The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients*

Nam Q. Nguyen, MBBS (Hons), FRACP, PhD; Robert J. Fraser, MBBS, FRACP, PhD; Laura K. Bryant, BHS; Carly Burgstad, BHS; Marianne J. Chapman, BMBS, FANZCA, FJIFCM; Max Bellon, Dip Med Tech, A Dip Nuc Med; Judith Wishart, BSc; Richard H. Holloway, MBBS, FRACP, MD; Michael Horowitz, MBBS, FRACP, PhD

**Background:** Enteral nutrient (EN) deprivation slows gastric emptying (GE) and increases plasma cholecystokinin (CCK) concentrations in healthy humans and may potentially contribute to the delayed GE in the critically ill. This study examined the impact of delayed feeding on GE, plasma CCK, and peptide YY (PYY) concentrations in the critically ill.

**Design:** Randomized controlled trial.

**Setting:** Mixed medical and surgical intensive care unit (ICU).

**Interventions:** Twenty-eight critically ill patients were randomized to receive EN either within 24 hrs of admission (“early feeding”): 54.9 ± 3.3 yrs; Acute Physiology and Chronic Health Evaluation (APACHE) II = 23.0 ± 1.8 or on day 4 of admission after GE assessment (“delayed feeding”: 56.1 ± 4.2 yrs, APACHE II = 21.7 ± 1.8). GE of 100 ml of Ensure was measured using scintigraphy on day 4 of admission. Blood was sampled for measurement of plasma CCK, PYY, and glucose concentrations.

**Results:** Demographics, APACHE II score, use of inotrope and morphine sedation were similar between the groups. The mean administered/prescribed caloric ratio in the “early feeding” group was 72 ± 4%. There were no differences in the retention of meal, intragastric meal distribution, proportion of patients with delayed GE (9/14 vs. 9/14), and plasma CCK and PYY concentrations during fasting and postprandially between the two groups. There was no relationship between the number of calories received and percentage of meal retention at 240 min (p > .05). However, delayed feeding was associated with longer duration of mechanical ventilations (13.7 ± 1.9 vs. 9.2 ± .9 days, p = .049) and length of stay in ICU (15.9 ± 1.9 vs. 11.3 ± 0.8 days, p = .048), but no difference in mortality.

**Conclusions:** In critical illness, delayed enteral feeding appears to have little impact on either GE or the enterogastric feedback hormones. However, the association between delayed feeding and increased duration of ventilation and length of stay in the ICU supports the current recommendation that enteral nutrition should be commenced early. (Crit Care Med 2008; 36:1469–1474)

**Key Words:** early feeding; critical illness; enteral nutrition; gastric emptying; cholecystokinin; peptide YY

In humans, nutrient deprivation is associated with slowing of gastric emptying (GE) and changes in the secretion of gut hormones (1–4). For example, in healthy and obese subjects, GE is slowed after 4 days of fasting. In patients who suffer from chronic nutrient deprivation such as those with anorexia nervosa and chronic malnutrition (5, 6), GE is frequently markedly delayed and normalized with re-establishment of adequate nutrition support (7). In humans, nutrient replenishment of at least 2-wk duration is required for normalization of GE (7).

Nutrient deprivation is also associated with elevation of plasma concentrations of enterogastric feedback hormones, particularly cholecystokinin (CCK) and peptide YY (PYY) (2–4), which are known to slow GE (8–14). Again, concentrations of these hormones revert to normal in response to an adequate nutrient intake (15, 16). In rodents, there is evidence that chronic malnutrition potentiates the inhibitory effects of CCK on GE (17). These findings, therefore, suggest that slowing of GE by nutrient deprivation may be mediated by increasing enterogastric hormonal feedback in response to small intestinal nutrients.

Nutrition deprivation and malnourishment are well recognized problems in critically ill patients (18, 19) because the ability to provide adequate caloric needs, via enteral feeding, is frequently compromised by: (i) the delay in commencement of feeds (18) and (ii) interruptions of feeds due to impaired gastrointestinal motility and procedure-related fasting (20, 21). Depending on techniques of GE assessment, delayed GE occurs in 40% to 80% of critically ill patients and manifests clinically as intolerance to enteral feeding (21–25). Consequently, it has been estimated that up to 45% of critically ill patients have no feeds in the first 3–5 days of admission (18, 21, 25) and only 50% to 68% of the daily requirement is delivered to these patients (18–21, 26).

