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CLINICAL RESEARCH

Proximal gastric response to small intestinal nutrients is abnormal in mechanically ventilated critically ill patients

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Abstract

AIM: To determine the response of the proximal stomach to small intestinal nutrients in critically ill patients.

METHODS: Proximal gastric motility was measured in 13 critically ill patients (49.3 ± 4.7 years) and 12 healthy volunteers (27.7 ± 2.9 years) using a barostat technique. Recordings were performed at baseline, during a 60-min intra-duodenal infusion of Ensure® (2 kcal/min), and for 2 h following the infusion. Minimum distending pressure (MDP), intra-bag volume and fundic wave activity were determined.

RESULTS: The MDP was higher in patients (11.7 ± 1.1 *vs* 7.8 ± 0.7 mmHg; $P < 0.01$). Baseline intra-bag volumes were similar in the 2 groups. In healthy subjects, a 'bimodal' proximal gastric volume response was observed. In patients, the initial increase in proximal gastric volume was small and delayed, but eventually reached a maximal volume similar to that of healthy subjects. In healthy subjects, the proximal gastric volume rapidly returned to baseline level after nutrient infusion (median 18 min). In contrast, the recovery of volume to baseline was delayed in critically ill patients (median 106 min). In 6 patients, the volume had not returned to baseline level 2 hours after nutrient infusion. In patients, fundic volume waves were less frequent ($P < 0.05$) and had lower amplitude ($P < 0.001$), compared to healthy subjects.

CONCLUSION: In critical illness, proximal gastric motor responses to small intestinal nutrient stimulation are abnormal.

Key words: Proximal gastric response; Small intestinal nutrient; Critical illness

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INTRODUCTION

Gastric intolerance to enteral feeding occurs frequently in critical illness and is a major obstruction to the provision of enteral nutrition[1,2]. Inadequate nutritional support adversely affects both morbidity and mortality[3,4]. The most common cause of feed intolerance is delayed gastric emptying[1,2,5], which has a prevalence of up to 50% in tertiary intensive care units[6]. Moreover, the mechanisms underlying poor gastric emptying in critical illness are not well understood.

Both proximal and distal gastric motility is considered important in normal gastric emptying of liquids[7,8]. In healthy subjects, there is a relaxation of the proximal stomach, reduction in antro-duodenal motility and an increase in isolated pyloric pressure waves in response to small intestinal feed-back[9,10]. This feed-back response is triggered by a caloric load of 2-3 kcal/min[9,10].

In critically ill patients, a marked reduction in antral motility and a poor coordination of antro-duodenal contractions has been reported during fasting[2,11]. There are, however, no data on the motor activity of the proximal stomach, during fasting or in response to small intestinal nutrients in these patients. The aim of the current study was to assess proximal gastric motor activity during small intestinal nutrient infusion in critically ill patients. We hypothesized that small intestinal feed-back to the proximal stomach in response to duodenal nutrients would be intensified, and increased proximal gastric relaxation would be observed. To minimize a variation in stimulation

due to erratic gastric emptying in critically ill patients, nutrient was infused directly into the duodenum. This provided a constant nutrient delivery at a physiological level to the small intestinal receptors.

MATERIALS AND METHODS

Subjects

Studies were performed in 13 medical, critically ill patients (11 male, mean age 49.3 ± 4.7 years), who were admitted to a level 3 intensive care unit between January and September 2004. Any patient aged greater than 17 years was eligible to be enrolled into the study if they were sedated, mechanically ventilated, required enteral nutrition and had no history of diabetes mellitus. Exclusion criteria comprised recent major abdominal surgery, any contra-indication to the passage of an enteral tube, usage of opioid analgesia, benzodiazepines or prokinetic therapy within the previous 24 h, previous gastric, oesophageal or intestinal surgery, unstable intra-cranial pressure or cervical spine injury. As part of the standard clinical practice in our intensive care unit, all subjects received a sliding scale insulin infusion to maintain blood glucose concentrations between 6 and 8 mmol/L. The demographic characteristics of the subjects are summarized in Table 1.

