

**A thesis submitted for the degree of
Doctor of Philosophy**

Title:

Gastro-duodenal motility & nutrition in the critically ill.

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List of abbreviations.

3-OMG - 3-O-methyl glucose
5-HT - serotonin
ACCP - American College of Chest Physicians
AD - antro-duodenal
APD – antro-pyloro-duodenal
APACHE II score – acute physiology and chronic health evaluation II score
ATP - adenosine triphosphate
AUC - area under curve
BMI - body mass index
BT₅₀ - breath test gastric half emptying time
cAMP - cyclic adenosine monophosphate
CCK - cholecystokinin
cGMP - cyclic guanosine monophosphate
CI – confidence interval
C_{max} - maximal concentration
CO₂ – carbon dioxide
EIT - Electric impedance tomography
EN- enteral nutrition
GE - gastric emptying
GEC – gastric emptying coefficient (breath test)
GLP-1 - glucagon-like peptide-1
GRV(s) – gastric residual volume (s)
h – hour(s)
ICH = intracranial haemorrhage
ICP- intracranial pressure
ICU – intensive care unit
IL-1 - interleukin-1
IPPWs - Isolated pyloric pressure waves
IV – intravenous
L/R - lactulose / L-rhamnose
min – minutes (s)
MMC - migrating motor complex
MRI - Magnetic Resonance Imaging
NGT - nasogastric tube.
NO - nitric oxide
NS - not significant
op - operative
OR- odds ratio
Postop - postoperative
Pts - patients
PYY - Peptide YY
REE - Resting energy expenditure
resp = respiratory failure
s – second(s)
SCI - spinal cord injury
scintigraphic t_{1/2} – scintigraphic half emptying time

SEM – standard error of the mean
TBI - traumatic brain injury
Tmax - time to maximal concentration
TMPD - transmucosal potential difference
TNF- α - tumour necrosis factor- α
TPN – total parenteral nutrition

Summary of thesis

Gastro-duodenal motility & nutrition in the critically ill

Inadequate delivery of nutrition to the critically ill is common, and may adversely affect clinical outcomes, including survival. This thesis reports studies designed to characterise the gastrointestinal dysfunction underlying feed intolerance in the critically ill, as well as the pathophysiology of these dysfunctions, and investigate potential therapeutic measures.

While it has been established that enteral nutrition is frequently unsuccessful in the critically ill, assessment of the success of feeding in an Australian intensive care unit (ICU) had not been performed previously. A prospective survey examined the incidence of, and risk factors for, feed intolerance in the ICU at the Royal Adelaide Hospital and demonstrated that, in 40 patients receiving enteral feeding, only about 60% of their nutritional requirements were met at the end of the first week. The main cause for this lack of success was large gastric residual volumes, indicative of delayed gastric emptying (GE). This study, accordingly, quantified the limitations of nutritional delivery in contemporary practice in a local ICU. The results suggest that a better understanding of the pathogenesis underlying this problem is warranted in order to direct research into improved therapies.

Scintigraphy is the most accurate technique to measure GE, but is difficult to perform in the ICU. A simpler, more convenient, test would increase the accessibility of GE measurement for both research and clinical purposes. A study comparing a breath test technique and gastric residual volume measurement to the scintigraphic measurement of GE in 25 mechanically ventilated patients demonstrated that GE measured by a breath test technique closely correlated with that measured by scintigraphy. While the breath test had a specificity of 100% it only had a sensitivity of about 60% in the prediction of delayed GE. Similarly, gastric residual volume measurement correlated with scintigraphic measurement of GE but also lacked sensitivity. The breath test has previously been demonstrated to be highly reproducible and it represents a useful option for repeated measurement of GE in the same patient. It is therefore likely to be useful to determine changes in GE over time or in response to a therapeutic intervention.

