Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations*

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Objective: Delayed gastric emptying and intolerance to gastric feeding occur frequently in the critically ill. In these patients, gastric motor responses to nutrients are disturbed. Cholecystokinin (CCK) slows gastric emptying. The aim of this study was to determine plasma CCK concentrations during fasting and in response to small-intestine nutrient infusion in critically ill patients.

Design: Randomized, controlled trial.

Setting: Level 3, mixed medical and surgical intensive care unit.

Subjects: A total of 31 mechanically ventilated, critically ill patients (23 men, 51 ± 3 yrs) and 28 healthy subjects (21 men, 43 ± 2 yrs).

Interventions: Subjects received two 60-min duodenal infusions of Ensure (complete balanced nutrition), at 1 and 2 kcal/min, in a randomized, single-blind fashion. The nutrient infusions were separated by a 2-hr “washout” period. Blood samples for measurement of plasma CCK concentrations were obtained immediately before and every 20 mins during nutrient infusion.

Measurements and Main Results: Baseline and nutrient-stimulated plasma CCK concentrations were higher in critically ill patients compared with healthy subjects (p < .001). The magnitude of the rise in plasma CCK in response to nutrients was also greater in the critically ill (p < .01). Of the 23 patients who received enteral nutrition before the study, nine were intolerant of gastric feeding. In these patients, both the baseline plasma CCK concentration and the magnitude of CCK increase during nutrient infusions were greater than in patients with feed tolerance (p < .002). Impaired renal function was associated with an increased baseline CCK concentration but had no effect on the CCK response to nutrients.

Conclusions: Both fasting and nutrient-stimulated plasma CCK concentrations are increased in critically ill patients, particularly in those with feed intolerance. This may provide a humoral mechanism for delayed gastric emptying seen in critical illness.

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Key Words: cholecystokinin; critical illness; enteral nutrition; feed intolerance

Enterogastric” feedback is a major factor regulating gastric emptying (1) and is mediated by both neural and humoral mechanisms. Cholecystokinin (CCK) is an important humoral mediator of the enterogastric feedback response, which also regulates appetite and controls energy homeostasis (2–6). CCK is released in a dose-dependent fashion from small-intestine entero-endocrine cells in response to the presence of fat and protein in the small intestine (4–6). Exogenous administration of CCK slows gastric emptying (2–4, 6), increases the sensation of fullness, and reduces the sensation of hunger and food intake (5, 6).

Plasma CCK concentrations are increased in subgroups of patients with reduced oral intake (7) and malnutrition (8–10), conditions that are associated with slow gastric emptying (11, 12). More recently, healthy aging has also been reported to be associated with an increase in plasma CCK, suggesting a possible contribution to anorexia and weight loss in the elderly (13). In healthy adults, antagonizing the effects of CCK with loxiglumide increases appetite and energy intake (14, 15). However, the effect of CCK antagonists on gastric emptying remains controversial. Although several studies have shown gastric emptying to be accelerated by CCK antagonists (14–16), two other studies failed to demonstrate an increase in gastric emptying rates (17, 18). Nevertheless, current data would suggest a close interaction between nutritional status, CCK, and gastric emptying.

Intolerance to gastric feeding due to delayed gastric emptying occurs frequently in critical illness (19, 20) and adversely affects both morbidity and mortality (21–23). A number of motor disturbances affecting both the proximal and distal stomach have been demonstrated in critically ill patients (19, 24, 25). Our group has previously shown a delay in the recovery of proximal gastric volume following small-intestine nutrient stimulation (24), a marked reduction in the number of antral pressure waves, an increase in phasic and tonic pyloric motor activity, and disordered organization of antroduodenal motility (19, 25). These motor disturbances, particularly in the

*See also p. 298.

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The aims of this study were to determine: 1) plasma CCK concentrations during fasting and in response to small-intestine nutrient infusion in critically ill patients and 2) whether feed intolerance is related to plasma CCK levels. We hypothesized that both fasting and nutrient-stimulated plasma CCK concentrations would be increased in critical illness, particularly in those patients who were intolerant of gastric feeding.

MATERIALS AND METHODS

Subjects

Patients. Studies were performed in 31 unselected critically ill patients (23 men) who were admitted to a level 3 intensive care unit. Any patient aged >17 yrs was eligible for the study if they were sedated, mechanically ventilated, and able to receive enteral nutrition. Exclusion criteria included any contraindication to passage of an enteral tube; previous esophageal, gastric, or intestinal surgery; recent major abdominal surgery; and administration of opioid analgesia or prokinetic therapy within 24 hrs before the study. All patients admitted with the above criteria between February and August 2004 were assessed for the study and were enrolled if written, informed consent was provided from the next of kin. All patients were receiving an insulin infusion according to a standardized protocol, designed to maintain the blood glucose concentration between 6 and 8 mmol/L (26). Nine patients were intolerant of gastric feeding, as defined clinically by a 6-hr gastric aspirate volume of >250 mL (27).