While the mechanisms underlying delayed GE in critical illness remain poorly understood, the impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients is a critical aspect of patient care.
defined, exaggerated inhibitory feedback on GE arising from the interaction of nutrients with the small intestine is likely to be important (27). This concept is further supported by findings which suggest that both fasting and nutrient-stimulation plasma CCK and PYY concentrations are elevated in critically ill patients (28, 29). Given the known relationship between nutritional status and GE in healthy subjects, the impacts of delayed enteral nutrition (EN) and the associated malnutrition on gastric motor function in these patients are also likely to be important. Although delayed nutritional support has been shown to increase septic complications and mortality (22, 30), its impact on GE or plasma concentrations of enterogastric feedback hormones has not been studied. This study, therefore, aimed to evaluate the effects of delayed enteral feeding on GE and plasma concentrations of CCK and PYY in the critically ill patients.

METHODS

Subjects

Studies were performed in 28 unselected critically ill patients (17M:11F; 55.3 ± 3.3 yrs; Acute Physiology and Chronic Health Evaluation (APACHE) II: 22.4 ± 1.2), who were admitted to a level 3, mixed medical and surgical intensive care unit (ICU). Patients were sedated, mechanically ventilated, able to receive EN and aged greater than 17 yrs. Exclusion criteria included patients receiving parenteral nutrition, recent (less than 4 wks) major surgery that involved opening the abdominal cavity or gastrointestinal tract, previous surgery of the esophagus or stomach, inability to place a naso- or orogastric feeding tube for feeding due to either technical failure or safety concerns (e.g., acute esophageal or gastric variceal bleeding), administration of prokinetic therapy (erythromycin or another macrolide antibiotic or metoclopramide) within 24 hrs prior to the study, and pregnancy or breast-feeding. All patients were receiving an insulin infusion according to a standard protocol, designed to maintain the blood glucose concentration between 6–8 mmol/l.

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. Written informed consent was obtained from the next of kin.

Study Protocol

Patients were enrolled within the first 10 hrs after admission to the ICU and were randomized to receive either early feeding within 24 hrs of admission or delayed feeding on day 4 of admission after GE assessment. Patients who were randomized to the delayed feeding group did not receive any other form of nutritional support including parenteral nutrition, although patients who were administered protocol for sedation received a low level of parenteral lipid as a component of this sedation.

A nasogastric tube (NGT) was inserted on admission in all patients and correct position of the tube was confirmed by routine X-ray. In the early feeding group, EN was commenced at a rate of 40 ml/h. Gastric aspirates were collected every 6 hrs as per clinical practice. If feeding was tolerated (aspirate volume <250 mL) the rate was increased by 20 ml/h until the prescribed maximum was reached. In accordance with usual practice in our ICU (20), nutritional requirements were determined by a dietician and based on the patient’s body mass index (BMI) (31), with feeding prescribed by an intensive care physician. If an aspirate >250 mL occurred, the feeding rate was reduced by half, or to the minimum rate of 20 ml/h. Prokinetic therapy was not administered throughout the study period. For patients in the late feeding group, the NGT was placed on free-drainage. For patients who received early feeds, the amount of calorie administered as well as the administered:prescribed caloric ratio over the first 4 days before the assessment of GE was collected.

Measurements of GE and gut hormones were performed on day 4 of admission. In the early feeding group, feeding was ceased 6 hrs before the study. The stomach was emptied by aspiration of the NGT and the volume of aspirate obtained was recorded. A test meal consisting of 100 mL of Ensure (complete, balanced nutrition; 1 kcal/mL; Abbott Australasia Pty Ltd) labeled with 20MBq 99mTc-sulphur colloid was instilled into the stomach over 5 mins via the NGT. GE was measured for 240 mins. Arterial blood samples were collected at predetermined intervals immediately before and following the meal for assessment of plasma glucose, and CCK and PYY concentrations. On completion of the study, nasogastric feeding was recommenced as clinically indicated.

All relevant details of the patient’s ICU admission were recorded, including demographics, admission diagnosis, type and level of sedation, inotropic support, days in ICU before study, APACHE II score on admission and on study day, and prior history of enteral feeding. The depth of sedation during and for 8 hrs prior to the study was assessed by Sedation-Agitation Scale (SAS) score (32). Sequential Organ Failure Assessment (SOFA) scores (33) on admission and on the study day were assessed and recorded.

Data regarding the patient’s secondary outcomes were also collected prospectively. These included: duration of mechanical ventilation, occurrence of ventilated associated pneumonia, length of ICU and hospital stay, and ICU and hospital mortality. Ventilator-associated pneumonia was defined as the presence of a new or progressive infiltrate along with at least two of the following signs and symptoms: a) purulent respiratory secretions; b) fever (body temperature >38°C) or hypothermia (body temperature <35°C); and c) leukocytosis (white blood cell count ≥10,000/ mm³) or leukopenia (total white blood cell count <<4500/mm³ or >15% immature neutrophils [bands] regardless of total peripheral white blood cell count) (34).