There is a lack of information about the prevalence and determinants of delayed GE in the critically ill. Previous studies have substantial limitations and scintigraphic measurement of GE has only rarely been used. A study comparing GE measured by scintigraphy in 25 patients to 14 healthy subjects demonstrated that GE was delayed in approximately 50% of the ICU patients (>10% retention at 4h) and markedly delayed in about 20% (>50% retention at 4h). Patients with trauma and sepsis appeared to have a relatively higher prevalence of delayed GE (80% and 75% respectively). In addition, the longer the patient had been in ICU the more normal the rate of GE. Quantification of delayed GE may prove useful by defining patients who may benefit from preventative or therapeutic options.

The abnormalities in gastrointestinal motility underlying delayed GE in the critically ill are poorly characterised. Simultaneous manometric and gastric emptying measurements were performed in 15 mechanically ventilated patients and 10 healthy subjects. These studies demonstrated that delayed GE was associated with reduced antral activity, increased pyloric activity and increased retrograde duodenal activity in the patients. Persistent fasting motility during feeding was also frequently observed. Furthermore, the feedback response to small intestinal nutrients was enhanced. This latter observation may provide an explanation for the delayed GE and warrants further investigation. Recent studies suggest that the hormone

cholecystokinin may be a mediator of increased small intestinal feedback and, if confirmed, this has clear therapeutic implications.

Nutrient absorption has rarely been measured in the critically ill. GE and glucose absorption (using 3-O-methyl glucose) were measured simultaneously in 19 ICU patients and compared to 19 healthy subjects. Glucose absorption was shown to be markedly reduced in the patients. Slow GE was associated with delayed, and reduced, absorption. However, glucose absorption was also reduced in patients with normal GE suggesting that reduced glucose absorption in critical illness is only partly due to delayed GE. Accordingly, measures to improve the effectiveness of GE and thereby improve overall nutritional status may be compromised by abnormal small intestinal absorption. The mechanisms underlying this warrant further investigation.

A number of therapeutic options directed at improving the delivery of nutrition were examined. In a study involving 20 mechanically ventilated patients, administration of 200mg erythromycin intravenously was shown to be superior to placebo for treating feed intolerance. The optimal dose of erythromycin, however, was unclear. In a subsequent study involving 35 ICU patients, GE was measured using a breath test technique, before and after 2 different doses of erythromycin or placebo and a 'low' intravenous dose (70mg) of erythromycin appeared to be as effective as a 'moderate' dose (200mg). Both doses were only effective in subjects who had delayed GE at baseline. Based on the outcome of these studies, low doses of erythromycin have subsequently been routinely used to treat feed intolerance in the critically ill patients at the Royal Adelaide Hospital.

Animal and human studies suggested that the antibiotic, cefazolin, may have a prokinetic effect. Cefazolin, however, did not demonstrate similar prokinetic activity at a 'low' dose (50mg) in a critically ill cohort. The results of this study do not support the use of this agent, at this dose, as a prokinetic, in this population. If nasogastric administration of nutrition proves unsuccessful an alternative is to infuse nutrient directly into the small intestine. However, the placement of feeding tubes distal to the pylorus is technically difficult. A novel technique for postpyloric tube insertion was examined with promising results.

In summary, the studies described in this thesis have provided a number of insights relevant to the management of the critically ill by quantifying the prevalence of feed intolerance and delayed GE, characterising some of the disturbances in gastrointestinal motility underlying this problem, and evaluating a number of therapeutic interventions.

Declaration

The work reported in this thesis has been submitted to the University of Adelaide for the degree of Doctor of Philosophy. The studies reported herein are entirely original and were performed by the author between 1999 and 2005. This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis (as listed in Appendix A) resides with the copyright holders of those works.

Signed

Marianne Chapman

Date

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Background and review of literature

Chapter 1

Introduction

Cachexia and weight loss are frequent sequelae of an admission to an intensive care unit. This is in part due to the metabolic response to critical illness but also reflects our inability to provide adequate, safe nutrition to these patients. This area has been neglected in the past in favour of research into resuscitation, monitoring and specific clinical therapies. The work by the candidate that is presented in this thesis was performed in an attempt to redress this deficiency. The aim of this work was to improve our understanding of nutritional issues in severe illness and evaluate ways of addressing this. The ultimate goal is to improve nutrition in the critically ill with the expectation that this will improve clinical outcomes.