Studies were also performed in 12 healthy volunteers (8 male, mean age 27.7 ± 2.9 years), none of whom had a history of systemic or gastrointestinal disease, or was taking any medication. Volunteers were instructed to refrain from smoking for 24 h prior to the study.

Written informed consent was obtained from healthy subjects and the next of kin of the critically ill patients prior to enrolment into the study. The protocol was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital.

Table 1 Demographic characteristics of the studied subjects

	Critically ill patients (n = 13)	Healthy subjects (n = 12)
Age (yr)	49.3 ± 4.7[b]	27.7 ± 2.9
Sex (M:F)	11:2	8:4
BMI (kg/m^2)	29.7 ± 1.7	24.1 ± 1.0
APACHE Ⅱ score		Not applicable
On admission	24.1 ± 1.3	
Study day	24.7 ± 1.8	
Days in ICU prior to study	5.0 ± 0.2	Not applicable
Diagnosis	Head injury (2), motor vehicle accident (2), cardiac arrest and failure(3), acute pancreatitis (2), subdural haemorrhage, uro-sepsis, chronic obstructed airway disease, asthma	Not applicable

[b]$P < 0.01$ *vs* healthy subjects.

Measurements

Proximal gastric motility: Proximal gastric motility was measured using an electronic gastric barostat (Distender Series Ⅱ; G&J Electronics, Ontario, Canada)[12,13]. A thin flaccid-walled bag with a maximum capacity of 1000 mL was attached to the distal end of the assembly, which was connected to the system via pressure and volume ports. Changes in proximal gastric volume were measured indirectly by changes in the volume of the polyethylene bag.

Data were stored onto a Powermac 7100 computer (Apple Computer, Cupertino, CA), using custom-written data-acquisition software (Labview: National Instruments, Austin, TX). This software was also used to program the barostat to perform distensions in stepwise increments[14]. Recorded data were imported into a display and analysis program (Acqknowledge, Biopac System, Goleta, CA) for manual analysis. Intra-bag volumes were determined at 2 min intervals and the mean baseline volume was measured over 10 min immediately before the infusion. Changes in intra-bag volume during nutrient infusion were calculated as the difference between the actual bag volume and the mean baseline volume. The serial changes in bag volume during the infusion were plotted and compared. Proximal gastric relaxation was indirectly inferred by an increase in intra-bag volume[12].

Assessment of fundic slow volume waves was also performed. These were defined as changes in proximal gastric volume of greater than 30 mL that reverted in less than 2 min to a volume within 50% of the previous level[15]. The number and volume amplitude of fundic slow waves (per 10 min) were determined during fasting and in response to small intestinal nutrient infusion.

Blood glucose concentration: Marked hyperglycaemia is one of the humoral factors that may play a role in mediating small intestinal feed-back and adversely affects gastric motility[16]. Blood glucose concentrations were measured using a portable glucometer (Precision Plus, Abbott Laboratories, Bedford, USA)[17] at timed intervals during the study.

Protocol

Patients and healthy subjects were studied after at least 6-hours fasting and in a 30 degree recumbent position. To standardise the sedative regime in patients, propofol alone was used, and opioids, benzodiazepines or prokinetic agents were not administered for 24 h prior to and during the study. In the healthy subjects, the barostat catheter and infusion tube were swallowed and allowed to pass into the correct position spontaneously, without the assistance of endoscopy. After insertion of the barostat catheter to a depth of 55 cm, the balloon was inflated with 400 mL of air and the catheter was pulled back until resistance was felt[18]. Duodenal nutrient infusion was achieved by inserting a silicon-rubber catheter (Dentsleeve, Adelaide, Australia) with a central feeding lumen and lead-weighted tip into the duodenum. The correct positioning of the infusion catheter was determined by continuous measurement of the antro-duodenal trans-mucosal potential difference (TMPD) gradient[18]. Radiological confirmation was not performed.