Techniques and Data Analysis

Gastric Emptying. The scintigraphic measurements of GE involved a dynamic study performed in ICU using a mobile gamma camera (Starcam 3200iXCT, General Electric, Milwaukee, WI, USA). Patients were studied supine at 30° head elevation and the camera was placed in the left anterior oblique position. Scintigraphic images were acquired for 240 mins (3-min frames). Data were corrected for radio-nuclide decay and y-ray attenuation (35). Regions of interest were drawn around the total stomach, which was subsequently divided into proximal and distal gastric regions. GE curves (expressed as percentage retention over time) were derived. The amount of the meal remaining in the total, proximal, and distal stomach at 0, 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 mins was calculated (35). The gastric half emptying time (t1/2) was not reported in the current study as the variable could not be determined in approximately one-third of the patients because the emptying did not reach 50% at 240 min. In the current study, delayed GE was defined by >10% meal retention at 240 mins (36).

Plasma CCK and PYY. Blood samples (5 ml) for the measurement of plasma CCK and PYY were collected into chilled ethylenediaminetetraacetic acid tubes, immediately before and at 60 mins and 120 mins after the delivery of the intragastric meal. Blood samples were centrifuged at 4°C within 30 mins of collection and stored at −70°C for subsequent analysis. Plasma CCK concentrations were measured by radioimmunoassay (37). The intra- 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. Plasma PYY concentrations were also measured by radioimmunoassay using an antiserum raised in rabbits against human PYY (1–36) (Sigma-Aldrich, St. Louis, MO). The intra- and interassay coefficients of variation were 12.3% and 16.6%, respectively. The minimum detectable concentration was 4pmol/l (37). Blood glucose concentrations were also measured using a portable glucometer (Precision
Statistical Analysis

Data are presented as mean ± SEM. Differences in the demographic characteristics, APACHE II score, SAS score, SOFA score, baseline blood glucose, and CCK and PYY concentrations between the two groups were compared using Student’s unpaired t-test. The differences in the proportion of patients with delayed GE, use of inotropes or morphine, and the secondary outcomes between the two groups were compared using Chi-square test, with Yate’s correction where appropriate. A two-way repeated measures analysis of variance (ANOVA) was used to evaluate the differences: (i) in the gastric retention of meal; (ii) in CCK and PYY responses to gastric nutrients between patients received early versus delayed feeds. The integrated changes in plasma CCK and PYY concentrations over the 120 mins after meal ingestion were expressed as area under the curve (AUC)

RESULTS

After randomization, 14 patients (8 male, 6 female; 54.9 ± 3.3 yrs) received enteral feeding within 24 hrs of admission. From ICU admission to the assessment of GE, the early feeding patients were fed for 60.4 ± 2.4 hrs and received a mean total calorie load of 2894 ± 198 kcal per patient, with an administered/prescribed caloric ratio of 72 ± 4%. Nutritional status was assessed in all patients as early nutritional support is recognized to play a crucial role in the care of those who are clinically malnourished. No patient had evidence of malnutrition or was severely underweight with all having a BMI of greater than 22 (Table 1). All patients in the early feeding group had feeds intermittently interrupted due to diagnostic imaging, therapeutic interventions, or nursing care activities (bed baths and dressing changes), all of which required fasting. The other 14 patients (10 male; 4 female; 56.3 ± 3.4 yrs) did not receive any form of nutrition before the measurement of GE on day 4. There were no differences in age, gender, BMI, APACHE score, admission diagnosis, types of sedation, the use of inotropic drugs, and SAS and SOFA scores between the two groups (Table 1). The scintigraphic procedure was tolerated well by all patients and no complications occurred in either group.

Gastric Emptying

GE as delayed in 18/28 (64%) of patients. In 32% (9/28) of patients, more than 50% of meal remained in the stomach at 240 mins after meal ingestion. The proportion of patients with delayed GE was similar between the groups (early feeding = 9/14 vs. delayed feeding = 9/14). Overall, there were no differences in the percentage of meal retained in the whole (p = .93; Fig. 1A), proximal (p = 0.53; Fig. 1B) or distal stomach (p = 0.54; Fig. 1C) among patients who received delayed or early feeding. The percentage of meal retained in the stomach did not correlate with the total number of calories received before the GE assessment at any time points (at 0 mins: r = .22, p = .19; at 60 mins: r = .22, p = .13; at 120 mins: r = .15, p = .22; at 240 mins: r = .21, p = .22).