Chapter 2

The role of enteral nutrition in the critically ill

2.1 Introduction

In the care of the critically ill, nutrition is likely to have an important impact on outcome, particularly in patients who remain in the intensive care unit (ICU) for a prolonged period of time. Although enteral delivery of nutrition is considered to be superior to intravenous infusion, it is often compromised by disordered gastrointestinal function. The prevalence, pathophysiology and treatment of feed intolerance in these patients represent a major focus of the work conducted by the author, thus an appreciation of the role of enteral nutrition is essential to the understanding of these studies.

The following issues will be addressed in this chapter:

1. The importance of nutrition in both general hospital and critically ill patients
2. Rationale and limitations for using the enteral route for administration of nutrition.
3. The importance of achieving nutritional goals.
4. Composition of nutrition.
5. Timing of initiation of nutrition after admission to ICU.

2.2 The importance of nutrition

While the importance of nutrition appears to require no confirmation, a short period of starvation may be harmless or even beneficial during severe illness. Furthermore the optimal timing of initiation, route, appropriate composition and amount of feeding is as yet unclear. Prior to exploring the literature on nutrition in the critically ill, an examination of the prevalence and sequelae of malnutrition in ward patients is relevant to this thesis for several reasons. Firstly, it gives an historical perspective of nutritional support. Secondly, it is likely to be indicative of the consequences of malnutrition in the intensive care patient. Also poor nutrition is likely to become most evident after the patient is discharged from the ICU to the ward.

2.2.1 Historical perspective

Historically, recognition of the increase in morbidity and mortality associated with malnutrition in surgical patients (Dempsey et al., 1988; Dudrick et al., 1968) underpinned the development of nutritional support which was initially in the form of total parenteral nutrition (TPN) (Warnold and Lundholm, 1984). The administration of TPN became common practice in ICUs in the 1960s (Warnold and Lundholm, 1984). Several technological advances in delivery systems, solutions and protocols were required before TPN became feasible (Dudrick, 2006). In temporal order these included; intravenous (IV) infusion of glucose using metal needles which occurred in 1924, infusion of hypertonic dextrose, insulin and protein by peripheral vein in surgical patients in 1944, and subclavian venous access which became possible in 1956. In 1967 long term TPN via a subcutaneously inserted sterile plastic subclavian line became a clinical possibility.

2.2.2 Prevalence, consequences and treatment of malnutrition in ward patients

Pre-existing malnutrition is common in hospitalised patients. The reported prevalence varies between 13 and 78% in acute care patients (Kubrak and Jensen, 2006); this substantial variation reflecting differences in definitions, diagnostic methodologies, and patient sub-populations. The consequences of malnutrition in hospital patients are significant, and include an increase in infective complications (Baker et al., 1982; Chandra, 1983; Shukla et al., 1985), prolonged length of stay (Robinson et al., 1987) and increased mortality (Hickman et al., 1980; Mullen et al., 1979; Studley, 1936). Furthermore, inadequate nutritional support (i.e. underfeeding) during hospital stay is also associated with increased mortality in elderly (over 65 years of age), general ward patients (Sullivan et al., 1999). However, death is likely to be preceded by a period of reduced nutritional intake, and it is conceivable that the ability to take oral and other forms of nutrition may be related to the severity of illness. As all these studies are observational and did not include an interventional arm they provide only indirect evidence that nutritional support is beneficial.

Few studies have examined the effect of nutritional support on the outcome of hospital patients. A multicentre trial demonstrated that the administration of TPN to malnourished surgical patients preoperatively did not improve mortality and increased the risk of infectious complications (1991). However, it is now accepted that enteral nutrition is superior to TPN (see section 2.3) and it is not known if preoperative *enteral* nutritional support to this group of patients may have a benefit. Large scale multicentre studies in patients following cerebrovascular accidents indicated that nutritional supplementation, enteral nutritional support and the use of percutaneous enterogastric tubes did not improve outcome overall (Dennis et al., 2005a, b). Early nasogastric feeding in those who could not swallow did improve mortality, but those who had improved survival had poor neurological outcome. The reasons for this are unclear. It is possible that the prognosis of stroke victims who require nutritional support is poor so that any beneficial effect is insignificant. In addition, adverse effects (e.g. aspiration, hyperglycaemia) associated with the administration of nutrition may counter balance any benefits. These studies may not be of great relevance to critical illness where many patients who are unable to sustain oral intake, sometimes for a prolonged period, potentially have an excellent long term outcome.