In patients, placement of both the barostat catheter and post-pyloric feeding tube was performed at the bedside with endoscopic assistance, without additional sedation to that required for ventilation. A 12 French x 114 cm naso-duodenal feeding tube (Flexiflo, Abbott,

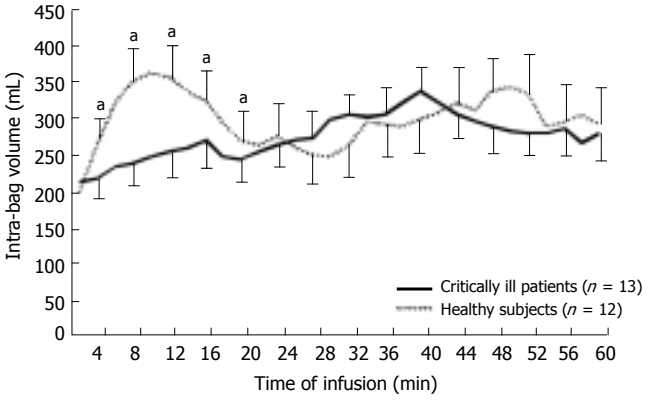

Figure 1 Changes in proximal gastric volume during the 2 kcal/min infusion, in healthy (dotted line, n = 12) and critically ill (solid line, n = 13) subjects. Data are mean ± SE. $^{a}P < 0.05$ *vs* healthy subjects.

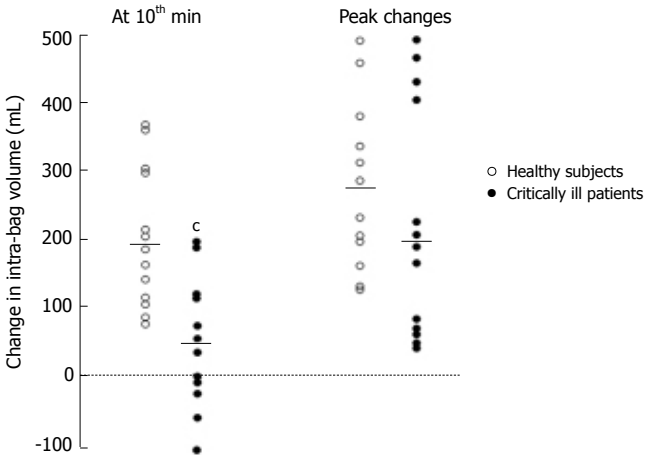

Figure 2 Changes in proximal gastric volume from baseline at the 10th minute and at peak level during the nutrient infusion, in healthy (open circle, n = 12) and critically ill (closed circle, n = 13) subjects. $^{c}P < 0.001$ *vs* healthy subjects.

Ireland) was inserted into the duodenum over a guide-wire (THSF-35-260, Cook, Australia). The barostat catheter was then guided through the mouth into the stomach by the endoscope. The barostat balloon was inflated with 400 mL of air and gently retracted into the fundus under direct vision. Gastric contents (air and fluid) were completely aspirated prior to withdrawal of the endoscope. Correct placement of the naso-duodenal feeding tube was confirmed at the time of placement by measurement of the TMPD gradient[18], and subsequently by radiography[11].

After confirming that the catheters were positioned correctly, air in the barostat balloon was aspirated and the catheter was connected to the barostat. The minimum distending pressure (MDP), defined as the first pressure level that provided an intragastric bag volume of more than 30 mL, was determined[19]. The baseline pressure for the study was then set at MDP + 2 mmHg[12]. All studies began with a 15-min baseline recording, during which normal saline was infused into the duodenum at 240 mL/h. Each subject then received a 60-min duodenal infusion of Ensure® (Abbott Laboratories, Ohio, USA; nutrient content: 13% protein, 64% carbohydrate, 21% fat; energy density: 1 kcal/mL) at 2 kcal/min. Barostat recordings were performed during the nutrient infusion and continued for 2 h after the infusion was ceased. Blood samples for the measurement of blood glucose concentrations were collected at baseline and at 20-min intervals during the nutrient infusion.