Table 1. Demographic data and characteristics of critically ill patients who received early and delayed enteral feeding (data are mean ± SEM)

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Early Feeding (n = 14)</th>
<th>Delayed Feeding (n = 14)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.9 ± 3.3</td>
<td>56.3 ± 3.4</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>8:6</td>
<td>10:4</td>
<td>.69</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.3 ± 1.7</td>
<td>27.4 ± 1.9</td>
<td>.70</td>
</tr>
<tr>
<td>APACHE II score Admission</td>
<td>24.0 ± 1.7</td>
<td>22.9 ± 1.7</td>
<td>.46</td>
</tr>
<tr>
<td>Study day</td>
<td>22.5 ± 1.7</td>
<td>21.2 ± 1.7</td>
<td>.48</td>
</tr>
<tr>
<td>Diagnosis,* n (%)</td>
<td>Head injury 6 (42%)</td>
<td>7 (50%)</td>
<td>.99</td>
</tr>
<tr>
<td>Sepsis</td>
<td>6 (42%)</td>
<td>6 (42%)</td>
<td>.99</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>5 (36%)</td>
<td>4 (29%)</td>
<td>.70</td>
</tr>
<tr>
<td>Trauma</td>
<td>4 (29%)</td>
<td>6 (42%)</td>
<td>.45</td>
</tr>
<tr>
<td>Dissecting aortic aneurysm</td>
<td>1 (7%)</td>
<td>2 (14%)</td>
<td>.38</td>
</tr>
<tr>
<td>Burns</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>.32</td>
</tr>
<tr>
<td>Baseline blood glucose level (mmol/L)</td>
<td>7.3 ± .2</td>
<td>7.8 ± .2</td>
<td>.86</td>
</tr>
<tr>
<td>Sedation data</td>
<td>Opioid ± Benzodiazepine, n (%)</td>
<td>8 (58%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Propofol, n (%)</td>
<td>6 (42%)</td>
<td>4 (29%)</td>
<td>.69</td>
</tr>
<tr>
<td>SAS score on study day</td>
<td>2.0 ± .2</td>
<td>1.9 ± .2</td>
<td>.95</td>
</tr>
<tr>
<td>Inotrope data, n (%)</td>
<td>6 (42%)</td>
<td>7 (50%)</td>
<td>.99</td>
</tr>
<tr>
<td>SOFA score on study day</td>
<td>5.3 ± .9</td>
<td>4.8 ± .8</td>
<td>.72</td>
</tr>
<tr>
<td>Calories received prior to gastric emptying assessment (kcal)</td>
<td>2894 ± 198</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Administered: prescribed calorie ratio (%)</td>
<td>72 ± 4%</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*p > .05.

Plasma CCK and PYY Concentrations

Both plasma CCK and PYY concentrations increased after the gastric meal in the early feeding and delayed feeding groups (Fig. 2). However, there were no differences in either fasting or postprandial plasma CCK and PYY concentrations between patients who received delayed or early feeding (Fig. 2). Between t = 0–120 min, the integrative changes in plasma CCK (AUC_{0–120 min} = 190 ± 47 vs. 141 ± 44 pmol/L min, respectively; p = .45) and PYY (AUC_{0–120 min} = 360 ± 126 vs. 266 ± 99 pmol/L min, respectively; p = .53) were also similar among patients who received delayed or early enteral feeding.
Relationship Between GE and Plasma CCK and PYY Concentrations

Both baseline and postprandial plasma CCK and PYY concentrations were higher in patients with delayed GE than those with normal GE (Fig. 3). There was a trend for a positive correlation between fasting plasma CCK concentrations and meal retention at 60 mins \(r = 0.35; p = 0.07\), 120 mins \(r = 0.33; p = 0.09\), 180 mins \(r = 0.31; p = 0.10\) and 240 mins \(r = 0.34; p = 0.07\). Similarly, there was a positive correlation between fasting plasma PYY concentrations and meal retention at 60 mins \(r = 0.43; p = 0.02\) and 120 mins \(r = 0.42; p = 0.02\). There was a trend for an inverse relationship between the integrated changes in plasma CCK, but not PYY, concentrations and meal retention at 180 mins \(p = 0.13\) and 240 mins \(p = 0.12\). Overall, there was no difference between the integrated changes in plasma CCK and PYY levels in patients with delayed and normal GE (CCK: \(\text{AUC}_{0-120\text{ min}}: 158 \pm 42\) vs. \(179 \pm 48\) pmol/L min, \(p = 0.76\); PYY: \(\text{AUC}_{0-120\text{ min}}: 265 \pm 100\) vs. \(344 \pm 71\) pmol/L min, \(p = 0.60\)).