2.2.3 Impact of malnutrition on critical illness

Based on the information above it would seem likely that malnutrition would frequently be present in patients admitted to ICU, and that it would affect survival. Dardaine et al performed an observational study on 116 consecutive admissions to ICU of patients over 70 years of age who were treated with mechanical ventilation. Nutritional status on admission was assessed by measuring mid arm circumference, which was less than 10% of normal in 16% of women, and 29% of men. This was associated with a higher mortality at 6 months (Dardaine et al., 2001). These data are supported by a recent Australian study evaluating 433 ICU admissions. A body mass index (BMI) of <18.5 occurred in 6% of admissions, and BMI was found to be linearly and inversely related to mortality (Peake et al., 2006). Not only is nutritional status on admission to ICU a concern. During ICU stay, patients exhibit both a pronounced catabolism and a down-regulation of normal anabolic activity, leading to significant loss of weight and body protein stores (Hill, 1998). The marked decrease in lean body mass and protein stores leads to the loss of essential structural and functional proteins required for restoring and maintaining homeostasis. The standard management of the catabolic response to injury and illness has centred on optimizing nutritional intake, and, although there is limited direct

evidence confirming that nutritional support of critically ill patients is associated with a beneficial outcome, this is widely accepted as best practice.

2.2.4 Nutritional support in the critically ill

Many studies relating to nutritional support in the critically ill are inconclusive due to significant flaws in their design. The most common problem relates to enrolment of inadequate numbers of patients rendering individual studies underpowered to demonstrate a benefit. In the absence of sufficiently powered multicentre trials, systematic reviews and meta-analysis, using statistical techniques to combine data from a number of small but otherwise high quality studies, may provide further information. Interpretation must take into account the possibility of publication bias, the selection criteria for including and excluding studies, and the degree of heterogeneity of the studies included. As well as small numbers, there is a lack of consistency in the outcome measures used. Only clinically relevant outcome measures can be considered important. For critically ill patients these should include survival, infective complications, and ICU and hospital length of stay (Simpson and Doig, 2005). Improvement in surrogate endpoints such as weight, or inflammatory markers may not translate into survival benefit. No studies have examined the effect of nutrition on long term survival or quality of life following critical illness.

2.2.4.1 TPN versus ‘standard care’

TPN has never been formally evaluated against ‘standard care’ (IV 5% dextrose and oral diet when possible) in a representative population of critically ill patients (Doig GS, 2005; Heyland, 1998). It has been evaluated against ‘standard care’ in a small group of critically ill patients after liver transplant. No clinically significant benefit of TPN was demonstrated, although nitrogen balance was better maintained, and there was a trend to a shorter stay in ICU (Reilly et al., 1990). However, this study was probably underpowered to demonstrate a benefit (28 patients enrolled). Also liver transplant patients are a highly specialised group and not truly representative of a mixed ICU population. Several studies have failed to show a benefit of TPN over standard care in surgical patients if oral nutrition can be started within 10 days (Brennan et al., 1994; Sandstrom et al., 1993; Wu, 1995). These include patients who would be admitted to ICUs in some centres, however, their sickness severity is not as high as a true mixed ICU population and extrapolation of these results to the management of patients in ICU should be done with caution. Based on this limited evidence it is now generally accepted that, when enteral nutrition (EN) is not possible initially, TPN should only be commenced if EN cannot be commenced for more than 7-10 days. It is suggested that the complications of TPN are equivalent to the complications of nutritional deprivation up to 10-14 days but as that time is exceeded, the complications of fasting become more significant. In summary, at this time there is no evidence to suggest that TPN is of benefit as a nutritional support in the critically ill population. In patients who cannot be given enteral nutrition for 10 days or more TPN is administered to prevent starvation but this practice is not based on any scientific evidence. There is currently an Australasian study ongoing which is randomising critically ill patients who can't be fed enterally to be given TPN or standard therapy and the results of this study should guide future management.