Statistical analyses

Data are presented as mean ± SE. The differences in demographic characteristics, baseline volume, MDP and fundic volume waves between the healthy subjects and critically ill patients were compared using Student's unpaired t-test. A repeated measures mixed-model analysis of variance (ANOVA) was used to compare the proximal gastric volume and blood glucose responses between the groups, with time and treatment as the factors. Student's unpaired t-test was used to compare the maximum changes in proximal gastric volume between the 2 groups. The time required for the proximal stomach to return to baseline volume following nutrient stimulation was expressed as median and interquartile range (IQR), and differences between the groups were assessed using the Mann-Whitney test. A $P < 0.05$ was considered statistically significant.

RESULTS

Oral intubation of the assembly was well tolerated by both patients and healthy subjects and no complications occurred in either group. At endoscopy, 2 patients had a small amount of feed residue (< 100 mL) in the stomach and duodenum.

Baseline measurements

The MDP was higher in critically ill patients than in healthy subjects (11.7 ± 1.1 mmHg *vs* 7.8 ± 0.7 mmHg, $P = 0.006$). Baseline proximal gastric volumes were similar between the two groups (patients: 211 ± 48 mL *vs* healthy: 191 ± 24 mL).

Proximal gastric volume response to small intestinal nutrients (Figures 1 and 2)

In the healthy subjects, there was a "bimodal" proximal gastric volume response to small intestinal nutrients, with the first peak occurring within 15 min of the infusion. The proximal gastric volume had reduced by 57 ± 4 % (mean volume reduction = 184 ± 24 mL) at 30 min of the infusion, after which it increased to a second smaller peak at 50 min. In critically ill patients, the increase in proximal gastric volume in response to small intestinal nutrients was initially slower and smaller than in healthy subjects (change in volume at 10th min: 45 ± 26 *vs* 196 ± 29 mL; $P < 0.001$). The proximal gastric volume did not peak until 40 min after the start of the infusion, but eventually reached a similar level to the healthy subjects. The maximal increase in proximal gastric volume did not differ between the two groups (patients: 199 ± 35 mL *vs* healthy: 233 ± 76 mL) (Figures 1 and 2).

Recovery of proximal gastric volume after duodenal nutrient stimulation (Figure 3)

The time course for the proximal stomach to return to baseline volume after nutrient stimulation was assessed

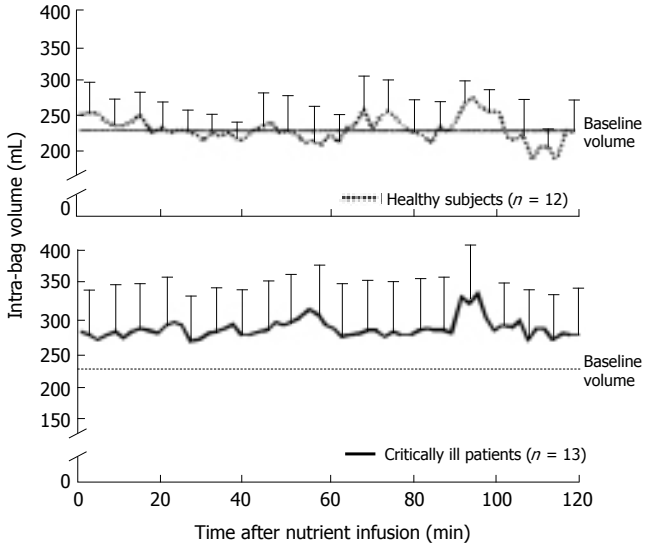

Figure 3 Time course for the proximal gastric volume to return to baseline level after nutrient stimulation, in healthy (dotted line, $n = 12$) and critically ill (solid line $n = 13$) subjects. Data are mean ± SE.

