Is There a Role for Enterohormones in the Gastroparesis of Critically Ill Patients?

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Objectives: Delayed gastric emptying occurs in critically ill patients and impairs the delivery, digestion, and absorption of enteral feeding. A pathophysiologic role of the enterohormones peptide YY and ghrelin is supported by preclinical data. To compare the circulating plasma levels of peptide YY and ghrelin in control subjects and in critically ill patients, during feeding and fasting, and to search for a correlation with gastric emptying.

Design: A prospective observational trial.

Settings: Mixed ICU of an academic hospital.

Subjects: Healthy volunteers and patients expected to stay in ICU for at least 3 days in whom enteral nutrition was indicated.

Interventions: None.

Measurements and Main Results: Plasma peptide YY and ghrelin (enzyme-linked immunosorbent assay) were measured once in 10 fasting volunteers (controls) and daily from admission until day 5 of the ICU stay in 30 critically ill patients (median [interquartile range] age 63 [57–67] yr, median [interquartile range] Acute Physiology and Chronic Health Evaluation II score 21 [14–24]). Eight patients could not be fed (fasting group). In fed patients, 13 never had a gastric residual volume higher than 250 mL (low gastric residual volume group), in contrast to the high gastric residual volume group ($n = 9$). The plasma levels of peptide YY did not differ between patients (6.4 [0–18.1] pg/mL) and controls (4.8 [0.3–17.7] pg/mL). Ghrelin levels were lower in patients than in control (213 [54.4–522.7] vs 1,435 [1,321.9–1,869.3] pg/mL; $p < 0.05$). Plasma peptide YY or ghrelin did not differ between fasting and fed patients or between the high and low gastric residual volume groups.

Conclusions: In critically ill patients, plasma concentration of ghrelin significantly differs from that of controls, irrespective of the feeding status. No correlation was found between the temporal profile of ghrelin or peptide YY plasma concentration with bedside functional assessment of gastric emptying. (*Crit Care Med* 2017; 45:1696–1701)

Key Words: enteral feeding; gastric emptying; ghrelin; gut dysfunction; peptide YY

Intolerance to enteral nutrition (EN), reflected by gastroparesis, delayed gastric emptying, and increased gastric residuals, is an important clinical concern, as it is frequent and impairs the delivery of nutrients to the duodenum, thereby delaying digestion and absorption. Impaired motility of the stomach, which delays gastric emptying, is the major determinant of the intolerance to EN. Even though inaccurate, gastric residual volume (GRV) is used as bedside monitoring tool of gastric emptying (1–3). However, the physiopathology of delayed gastric emptying in the critically ill is only partially understood (4–6). A better understanding of the determinants of gastric dysmotility is definitely required, in order to develop specific and efficient promotility agents (3, 7, 8).

Among potential mechanisms underlying the critical illness-associated gastric dysmotility, a role of the enterohormones peptide YY (PYY) and ghrelin is plausible (9). PYY released by L cells of the distal ileum and colon slows gastric emptying and is involved in energy homeostasis as it inhibits food intake after binding to selective Y2 receptor agonist on hypothalamic arcuate neurons (10–12). Recently, increased PYY levels were measured in critically ill patients (13) with a slight but significant relationship with gastric emptying measured using a ^{13}C-octanoate breath test (11). Ghrelin, an enterohormone released from the parietal cell of the gastric fundus, accelerates gastric emptying. Ghrelin is a 28 amino-acid gastric peptide produced from chromosome 3p25–26 by an alternative splicing

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mechanism with multiple functions including prokinetic and proabsorptive effects (14–16). Ghrelin biological activity depends on the modification of the acyl group on the 3-serine residue by an esterification process. Only the acylated form of ghrelin is biologically active on gastric motility (16, 17). In critically ill and postoperative patients, abnormally high and low plasma levels of ghrelin have been reported by different teams of investigators (13, 14, 18–20). Importantly, the plasma levels of enterohormones can be influenced by renal function and by the feeding status, as physiologically PYY increases and ghrelin decreases after a meal (21, 22). The effects of continuous feeding, the usual modality of EN in critically ill patients, on the circulating levels of enterohormones are however unknown.