2.2.4.2 EN versus ‘standard care’

While there is no evidence that the administration of TPN is better than a short period of starvation, there is some evidence to suggest that EN is better than standard care in ICU

patients. Hasse et al in 1995 showed that starting EN after liver transplant in 31 patients reduced the incidence of postoperative infections when compared to usual isotonic fluids and oral diet when possible (Hasse et al., 1995). However, this study is small and in a highly selected group. A recent meta-analysis of 5 studies (including patients with trauma, pancreatitis, post-oesophagectomy, bleeding oesophageal varices and acute alcoholic hepatitis) showed a 12% reduction in mortality with enteral feeding compared to 'standard care' (95% confidence interval (CI); 2%-21%; p=0.02) (Doig GS, 2005) (Figure 2.1).

NOTE:
This figure is included on page 28
of the print copy of the thesis held in
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Figure 2.1 Results of meta-analysis of 5 studies evaluating EN vs. 'standard care' (IV fluids and oral nutrition when possible). The data demonstrate that EN is associated with reduced mortality compare to standard care. Reproduced with permission (Doig GS, 2005).

In summary, current evidence suggests that nutritional support is important in the critically ill particularly in longer stay patients. There is no evidence to support commencing TPN before about day 10 of fasting but enteral nutrition is better than IV fluids alone. However a comparison between the administration of enteral and parenteral administration of nutrition would be of interest. (See below).

2.3 Route of feeding

While there are little data on the benefits of nutritional support in general, several studies have been performed in ICU patients examining the optimal route of feeding. Since oral intake is usually impossible in critically ill patients, both the enteral and parenteral routes are routinely used, sometimes in combination. Where possible, EN alone is the preferred route for administration of nutrient in most Australasian intensive care units (unpublished data from survey by D Heyland et al). The evidence for this is discussed below. Most studies have been performed on specific groups of ICU patients and the extrapolation of these results to a mixed ICU population should be done with caution.

2.3.1 EN versus TPN in critically ill trauma patients

EN has been compared to TPN in several studies in patients following severe trauma. In a study reported in 1992, Kudsk et al randomised 92 abdominal trauma patients to EN (via a jejunostomy) or TPN and demonstrated that sepsis was less frequent in the EN group. Thus, pneumonia occurred in about 30% of patients on TPN and about 10% of those on EN. The benefit was greatest in those with a higher abdominal trauma index (Kudsk et al., 1992). A meta analysis (excluding the Kudsk data), of 8 randomised controlled trials including 230 patients following blunt or penetrating trauma or complicated surgery (Moore et al., 1992), indicated that the risk of septic complications was reduced by half with the use of EN compared to TPN. It is not clear how many of these patients were in an ICU, however as the overall mortality rate was only about 10% it is likely that many of them were not. Only 2 of these studies have been published so complete details on the patients enrolled are not available. A subsequent study by Dunham et al comparing EN to TPN and to combined EN and TPN showed no difference between the groups but was probably underpowered (27 patients randomised to EN or TPN) (Dunham et al., 1994).

Patients with severe traumatic brain injury are a subgroup of trauma that are of particular interest as they may stay in ICU and hospital for a prolonged period of time and are at risk of malnutrition. A Cochrane publication has reported the result of a systematic review which identified seven trials comparing parenteral to enteral nutrition in this group. Five of the trials reported mortality (Borzotta et al., 1994; Chiarelli et al., 1996; Hadley et al., 1986; Rapp et al., 1983; Young et al., 1987) (207 participants). The relative risk for mortality at the end of follow-up period was 0.66 (95% CI 0.41 to 1.07), with the trend in favour of parenteral feeding. The relative risk for poor outcome associated with TPN was 0.69 (95% CI 0.40 to 1.19) from two of the five trials (Hadley et al., 1986; Rapp et al., 1983). In these trials, feeding was earlier and more successful in the TPN group, and it is possible that the trend to a benefit with TPN merely reflects a better outcome associated with early successful administration of nutrition. The preferable route for administration of nutrition in this group remains uncertain.