Healthy Subjects. During the same time period, 28 age- and sex-matched healthy subjects (21 men, aged 43 ± 2 yrs, body mass index of 25.5 ± 1.0 kg/m²) were studied. No subject had evidence or a history of systemic or gastrointestinal disease, previous abdominal surgery, or was taking any medication that is known to affect gastrointestinal motility. Healthy subjects were instructed to refrain from smoking for 24 hrs before the study. All healthy volunteers provided written, informed consent before entering the study. Healthy subjects were recruited through advertisement within the local community and offered an honorarium for time spent in the laboratory.

The study was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and run according to the National Health and Medical Research Committee Guidelines for the conduct of research on unconscious patients.

Study Protocol

Critically ill patients were studied after a minimum of 8 hrs of fasting. All patients received propofol for sedation throughout the study. Analgesia with an intermittent bolus of fentanyl was given to patients for whom pain was an issue, such as those with multiple trauma, burns, or pancreatitis. A 12-Fr × 114-cm nasoduodenal feeding tube (Flexiflo, Abbott, Ireland) was inserted into the distal duodenum via an endoscopically placed guide-wire (THSF-35-260, Cook Australia, Brisbane, Australia). Correct placement of the nasoduodenal feeding tube was confirmed by 1) measurement of the duodenal transmucosal potential difference of greater than −15 mV (28) and 2) routine radiography as performed as part of clinical care.

In healthy volunteers, the study was performed after an overnight fast. A silicone rubber catheter (Dentsleeve, Adelaide, Australia) with a central feeding lumen was used to deliver nutrients into the duodenum. The catheter was inserted into the stomach via an anesthetized nostril and allowed to migrate into the duodenum by peristalsis, without the assistance of either sedation or endoscopy. Passage of the assembly beyond the pylorus was facilitated by small weights located at the catheter tip. Postpyloric positioning of the assembly was determined by continuous measurement of the antroduodenal transmucosal potential difference gradient (28). Radiologic confirmation was not performed.

Both healthy and patient studies were performed in the morning. After confirmation that the catheter tip was placed correctly in the duodenum, normal saline (0.9%) was infused through the tube at a rate of 4 mL/min for 15 mins (Fig. 1). Each subject then received two 60-min duodenal infusions of Ensure (Abbott Laboratories, Columbus, OH; composition: 13% protein, 64% carbohydrate, 21% fat; energy content: 1 kcal/mL), at 1 kcal/min and 2 kcal/min, in a randomized, single-blind fashion. Before the study, the order of infusions was determined by blind selection from a concealed box. Ensure was diluted with normal saline (0.9%) to 1:4 for the 1 kcal/min infusion and to 1:2 for the 2 kcal/min infusion; the resulting solutions were infused at a rate of 4 mL/min. The nutrient infusions were separated by a 2-hr “washout” period, which consisted of 1.5 hrs of no infusion followed by 30 mins of intraduodenal infusion of normal saline. Blood samples for the measurement of plasma CCK concentration were collected at baseline and at 20, 40, and 60 mins during the nutrient infusions.

Measurement of Plasma CCK

Blood samples (8 mL) were collected into chilled EDTA tubes, centrifuged at 4°C within 30 mins of collection, and the plasma stored at −70°C for subsequent analysis. Plasma CCK concentrations were measured by radioimmunoassay, using an adaptation of the method of Santangelo et al (29). The intra-assay and interassay coefficients of variation were 9% and 15%, respectively. The detection limit of the assay was between 0.5 and 1 pmol/L in plasma (29).

Subgroup Analyses

Because of the interaction between previous nutrient intake and CCK concentrations, the effects of successful feeding and previous nutritional support were assessed. The influence of acid suppression on CCK concentrations was also determined. Other factors such as sepsis and inotropic support have been associated with disturbed gastric motility in critical illness (30). Their effects on CCK concentrations were determined. As plasma CCK clearance is primarily dependent on renal function, creatinine clearance in all patients was assessed using the Cockcroft-Gault equation and was considered to be impaired when creatinine clearance was <65 mL/hr (31).