To bring clues to answer some of the unsolved issues, this study was undertaken with three aims: 1) to compare the circulating plasma levels of PYY and ghrelin in healthy subjects with those of critically ill patients, 2) to assess whether the plasma levels of these enterohormones were influenced by continuous feeding, and 3) to search for a temporal correlation between plasma concentrations of PYY and ghrelin and gastric emptying assessed by GRV.

MATERIALS AND METHODS

This study was approved by the local institutional review board (P2015/224). Signed informed consent was required from patients or relatives and controls. Thirty consecutive adult (≥ 18 yr) patients admitted in the Medico-Surgical Department of Intensive Care of the Erasme University Hospital in Brussels, Belgium, were enrolled. To be eligible, an expected length of stay (LOS) of at least 3 days in the ICU and an indication for EN were required. Pregnant women and patients with a life expectancy shorter than 5 days were not eligible. Ten fasting healthy volunteers served as control group. They were instructed to fast for a maximum of 8 hours before the blood sampling at 7 AM.

Data Collection

Demographic variables, body mass index (weight/height^2), category of admission (medical, scheduled surgery, emergency surgery, and trauma), disease severity assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score (23) and by the Sequential Organ Failure Assessment (SOFA) score (24), a diagnosis of sepsis, the requirement for mechanical ventilation, and plasma creatinine levels were recorded at admission.

The prescription of early EN was systematic unless contraindicated. The type of contraindication and/or the reasons underlying the impossibility to deliver EN were noted. When possible, EN was delivered via a nasogastric tube. A standard polymeric isocaloric protein-rich formula (Nutrison Protein Plus; Nutricia, Zoetermeer, The Netherlands) was infused at a rate adapted to the individual tolerance assessed by GRV (25, 26). Initial infusion rate was started at 20 mL/hr and increased according to tolerance to achieve 20 kcal/kg during the first week. In case of GRV higher than 250 mL, the previous infusion rate was decreased by half. GRV was measured in all patients per local practice, every 4–6 hours without predefined time schedule (26). If after this time, high GRV was not present, EN volume gradually increase up to 20 kcal/kg/24 hr in the first week of ICU stay. Total GRV, the amount of EN delivered, and the total amount of energy delivered, including nutritional and nonnutritional caloric intakes, expressed in kcal/kg/d, were collected daily. Patients with high GRV were treated with prokinetic agents (IV Metoclopramide 10 mg each 8 hr). All patients also received a stress ulcer prophylaxis (IV Pantoprazole 40 mg/d).

The patients were categorized as "fasting" (contraindication to enteral feeding or intolerance) or "fed." The "fed" patients were divided according to the tolerance to EN, assessed by the maximal level of GRV ("high GRV" when at least one value > 250 mL was recorded during the 5-d period or "low GRV" when all GRV values were ≤ 250 mL), according to a published definition (1).

Blood Sampling and Enterohormones

Sampling was performed for 5 consecutive days in ICU patients and once in the control group. Two sets of blood samples were taken immediately at the same time after ICU admission in the patients group. For 5 consecutive days after ICU admission, two sets of blood samples were taken at 8 AM. PYY samples were taken with EDTA tubes (BD Diagnostics, Franklin Lakes, NJ). Ghrelin samples were taken in EDTA-Aprotinine tubes (BD Diagnostics). Immediately after sampling, blood samples were centrifuged at 3,000 g for 10 minutes at 4°C. Ghrelin samples were acidified to pH 4, and then all samples were stored at −80°C. Acylated ghrelin plasma concentrations were measured using a Quantikine enzyme-linked immunosorbent assay (ELISA) test (R&D Systems, Minneapolis, MN). According to the manufacturer, intraassay (same sample) and interassay (different sample) variabilities were 1.79% and 6.07%, respectively, for a standard curve ranging from 0.1 to 1000 pg/mL. PYY serum concentrations were measured using an ELISA test (Merck Millipore, Darmstadt, Germany). According to the manufacturer, plasma intraassay variability was 0.9–5.8% and interassay variability was 3.7%–16.5%.