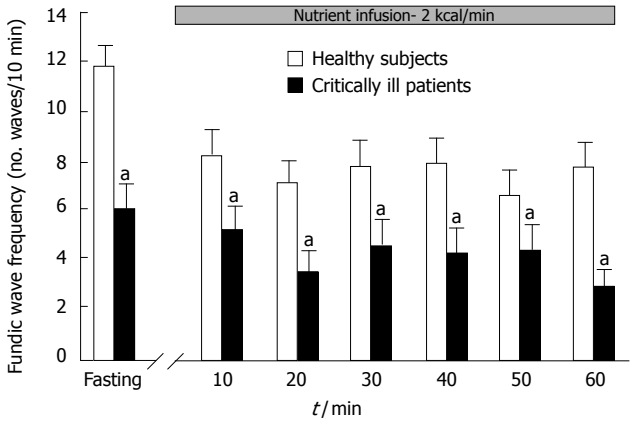

Figure 4 Fundic slow volume waves (per 10 min) during the 2 kcal/min nutrient infusion, in healthy (open bar, $n = 12$) and critically ill (closed bar, $n = 13$) subjects. Data are mean ± SE. [a]$P < 0.05$ *vs* healthy subjects.

by analysis of the proximal gastric volume during the 2 hour period following the infusion. In healthy subjects, the proximal gastric volume had returned to baseline level within 30 min after cessation of the nutrient infusion (median = 18 min; IQR: 0-24 min). In patients, the time required for the proximal stomach to return to baseline was significantly longer than in healthy subjects (median = 106 min; IQR: 47-120 min; $P < 0.001$). In only 2 of the 13 patients, the volume had returned to baseline within 30 min of cessation of the infusion. In 6 patients, the proximal gastric volume had not returned to baseline level at 2 h after the nutrient infusion was ceased (Figure 3).

Fundic volume waves during fasting and in response to small intestinal nutrients (Figure 4)

The frequency of fundic volume waves was less in critically ill patients during both fasting and nutrient infusion, compared to healthy subjects ($P < 0.05$) (Figure 4). In addition, the volume amplitude of fundic waves was smaller in patients than in healthy subjects (44 ± 3 mL *vs* 87 ± 8 mL; $P < 0.001$).

Blood glucose concentration

Blood glucose concentrations were higher in critically ill patients at baseline (7.0 ± 0.3 mmol/L *vs* 5.2 ± 0.2 mmol/L; $P < 0.001$) and during nutrient infusion (8.3 ± 0.2 mmol/L *vs* 7.2 ± 0.2 mmol/L; $P < 0.01$), compared to healthy subjects. However, the magnitude of increase in blood glucose concentration during the infusion did not differ between the 2 groups.

DISCUSSION

This is the first study to evaluate the motor responses of the proximal stomach to small intestinal nutrient infusion in critically ill patients. Our data demonstrate that in these patients, (1) proximal gastric relaxation is delayed with no change in the magnitude of the response, (2) fundic wave activity is reduced, and (3) the recovery of proximal gastric volumes to pre-stimulation levels is delayed.

Although delayed gastric emptying is a major clinical problem in critically ill patients, only distal gastric motor activity has been previously examined[2,11]. However, abnormal proximal gastric motility has been demonstrated in non-critically ill patients with gastroparesis, such as those with diabetes mellitus[14,20,21], and may play an important role in slowing gastric emptying[7,8]. Our findings provide a possible mechanism for the delay in liquid gastric emptying frequently found in critical illness. Failure of the relaxed proximal stomach to return to baseline volume after nutrient stimulation in these patients provides a reservoir for retention of gastric residue in the fundus. Such a prolonged pooling of gastric content is likely to contribute to both delayed gastric emptying and gastro-oesophageal reflux[5,7,8,22]. Fundic volume waves are thought to be involved in the redistribution of proximal gastric content distally for emptying and high fundic wave activity is associated with accelerated gastric emptying of liquids[23]. It would seem likely that reduced fundic wave activity may contribute to the slowing of gastric emptying.