In summary, these data demonstrate that, in the group of ICU patients with severe trauma, EN is preferable to TPN for nutritional support as it is associated with less septic complications.

However in the subgroup of patients with traumatic brain injury it is still unclear which route is optimal.

2.3.2 EN versus TPN in critically ill patients with pancreatitis

In the past it was believed that patients with severe pancreatitis should not be fed enterally as this may stimulate pancreatic enzyme secretion and worsen the disease process. Recent studies have confirmed the safety and benefits of enteral feeding. For example, in patients with moderate to severe pancreatitis (about 60% in ICU), randomized to receive either elemental jejunal feeding (EN) or TPN, the duration of feeding was shorter with EN (6.7 vs. 10.8 days; $P < 0.05$). In addition, nutrition costs were substantially lower, representing an average cost saving of \$2362.00 per patient compared to TPN. Despite reduced efficacy in reaching nutritional requirements (54 vs. 88%; $P < 0.001$), metabolic (hyperglycaemia) ($P < 0.003$) and septic complications ($P = 0.01$) were lower. Subgroup analysis of patients with severe disease showed similar findings and a reduced period of requirement for nutritional support (Abou-Assi et al., 2002). Enteral feeding is now widely recognised as standard care in patients with pancreatitis.

2.3.3 EN versus TPN in a mixed ICU population

While data from studies involving patients with trauma, head trauma or pancreatitis may be extrapolated to a mixed ICU population, it is useful to examine studies that have specifically included a heterogeneous critically ill group. Two meta-analyses have been published recently addressing this issue. Gramlich et al evaluated 13 randomised controlled trials, involving 856 patients, that compared EN with TPN in different populations of critically ill patients (Gramlich et al., 2004). All but 3 of the 13 studies have been referred to under trauma (2.3.1) or pancreatitis (2.3.2) above. Of the 3 additional studies, one was a study on cardiac surgical patients, (Hadfield et al., 1995) and one was a study involving patients with sepsis (Cerra et al., 1988). Only one study has been done where a mixed group from an ICU has been recruited (Woodcock et al., 2001). Only clinically important outcomes were assessed. EN was associated with a significant decrease in infections (relative risk = 0.64, 95% CI = 0.47 to 0.87; $P = 0.004$), but no difference in mortality (relative risk = 1.08, 95% CI = 0.70 to 1.65; $P = 0.7$). There were also no differences in the number of days on a ventilator or length of hospital stay between the 2 groups (Standardized Mean Difference = 0.07, 95% CI = -0.2 to 0.33; $P = 0.6$). TPN was, however, associated with a higher incidence of hyperglycaemia (actual values not given). This may have contributed to the increased incidence of sepsis. Four studies examined the effect of route of nutrition on cost and documented savings with EN as opposed to TPN (Adams et al., 1986; Borzotta et al., 1994; Cerra et al., 1988; Kalfarentzos et al., 1997). Three studies reported increased incidence of diarrhoea (Cerra et al., 1988; Kudsk et al., 1992; Young et al., 1987) with the use of EN while one reported a decrease (Borzotta et al., 1994). The authors concluded that EN was superior and should be used when possible in the management of the critically ill (Gramlich et al., 2004).

A subsequent meta analysis was performed by different authors on a different group of studies which generated slightly different results (Simpson and Doig, 2005). This second meta-analysis included 11 studies. Eight of them were included in the 13 reported in the meta-analysis by Gramlich et al above. Five of the 13 studies were not included for the following reasons; inclusion of subjects from other studies (Moore et al., 1992), pseudo-randomised (Hadley et al., 1986), use of immune-enhancing feed (Hadfield et al., 1995), loss to follow up of 12% (Young et al., 1987) and 21% (Moore and Jones, 1986). An additional 3 studies were included that