Statistical Analysis

Data are presented as mean ± SEM. Demographic characteristics and the differences in CCK responses between critically ill patients and healthy subjects were compared using Student’s unpaired t-test. A two-way repeated-measures analysis of variance with post hoc comparisons was used to evaluate 1) the effects of the two nutrient loads on plasma CCK in each group, 2) differences in the plasma CCK responses to small-intestine nutrients between the two groups, 3) differences in CCK responses to nutrients between patients who were tolerating gastric feeding and those who were not, and 4) the effect of renal function.
RESULTS

The study procedure was tolerated well by all subjects, and no complications occurred in either group. Demographic data and characteristics of critically ill patients are summarized in Table 1. There were no statistical differences in age, sex, or body mass index between the two groups. The admission diagnosis of patients were: sepsis (n = 11), head injury (n = 5), pneumonia (n = 5), pancreatitis (n = 3), cardiac failure (n = 3), multiple trauma (n = 2), burns (n = 1), and idiopathic angioedema (n = 1). The duration of feeding was similar between feed-tolerant and feed-intolerant patients (3.2 ± 0.7 vs. 3.9 ± 1.0 days, respectively). Twelve patients (39%) required inotropic support with either adrenaline or noradrenaline. Acid suppression therapy (ranitidine or pantoprazole) was given to 23 patients. At the time of study, ten patients had renal impairment and seven patients were receiving hemodialysis. Both age and Acute Physiology and Chronic Health Evaluation II scores of these patients were higher than those with normal renal function (Table 1). At the time of endoscopic placement of the feeding tube, two patients had a small amount of feed residue (<100 mL) in the stomach and duodenum.

Effects of Critical Illness on Plasma CCK Concentrations. In both healthy subjects and critically ill patients, baseline CCK concentrations before the 1- and 2-kcal/min infusions were similar. In both groups, there was a dose-dependent increase in plasma CCK concentration in response to the different nutrient loads (Fig. 2).

Plasma CCK concentrations at baseline were significantly higher in the critically ill patients than the healthy subjects (1 kcal/min: 8.6 ± 1.0 vs. 4.4 ± 0.4 pmol/L, p < .001; and 2 kcal/min: 8.7 ± 1.1 vs. 4.7 ± 0.4 pmol/L, p < .05; respectively) (Fig. 2). Plasma CCK concentrations during the 1-kcal/min and 2-kcal/min infusions were also higher in critically ill patients (p < .01) (Fig. 2). In patients, the increase in plasma CCK during both nutrient infusions was 1.5-fold greater than in healthy subjects (p < .01) (Fig. 3a).

Table 1. Demographic data (mean ± SEM) and characteristics of critically ill patients.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 31)</th>
<th>Previous nutritional support</th>
<th>Feed intolerance</th>
<th>Renal function</th>
</tr>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>51.0 ± 3.0</td>
<td>Yes (n = 23)</td>
<td>49.3 ± 3.1</td>
<td>Normal (n = 21)</td>
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<td></td>
<td></td>
<td>No (n = 8)</td>
<td>59.6 ± 3.2</td>
<td>Absent (n = 14)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>30.5 ± 1.5</td>
<td>Yes (n = 23)</td>
<td>29.7 ± 1.3</td>
<td>Normal (n = 21)</td>
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<tr>
<td></td>
<td></td>
<td>No (n = 8)</td>
<td>32.7 ± 1.7</td>
<td>Absent (n = 14)</td>
</tr>
<tr>
<td>APACHE II (Admission)</td>
<td>25.6 ± 0.9</td>
<td>Yes (n = 23)</td>
<td>24.8 ± 0.9</td>
<td>Normal (n = 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (n = 8)</td>
<td>27.4 ± 0.9</td>
<td>Absent (n = 14)</td>
</tr>
<tr>
<td>APACHE II (Study Day)</td>
<td>23.6 ± 1.0</td>
<td>Yes (n = 23)</td>
<td>23.2 ± 1.1</td>
<td>Normal (n = 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (n = 8)</td>
<td>24.7 ± 0.9</td>
<td>Absent (n = 14)</td>
</tr>
<tr>
<td>Days in Intensive Care</td>
<td>6.0 ± 0.7</td>
<td>Yes (n = 23)</td>
<td>20.5 ± 1.0</td>
<td>Normal (n = 21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No (n = 8)</td>
<td>27.4 ± 1.6</td>
<td>Absent (n = 14)</td>
</tr>
</tbody>
</table>

APACHE II, Acute Physiology and Chronic Health Evaluation II score.

*Defined as 6-hour gastric aspirate volume of >250 mL; **p < .05 vs. critically ill patients with feed tolerance; ***creatinine clearance rate of <65 mL/hr; ****p < .05 vs. critically ill patients with normal renal function.