The mechanisms underlying the changes in proximal gastric motility in critical illness are unknown. The initial delay in proximal gastric relaxation could relate to physical restriction from a combination of positive mechanical ventilation and high intra-abdominal pressure (reflected by a higher MDP) present in critical illness[24]. However the eventual relaxation to normal values suggests that this is unlikely to be the cause. Impaired gastric accommodation has been described in diabetes mellitus with autonomic neuropathy[25-27]. Autonomic dysfunction has also been reported in critically ill patients[28] and could cause both a delay in gastric relaxation and potentially a prolonged recovery in gastric volume via impairment of different components of the autonomic nervous system. In light of recent reports of interactions between inflammatory mediators, neurotransmitters and intrinsic neural pathways[26,29], it is also possible that increased cytokine production in critical illness may play a role. Sedative drugs have been reported to alter gastric emptying and proximal gastric motility[30,31]. While propofol inhibits gastric emptying in animals[30], its effects in humans are

less clear[31,32]. A small study in humans showed that a combination of propofol and morphine could result in a smaller proximal gastric volume compared to morphine alone, but gastric emptying is similar between the two groups[31]. The mechanisms underlying the prolonged recovery of the proximal stomach to baseline volume are also unknown. Although hyperglycemia increases proximal gastric relaxation in both healthy and diabetic subjects[16,17], the elevation of blood glucose levels in our patients was minimal and in the 'physiological hyperglycemia' range, which seems unlikely to significantly contribute to the prolonged relaxation. Similarly, gastric relaxation due to opiate drugs such as morphine[32] is unlikely to explain our findings, as they were withheld for 24 h prior to the study. The neurotransmitter nitric oxide is important in mediating proximal gastric relaxation[33]. Nitric oxide synthesis is increased in critically ill patients[34,35] and could contribute to prolonged proximal gastric relaxation. The discordant findings of impaired relaxation followed by failure to regain normal tone suggest the involvement of multiple mechanisms. Further studies are required to determine the involvement and interaction of potential mechanisms.

The bimodal pattern of proximal gastric relaxation in our healthy subjects in response to small intestinal nutrients is intriguing. This was a consistent observation in all the 12 healthy subjects. Physiologically, it is possible that the proximal gastric volume reduction in the middle of the infusion represents proximal gastric contractions to redistribute feed to the distal stomach. This pattern of proximal gastric response, however, has not previously been reported in barostat studies during intra-gastric[22,23] or intra-duodenal[36] nutrient delivery. In the Barbara *et al*[36] study, intra-gastric volume recording was only performed for 30 min during duodenal nutrient infusion, which may have been too short to detect the second peak. Although the reasons for differences in the proximal gastric response reported to date remain unclear, they may relate to the site of nutrient administration and duration of infusion.

There were a number of issues that should be acknowledged in the current study. Intra-gastric delivery of nutrient was avoided for several reasons. Firstly, the frequently observed slow gastric emptying in this group of patients[6] may lead to an unreliable assessment of the feed-back response, as a constant delivery of 2-3 kcal/min of nutrient to the small intestine is required[9,10]. Secondly, gastric motility and emptying of a liquid meal can be altered by the presence of a barostat balloon, which redistributes the meal to the distal stomach, increases intra-gastric pressure and accelerates gastric emptying, with 50% of the liquid meal emptying in the first 10 min[22]. Thereafter, the rate of emptying is dependent on the phasic-tonic contraction of the proximal stomach. In addition, although the effects of performing endoscopy on gastric motility are unknown, they are unlikely to be important in the context of nasogastric tube intubation. The procedure was performed using a skinny endoscope with minimal air inflation and all gastric contents were aspirated from the stomach immediately prior to the study. Barostat studies are best performed in the sitting, upright position[19], but it is impossible to study critically ill patients in this posture. The current study was thus performed in a 30 degree recumbent position in both patients and healthy subjects, to minimize the effects of posture on bag volume. Hebbard *et al*[37] recommended that if upright posture is not possible, then the same posture should be controlled between the study groups. In addition, proximal gastric compliance was not assessed. Although this would be of major interest, it was not performed because of concern that positive intra-bag pressures would potentially interfere with patient ventilation, due to splinting of the diaphragm. Finally, although our patients were significantly older, we do not believe this would substantially affect the study results, as healthy aging does not affect proximal gastric motor responses to a meal[38].

In conclusion, the proximal gastric response to small intestinal nutrients is abnormal in critical illness, characterised by a prolonged relaxation after nutrient stimulation and a reduction in fundic wave activity. The potential contribution of these proximal gastric motor abnormalities to delayed gastric emptying in critically ill patients requires further study.

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