Gramlich et al had not assessed. These were 3 studies that enrolled elective surgical patients who went to ICU postoperatively (Gianotti et al., 1997; Rayes et al., 2002; Reynolds et al., 1997). Nine of the eleven trials presented intention to treat analysis and when these were aggregated, a mortality benefit was evident for the use of TPN (odds ratio 0.51, 95% CI 0.27–0.97, $p=0.04$). TPN was, however, still associated with increased septic complications (6 trials; odds ratio 1.66, 95% CI 1.09–2.51; $p=0.02$; Fig. 3). Simpson et al then go on to divide the studies into those that did and did not initiate EN early in the patients stay in ICU. They then demonstrate that the favourable outcome with TPN is only evident in trials in which there is a delay in initiation of EN. They conclude that it is the timing rather than the route of delivery of nutrition that has an important effect on outcome (Simpson and Doig, 2005).

The difference in the results of these 2 rigorously performed meta-analyses demonstrates how the choice of inclusion of studies influences the result of a meta-analysis. A large multicentre trial is needed to clarify whether EN is superior to TPN however current belief is that EN should be administered if possible. It should also be noted that some of the studies presented are now quite old, and the methods of administration of nutrition may now have changed. This is particularly relevant to TPN administration. Current practices of using antibiotic impregnated central venous lines, tight glucose control and newer types of lipid, may reduce the septic complications associated with the use of TPN.

2.3.4 EN & gut mucosal integrity

Stress and trauma are associated with loss of small intestinal mucosal integrity (Mochizuki et al., 1984), and this may result in bacterial translocation and subsequent sepsis (MacFie et al., 2006). EN administration may attenuate the loss of gut mucosal integrity and this could contribute to the reduction in infective complications with the use of EN compared to TPN. Hadfield et al compared the effects of TPN with EN on gastrointestinal function in 24 critically ill patients. Measurement of absorption of D-xylose and 3-O-methyl glucose (3-OMG), and permeability using lactulose and L-rhamnose (L/R) ratios, showed that, baseline recovery of D-xylose and 3-OMG was reduced and intestinal permeability increased in the critically ill patients compared to healthy controls. In the EN group, the L/R ratio progressively fell, indicating an improvement in mucosal integrity, whereas there was no change in the TPN group (see Figure 2.2) (Hadfield et al., 1995). These results indicate that gastrointestinal mucosal dysfunction is common in critically ill patients. Furthermore, the loss of mucosal integrity can be reversed by EN, but not by TPN. Preservation of mucosal integrity may act as a barrier against endogenous bacteria implicated in the pathogenesis of nosocomial pneumonia, sepsis and multiple organ failure (Carrico et al., 1986; Heyland et al., 1992). Thus measures, such as EN, which improve mucosal integrity, may be of potential benefit to critical care. Bacterial translocation is reduced by the use of EN in animal models fed with TPN but this has never been demonstrated in humans (Sax et al., 1996).

NOTE:
This figure is included on page 32
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*Figure 2.2 Reduced absorption and increased permeability in the small intestine of critically ill patients, with an improvement over time. Sequential data for percent recovery of 3-OMG (A) and D-xylose (B), and serial values for L/R ratios (C). Patients receiving EN are represented by solid columns and squares and patients given TPN by hatched columns and open squares. * signifies a significant change from baseline ($P < 0.05$); ** signifies a significant difference between the 2 groups ($P < 0.05$). Reproduced with permission (Hadfield et al., 1995).*

2.3.5 Combination of EN with TPN

Although the enteral route is considered preferable to the intravenous in the provision of nutrition to the critically ill, enteral delivery frequently does not achieve prescribed nutritional goals (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). To ensure adequate delivery of nutrition, combined feeding with both TPN and EN has been advocated in some centres (particularly in Europe) (Rohm et al., 2008). In a group of critically ill burns patients, the administration of EN combined with TPN resulted in an increase in mortality when compared to the administration of EN alone (mortality TPN & EN- 62%; EN alone 26%; $P < 0.05$) (Herndon et al., 1989). The administration of TPN also reduced the amount of *enteral* calories that the patients could tolerate. Thus, in patients who survived, enteral nutrition alone administered a mean of about 1990 kcal/day, but if supplemented with TPN, only 1770 kcal/day were administered by the enteral route. In a subsequent meta-analysis which included this and 4 other studies, involving differing groups of critically ill patients (severe burns 1, trauma 1, mixed 2), no clinical benefit was demonstrated by supplementing EN with TPN despite more successful nutritional delivery (Dhaliwal et al., 2004). Conversely, however, increased complications with the use of TPN were not seen. Thus there is no evidence at present to support the administration of TPN in combination with EN.