Statistical Analysis

Statistical analysis was performed using *R* language version 3.2.4 and IBM SPSS 24 for Windows (IBM Corporation, Somers, NY). We report data as means with (SD), medians and interquartile ranges (IQRs), or numbers and percentages. The Shapiro test and histograms and normal quantile-quantile plots were examined to verify whether there were significant deviations from the normality assumption of continuous variables. Difference between groups was tested using Mann-Whitney *U* test, chi-square test, or Fisher exact test as appropriate. Mixed-effects polynomial regression models with restricted maximum likelihood estimation and first-order autoregressive covariance structure were used to examine the differences in all analyzed variables among the groups at five time points (d). When the trajectory of an analyzed variable was unlikely

to follow a straight line, we considered up to the second-degree polynomial models of time (d) so that the effects of day and day^2 on that variable were tested as fixed effects. Interaction effects between groups and day and day^2 were also tested. Model checking was performed by inspection of residual and normal plots. Ghrelin and PYY enterohormones correlation with GRV was done using Pearson correlation test. All tests were two sided, and p value of less than 0.05 was considered statistically significant.

RESULTS

Study Participants

The study was conducted between May and September 2015. Among the 31 screened patients, one refused to participate. Of the 30 included patients, eight did not receive enteral feeding ("fasting" group) for various reasons (impossibility or contraindication to insert the nasogastric tube, such as multiple surgical interventions, caustic esophagitis, skull base fracture, esophageal perforation, or persistent ileus resulting in high GRV). No attempts to initiate early EN were made for this group during the study period. Among the 22 patients fed enterally ("fed group"), nine (41%) had at least once a GRV greater than 250 mL ("high GRV" group), whereas the GRV of the other 13 patients was always less than or equal to 250 mL. No patient received postpyloric feeding.

The characteristics of the groups were similar (**Table 1**), although the APACHE II and SOFA scores were slightly higher in the "high GRV" group than in the other groups. A higher proportion of patients in the fasting group had a diagnosis of sepsis than in the fed groups. Most patients were admitted for medical reasons and were mechanically ventilated at admission. No patient required renal replacement therapy, and the plasma creatinine levels were stable over the 5-day study period. The LOS lasted at least 5 days in all patients, allowing a complete collection of data and blood samples.

During the 5 days of observation, GRV averaged 102 mL (0–1,060 mL) with the lowest values recorded on days 1 and 5. In the "high GRV "group, the median GRV was higher than in the "low GRV group" for the 4 first days, confirming the persistence of delayed gastric emptying in those patients. Despite these differences, the energy delivered by the enteral route did not differ significantly between these groups, as a result of the delivery of a higher amount of nonnutritional calories in the "high GRV" group (**Table 2**).

Enterohormones

Plasma PYY. The plasma levels of PYY measured ranged from 0 to 579 pg/mL and did not differ between control subjects and patients (median 6.4 [0–18.1]) (**Fig. 1*A***). The values recorded in the fed group were slightly higher than in fasting groups and in those with high GRV slightly higher than in the low GRV group (day-by-day comparisons, **Table 3**). There was no significant difference between the values recorded in the high and low GRV groups. No correlation was found between GRV and PYY values.