Secondary Outcomes

Critically ill patients in whom enteral feeding was delayed had a significantly greater duration of mechanical ventilation (13.7 \(\pm 1.9\) vs. 9.2 \(\pm 0.9\) days, \(p = 0.049\)) and length of stay in the ICU (15.9 \(\pm 1.9\) vs. 11.3 \(\pm 0.8\) days, \(p = 0.048\)) compared to patients who received early feeding. There was a strong correlation between the duration of ventilation and length of stay in the ICU \((r = 0.93, p < 0.05)\). However, the proportion of patients who developed ventilated-associated pneumonia did not differ between delayed and early feeding groups (6/14 vs. 3/14, \(p = 0.22\)). The overall mortality rates during both ICU (4/14 vs. 4/14, respectively) and hospital stays (6/14 vs. 6/14, respectively) were identical between the two groups.

DISCUSSION

This is the first randomized controlled study to examine the impact of delaying enteral feeding on GE and the entero-gastric hormonal responses. In critically ill patients who were well matched for age, gender, and other factors that are known to influence GE, delaying enteral feeds for 4 days had no effect on either GE or plasma concentrations of CCK and PYY. Delaying enteral feeding was, however, associated with prolonged mechanical ventilation and length of stay in ICU but no difference in mortality. These observations indicate that while the timing of initiation of enteral feeding is not a significant determinant of GE during critical illness, delaying enteral feeding adversely influences short-term outcomes in the critically ill, and supports the current recommendation that nutrition support should be commenced as early as possible.

Despite the relatively small sample size, the current study has a number of strengths. First, the randomization of patients in the timing of enteral feeding is likely to minimize selection bias. Second, GE was assessed by the gold standard technique, gastric scintigraphy (38). Third, the “4-day” criterion in the delayed feeding group was clinically relevant as this is the mean duration for which EN
was delayed in many studies reported in the literature (18, 21, 22, 25).

In contrast to healthy subjects (1), short-term nutritional deprivation of 4 days did not slow GE or disturb entero-gastric hormonal feedback activity in critically ill patients. There are a number of possible reasons that may account for this discrepancy. Although the similarity in GE between the early and delayed feeding groups could represent a type II error due to the small sample size, the differences in secondary outcomes between the groups argue against this possibility. As recent data suggest that GE in critically ill patients is related to the plasma concentrations of CCK and PYY (39), the lack of difference in the entero gastric hormonal responses between the early and delayed feeding groups are in accordance with the similarities in GE between the groups. Furthermore, the high prevalence of delayed GE (64%) in these patients with no apparent difference between the groups indicates that even with a very large sample size, there is unlikely to be any effect. Thus, the lack of impact of timing of feeding on GE suggests that other factors such as sedation, inotropic therapy, admission diagnosis, and illness severity are more likely to be important in mediating gastric motor dysfunction in critical illness (23–25), and overriding any effect of acute fasting on GE.

As only 72 ± 4% of prescribed nutrients were delivered to the patients, it is possible that the patients in the early feeding group received insufficient amount of nutrients to prevent the inhibitory effect of nutritional deprivation. While this amount of delivered calories appears inadequate, it does reflect the true performance of nutritional support in the clinical setting with the reasons for the interruption of feed consistent with those described by McClave et al (1999). The “threshold” of nutrient deprivation necessary to impair gastric motor function is currently unknown. It is also unclear whether the 4-day duration of deprivation in the current study was sufficient to alter GE. Re-feeding data from patients with anorexia nervosa suggest that the adaptive changes underlying fasting-induced slow GE may take as long as 2 wks to develop or revert (7). While determination of the “threshold” and “duration” of nutritional deprivation required to induce gastric dysmotility is of interest, it is of limited relevance to nutritional support during critical illness because of the adverse effects of delayed feeding on the duration of ventilation and ICU stay in these patients.

Fasting and postprandial plasma CCK and PYY concentrations were evaluated in the current study because of recent data suggesting that delayed GE in critically ill patients may be related to an enhanced entero gastric inhibition by duodenal nutrients (27) and that elevated plasma CCK and PYY concentrations in these patients may have a role in this phenomenon (39). In the current study, the higher fasting and postprandial plasma CCK and PYY concentrations in patients with delayed GE are in agree-
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