesting that sepsis might be a second factor to explain plasma citrulline reduction (23, 24). Indeed, since citrulline synthesis takes place in the mitochondria, one possible hypothesis could be that mitochondrial dysfunction during sepsis decreases gut citrulline synthesis, even without enterocyte damage.

CONCLUSIONS

Enterocyte damage in critically ill patients is frequent and is associated with presence of shock. Plasma I-FABP concentration, plasma citrulline concentration, and SOFA score at admission to the ICU are independently associated with 28-day mortality. Understanding the relationship between plasma concentrations of I-FABP and citrulline requires further evaluation.

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