TABLE 1. Characteristics of the Study Population at Admission

Characteristics	All ($n = 30$)	Fasting ($n = 8$)	Fed		
			All	High GRV ($n = 9$)	Low GRV ($n = 13$)
Admission data					
Sex, male, %	52	71	44	56	33
Age (yr), median (IQR)	63 (57–67)	58 (38–59)	66 (59–69)	66 (45–68)	66 (60–71)
Body mass index, median (IQR)	26 (24–28)	26 (25–28)	26 (24–28)	27 (26–28)	24 (24–26)
Admission category, %					
Medical	64	57	67	56	78
Elective surgery	16	0	22	22	22
Emergency surgery	8	0	11	22	0
Trauma	13	38	0	0	0
Acute Physiological and Chronic Health Evaluation II score, median (IQR)	21 (14–24)	23 (16–24)	21 (14–24)	25 (21–28)	18 (11–19)
Admission Sequential Organ Failure Assessment, median (IQR)	9 (7–10)	10 (10–10)	9 (7–11)	25 (21–28)	18 (11–19)
Sepsis at admission, %	36	50	22	33	11
Mechanical ventilation support, %	76	57	83	89	78
Creatinine (mg/dL) (mean ± SD)	1.1 ± 0.1	0.75 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.8 ± 0.3

GRV = gastric residual volume, IQR = interquartile range.

TABLE 2. Gastric Residual Volumes and Energy Delivered to the Fed Patients (Mean ± SD)

		GRV and Energy Delivered (kcal/kg/d)	
Day	Group	High GRV	Low GRV
1	Energy	3.3 ± 3.8	6.4 ± 7.8
	GRV	188.3 ± 166.7[a]	19.1 ± 37.1
2	Energy	11.6 ± 9.6	14.7 ± 10.8
	GRV	258.1 ± 319.6[a]	35.2 ± 80.8
3	Energy	15.1 ± 10.8	15.2 ± 11.1
	GRV	307.7 ± 303.4[b]	26.2 ± 51.6
4	Energy	15.4 ± 9.3	18.9 ± 12.0
	GRV	248.7 ± 313.6[b]	12.7 ± 32.1
5	Energy	18.1 ± 11.4	19.4 ± 9.2
	GRV	94.4 ± 170.3	32.5 ± 100.6

GRV = gastric residual volume.
[a]$p < 0.05$ vs low gastric residual volume (GRV).
[b]$p < 0.01$ vs low GRV.

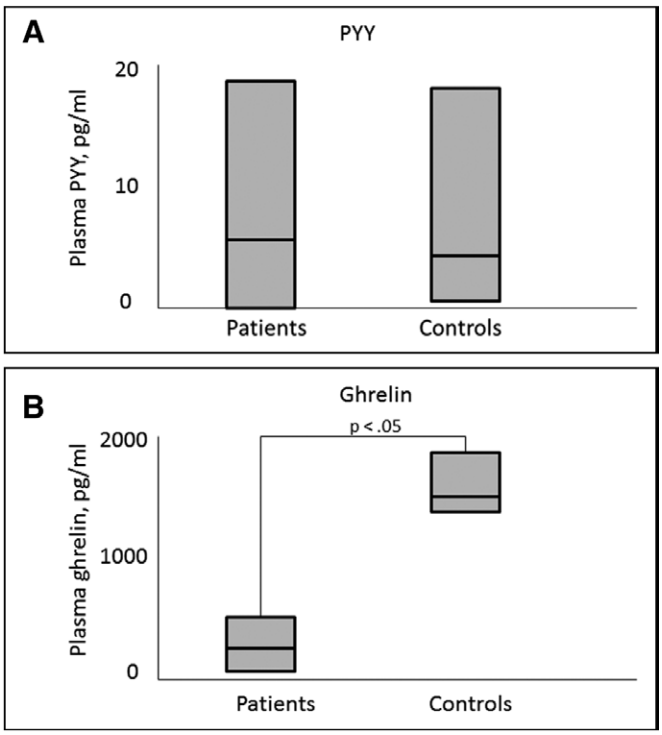

Figure 1. Values of plasma peptide YY (PYY) levels (**A**) and of plasma ghrelin levels (**B**) in patients (*left bars*) and in control subjects (*right bars*). Values are expressed as median (interquartile range). *$p < 0.05$ as compared with patients.