Figure 2. Plasma cholecystokinin concentrations (CCK) at baseline and during intraduodenal nutrient infusion in critically ill patients (n = 31) and healthy subjects (n = 28). *p < .001; **p < .05; ***p < .01 vs. healthy subjects.

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Both inotropic and acid-suppression therapies had no effect on plasma CCK concentrations, either at baseline or during the nutrient infusions. Plasma CCK concentrations were similar between patients with and without sepsis.

Effects of Feed Tolerance and Previous Nutritional Support on Plasma CCK Concentrations. Baseline plasma CCK concentrations were higher in critically ill patients who were intolerant of gastric feeding compared with patients who were feed tolerant ($p < .01$) (Fig. 4). The increase in plasma CCK in response to both nutrient infusions in feed-intolerant patients was 2-fold higher than in feed-tolerant patients ($p < .01$) (Fig. 3b). There were no differences in either the baseline or nutrient-stimulated plasma CCK concentrations between patients tolerant of gastric feeding and healthy subjects (Fig. 4). The magnitude of plasma CCK increase during both infusions did not differ between these two groups.

There were no differences in either the baseline or nutrient-stimulated plasma CCK concentrations between patients with or without previous nutritional support. In patients without previous feeding, there was a trend for baseline plasma CCK concentrations to be higher than feed-tolerant patients ($p = .09$) and lower than feed-intolerant patients ($p = .07$).

Effects of Renal Function on Plasma CCK Concentrations. Plasma CCK concentrations at baseline and during the

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**Figure 3.** Changes in plasma cholecystokinin concentrations (CCK) from baseline during nutrient infusion in (a) critically ill patients ($n = 31$) and healthy subjects ($n = 28$) and (b) feed-tolerant ($n = 14$) and feed-intolerant ($n = 9$) critically ill patients. *$p < .01$ vs. healthy subjects; **$p < .01$ vs. feed-tolerant patients.

**Figure 4.** Plasma cholecystokinin concentrations (CCK) at baseline and during intraduodenal nutrient infusion in feed-tolerant ($n = 14$) and intolerant ($n = 9$) critically ill patients and in healthy controls ($n = 28$). *$p < .01$ vs. feed-tolerant patients.
1-kcal/min infusion, but not 2-kcal/min infusion, were higher in patients with impaired renal function compared with those with normal renal function (baseline: 11.7 ± 2.0 vs. 6.7 ± 1.0 pmol/L, p = .056; nutrient-stimulated: p < .05). After exclusion of renally impaired patients, plasma CCK concentrations were still higher in critically ill patients than in healthy subjects (p < .001) (Fig. 5).

DISCUSSION

This study, to our knowledge, is the first to evaluate plasma CCK concentrations in critical illness. The major observations are that plasma CCK concentrations in critically ill patients, during both fasting and in response to small-intestine nutrient infusion, are 1) 1.5-fold higher than those of healthy subjects and 2) 2-fold higher in feed-intolerant patients compared with those who tolerated gastric feeding. Although renal impairment was associated with a higher baseline plasma CCK level, it did not affect nutrient-stimulated CCK responses in critically ill patients. Neither sepsis nor inotropic support affected the plasma CCK concentrations. These results provide a rationale for the assessment of CCK antagonists in the treatment of delayed gastric emptying and feed intolerance in critical illness.

The increased CCK responses to small-intestine nutrients in critically ill patients, particularly in those who did not tolerate gastric feeding, provides a potential mechanism for the disturbances in gastric motility and emptying that occur in critically ill patients (19, 20). Supporting this speculation is the similarity in CCK responses between feed-tolerant patients and healthy subjects. Intolerance to gastric feeding is an indirect marker of delayed gastric emptying in critically ill patients (20, 27, 32). The definition encompasses a wide range of gastric residue volumes, from 75 mL to 500 mL (32, 33). Furthermore, the relationship between gastric residue volumes and feed intolerance is controversial (33). The cutoff gastric aspirate volume of >250 mL used in this study is a clinical marker of feed intolerance in our unit and had been used by other studies that examined the issue of feed intolerance (20, 27, 34). The reported proximal and distal gastric motor disturbances in critically ill patients (19, 24, 25) resemble the known effects of CCK infusion on gastric motility in healthy humans (2–6). Exogenous administration of CCK slows gastric emptying by relaxation of the fundus (3, 35), an inhibition of antral motility, and the stimulation of isolated pyloric contractions (4). In part, these inhibitory effects of CCK on gastric emptying are mediated by CCKR receptors on the sensory fibers of the vagus nerves (36, 37). It is therefore conceivable that an abnormally high CCK response in critical illness may contribute to the disturbed gastric motility that leads to slow gastric emptying in these patients.