Plasma Ghrelin. The plasma levels of ghrelin ranged from 0 to 4426 pg/mL and were higher in control subjects than in patients ($p < 0.05$) (**Fig. 1*B***). The values (median, IQR) recorded in control subjects were higher than the values recorded in patients ($p < 0.05$ for each day) (Table 3).

There was no difference between the values recorded in the fed and fasting groups and no difference between the values recorded in the high and low GRV groups (day-by-day comparisons, Table 3).

DISCUSSION

The results of this study brought some answers to the research questions raised on a representative sample of critically ill patients requiring a prolonged ICU stay.

During critical illness, we observed a nonsignificant trend of higher circulating levels of PYY and consistently lower levels of ghrelin than in healthy fasting subjects. We found no difference between the values recorded in the "fed" and "fasting" patients that would support an influence of continuous enteral feeding on the release of both enterohormones. However, testing this contention would require serial measurements before the initiation and during continuous enteral feeding, and at different infusion rates. Nonetheless, the absence of effect of feeding sharply contrasts with the former findings in healthy subjects, that is, PYY decreasing preprandially and increasing postprandially, whereas ghrelin increases preprandially and decreases postprandially (21, 22). Hypothetically, functional changes of the gut-brain axis related to the critical illness can be advocated to explain the different effects of food ingestion on the circulating levels of enterohormones.

The lack of significant increase of PYY levels contrasts with the findings reported by Nematy et al (13), who reported a transient three-fold increase in PYY concentration in patients compared with control subjects (11). Taken together, these findings do not support a prominent role of plasma PYY concentration in the critical illness-associated anorexia (5).

The decrease of ghrelin confirms some of the previous data (11, 13, 14, 18) but not the findings of the largest study (19, $n = 170$ critically ill patients and 60 healthy subjects). This discrepancy is probably explained by the type of assay: one measured total ghrelin (19), while the active acylated form of ghrelin was measured by the other researchers (11, 13, 14, 18). The comparison of total, acylated, and deacylated ghrelin levels supports this hypothesis (18, 20).

The consequences of the decreased ghrelin level could include the critical illness-associated decrease in appetite and the gastrointestinal dysfunction, including the delayed gastric emptying. We did not found a consistent correlation between plasma PYY or ghrelin enterohormones and GRV during the study period. However, as in healthy subjects or in ambulant patients with gastroparesis and in animal models of sepsis-induced gastroparesis ghrelin agonists accelerate gastric emptying, in spite of a "normal" plasma ghrelin concentrations, our findings do not necessarily imply that synthetic ghrelin agonists would be inefficient to improve gastric dysmotility in the critically ill.

The present study has strengths and limitations. The strengths include the inclusion of consecutive and representative patients, the daily serial determination of plasma concentrations of PYY and ghrelin over a 5-day period, and the systematic monitoring and recording of GRV several times a day. The patients included in this study performed in a medico-surgical department are

TABLE 3. Concentrations of Ghrelin and Peptide YY Recorded in the Different Subgroups

Day	1	2	3	4	5
All patients ($n = 30$)					
PYY (pg/mL), median (IQR)	4.8 (0.0–59.9)	17.5 (1.3–82.3)	20.3 (0.0–52.3)	16.0 (2.8–84.9)	24.7 (0.0–78.6)
Ghrelin (pg/mL), median (IQR)	213.0 (54.4–522.7)	183.6 (64.6–451.0)	237.1 (106.2–472.0)	300.1 (77.8–1,364.1)	256.4 (115.2–448.4)
Fasting ($n = 8$)					
PYY	4.8 (2.1–13.2)	10.2 (0.0–19.9)	2.9 (0.0–40.4)	9.8 (0.0–84.9)	16.0 (2.2–42.5)
Ghrelin	213.0 (49.8–492.5)	284.4 (57.7–587.8)	188.2 (100.3–836.9)	597.8 (188.3–1,127.0)	338.3 (58.1–1,037.9)
Fed ($n = 22$)					
PYY	6.1 (0.0–63.3)	22.0 (2.7–112.6)	27.1 (9.0–67.1)	16.6 (4.6–117.7)	24.7 (0.0–95.0)
Ghrelin	213.0 (78.4–522.7)	158.8 (83.4–435.1)	250.2 (122.4–472.0)	197.4 (77.8–1,364.1)	256.4 (128.8–334.6)
High GRV ($n = 9$)					
PYY	1.1 (0.0–59.9)	80.5 (28.9–168.5)	38.0 (0.0–103.8)	20.9 (0.0–190.5)	67.1 (0.0–95.0)
Ghrelin	153.8 (104.3–291.2)	126.5 (112.2–387.1)	225.8 (163.1–287.7)	222.2 (106.8–1,765.4)	183.5 (143.9–332.9)
Low GRV ($n = 13$)					
PYY	5.3 (0.0–63.3)	11.3 (0.4–24.2)	15.5 (0.0–43.6)	16.0 (4.4–74.9)	18.5 (0.0–52.6)
Ghrelin	290.5 (51.5–776.9)	197.4 (55.6–748.2)	266.5 (87.0–792.8)	377.8 (76.5–1,364.1)	307.9 (103.9–792.8)

GRV = gastric residual volume, PYY = peptideYY.

Enterohormone values recorded during the ICU stay (median [interquartile range]). All differences (fasting vs fed and high GRV vs low GRV) are not significant.

probably representative of the "real-world" situation, for example, the patients of the "high GRV" group tended to be sicker and more often septic than the patients of the "low GRV" group (25). In spite of the persistent impairments of gastric emptying over the 5-day period (Table 2), there was no difference in the levels of PYY and ghrelin between the high and low GRV groups.

Limitations include the relatively small sample size and the selection of the two enterohormones, when other hormones released by the gastrointestinal tract, such as cholecystokinin, motilin, and glucagon-like peptide-1, which could also be involved in the gastrointestinal dysfunction of critical illness (22). The currently available evidence, however, supported a prominent role of PYY and ghrelin in pathogenesis of critical illness-associated gastric dysmotility. Arguably, GRV is less accurate than other methods including scintigraphy, ultrasonography, or breath tests to evaluate gastric emptying (2). However, GRV can be easily and repeatedly measured at bedside using a standardized technique, while the other methods cannot be used routinely, as they require a particular expertise and technical equipment. GRV can be used as an index of intolerance to enteral feeds together with other gastrointestinal symptoms (25). In a recent systematic review (1), the pooled proportion ($n = 31$ studies) of food intolerance was 38.3% and was associated with increased mortality and ICU LOS. Using large GRV greater than 250 mL as threshold to define impaired gastric motility has been validated in our center (26). The frequency of intolerance to EN was of the same magnitude (30%). Of note, recent data from large clinical trials do not support the use of a 250-mL threshold as a predictor of the risk of inhalation or ventilator-associated pneumonia (27, 28). Another limitation is the possible variations of plasma ghrelin/PYY enterohormones related to transient changes in hemodynamic status, renal function, magnitude of the vasoactive and respiratory support, and probably, changes in EN volume administration. However, while sampling blood every time, there is a change in status in a critically ill patient, which is technically very difficult.

Also, categorizing continuous variables is associated with loss of statistical power and precision, increasing the probability of a type 2 (Beta) error, especially in patients with some degree of EN intolerance (GRV below our prespecified threshold). We also analyzed together patients with contraindication to enteral feeding or intolerance ("fasting group"). Ideally, a comparison

of the levels of enterohormones of patients with actual intolerance to feeding with those with an a priori contraindication to enteral feeding would be informative but would be irrelevant with the sample size of the fasting subgroup ($n = 8$).

CONCLUSIONS

In critically ill patients, mean plasma concentration of ghrelin was consistently lower than in healthy controls and was not consistently altered by continuous enteral feeding. The lack of consistent association between the circulating levels of enterohormones and the magnitude of the impairment of gastric emptying does not argue for changes in plasma levels of PYY and ghrelin as the mechanism of increased GRV. The confirmation of this contention requires studies on larger populations.

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