The mechanisms underlying the abnormally high plasma CCK during fasting and in response to small-intestine nutrient infusion in critically ill patients remain unknown. Nutritional deprivation, which occurs in up to 50% of critically ill patients, may be relevant because conditions such as starvation and malnutrition with chronic medical illnesses are associated with both slow gastric emptying and higher basal CCK concentrations (38, 39). The duration of caloric deprivation required for the development of these adaptive changes in gastric emptying may be as short as 4 days (39). There are no human data related to the changes in plasma CCK and acute fasting. In animals, acute (48 hrs) nutrient deprivation is associated with decreased, rather than increased, plasma CCK concentrations, and the levels return to predeprivation values within 16 to 24 hrs of re-feeding (40). In the current study, the duration of nutrient deprivation varied between patients with and without previous nutritional support. However, there were no differences in plasma CCK concentrations, and the levels return to predeprivation values within 16 to 24 hrs of re-feeding. In addition, plasma CCK levels were found to be lower in patients without previous nutrients than patients with feed intolerance. These data suggest that nutritional deprivation is not the sole contributor to elevated CCK concentrations in the critically ill.
turbed gastric motility of critical illness and the possible role of CCK in the dis-
eral function. Thus, acute renal impair-
ment is frequently impaired in the critically ill. It should be recognized that the
frequently observed slow gastric empty-
ing in critical illness could lead to more prolonged proximal small-intestine nu-
trient stimulation and, thereby, higher levels of CCK. However, this seems un-
likely because all patients had fasted for ≥8 hrs before the study and only two patients had a small amount of feed resid-
ue in the stomach at the time of endos-
copy. Furthermore, plasma CCK concen-
trations had returned to baseline level before each infusion. The potential assay
cross-reactivity between gastrin and CCK could also contribute to the increased CCK concentrations, as a majority of our patients were receiving acid suppression therapy, which is known to increase se-
rum gastrin concentrations. This seems most unlikely given that the assay cross-
reactivity is <2% (29) and that plasma CCK concentrations in patients who were given acid suppression did not differ from those without therapy.

As plasma CCK is renally cleared, pa-
tients with chronic renal impairment may have elevated CCK (38). In the cur-
rent study, although the plasma CCK concentrations in patients with renal im-
pairment were higher during the 1 kcal/
min infusion, this elevation was mainly
due to higher baseline levels, which may be related to impaired clearance (41). The overall CCK response to nutrients in these patients was, however, similar to that observed in patients with normal re-
nal function. Thus, acute renal impair-
ment seems unlikely to account for the increased plasma CCK response to nutri-
ents in critical illness.

One of the strengths of this study was
the ability to reliably assess the magni-
tude of the small-intestine regulatory re-
sponse by delivering nutrients directly into the duodenum, with different caloric concentrations. The delivery of 2 kcal/
min of nutrient into the small intestine is similar to the rate of gastric emptying by a normally functioning stomach (1). In-
tragastric delivery of nutrients was not used in our study because gastric emptying is frequently impaired in the critically ill. Delayed gastric emptying would not have allowed a reliable assessment of the enterogastric hormonal response. In ad-
dition, the use of infusions of 1- and 2-kcal/min allowed us to examine the dose dependency of the CCK response to small-intestine nutrient stimulation.

The relationship between our findings and the possible role of CCK in the dis-
turbed gastric motility of critical illness requires further investigation using spe-
cific CCK antagonists. The CCK antago-
nist loxiglumide accelerates gastric empty-
ing of lipid-rich liquid meals in healthy subjects (15) and in patients with func-
tional dyspepsia and irritable bowel syn-

drome (42, 43). Given the limited choice and relatively poor efficacy of current prokinetic therapy for feed intolerance in critical illness (44), the outcome of stud-
ies using CCK antagonists may provide alternative therapeutic agents for this
common clinical problem.

Many of the patients in the current study were overweight or obese, accord-
ing to body mass index criteria. The effect of extremely high body mass index, >40 kg/m² (i.e., morbid obesity), on gastric emptying is unclear (45). However, the relatively minor differences in body size between the patients and healthy subjects (30.5 kg/m² vs. 25.5 kg/m², respectively) are unlikely to contribute significantly to the results of the current study. The het-
erogeneity of the patient population is another potential limitation; however, our data (24, 25, 46) and that of others (19, 47, 48) show that the commonality of critical illness is of greater importance.

CONCLUSIONS

In conclusion, plasma CCK concentra-
tions are increased in critically ill pa-
tients, particularly in those who do not tolerate gastric feeding. This may provide a humoral mechanism for delayed gastric emptying seen in critical illness.

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