2.3.6 Complications associated with enteral nutrition

In addition to an inability to reach nutritional goals, enteral nutrition may result in a number of potential adverse effects. Gastro oesophageal reflux is common in the critically ill (Metheny et al., 2006; Wilmer et al., 1999), and this reflects loss of the barrier function of the lower oesophageal sphincter (Nind et al., 2005). The risk is increased in patients who are sedated or paralysed with loss of their protective reflexes. Intra-gastric administration of feed can thus result in regurgitation and pulmonary aspiration, which can be 'silent' (i.e. unwitnessed). This can occur even when a cuffed endotracheal tube is in place. Consistent with this, administration of enteral nutrition is recognised to be a risk factor for the occurrence of ventilator-associated pneumonia in the critically ill (Cook et al., 1998; Pingleton et al., 1986). Metheny *et al* have demonstrated that aspiration of stomach contents occurred at least once during ICU stay, in about 90% of mechanically ventilated patients, and that this was associated with an increased risk of ventilator-associated pneumonia (Metheny et al., 2006). Nursing patients in a head up position and avoidance of over sedation and paralytic agents may reduce the incidence of aspiration (Metheny et al., 2006). Small bowel feeding may also be beneficial (Heyland et al., 2002). It is suggested that the use of prokinetics may also reduce the risk but this has not been demonstrated.

Enteral feeding may also cause gastrointestinal dysfunction, such as distension (occurs in 12%) or diarrhoea (15%), metabolic sequelae (hyperglycaemia, refeeding syndrome; 2%), and mechanical problems with delivery (4%) (Cataldi-Betcher et al., 1983; Montejo, 1999). These mechanical problems can include malpositioning of the feeding tube which when placed inadvertently into the lungs can cause life threatening problems. Distension or diarrhoea sometimes result in cessation of enteral delivery of nutrition. Hyperglycaemia or refeeding syndrome can have more serious consequences such as increased risk of sepsis or cardiac arrhythmias.

A rare but serious complication, which has been reported in association with enteral feeding, is non occlusive small bowel necrosis with small bowel infarction in the presence of normal mesenteric vessels (Frey et al., 2001; Thaler et al., 2005). The mechanisms responsible for this

are unclear and the cause may be unrelated to the administration of enteral nutrition. Severe hypotension compromising intestinal blood flow has been implicated (Wiklund et al., 1976).

2.3.7 Conclusions on the route of feeding

In summary, current belief is that the optimal route of administration of nutrition in critically ill patients is enteral (nasogastric or nasoenteric) with parenteral reserved only for those who cannot tolerate enteral feeding. Enteral administration of nutrition has benefits, including reduced septic complications and improved gut mucosal integrity but also has risks including reduced delivery of nutrition, possible increased regurgitation and the associated risk of ventilator-associated pneumonia as well as gastrointestinal complications.

2.4 Calculation and Delivery of Nutritional Goals

In view of the inconsistent results in the studies described above (2.3), it is unsurprising that there is little reliable information on either the amount or types of nutrition (energy & nitrogen) required to optimise outcomes in the critically ill. Individual nutritional requirements can be assessed in a number of ways but no method has been demonstrated to be better in terms of improving clinical outcomes. Resting energy expenditure (REE) can be calculated from measurements of oxygen consumption and CO₂ production using indirect calorimetry (Boullata et al., 2007; Scheinkestel et al., 2003). This method is used to guide nutritional delivery in some centres, however, more commonly, REE is estimated using formulae based on height, weight, gender and age, (e.g. the Harris Benedict or Schofield equations) (Boullata et al., 2007; Harris and Benedict, 1918; Scheinkestel et al., 2003; Schofield, 1985). Studies using indirect calorimetry have demonstrated that patients in ICU have increased nutritional requirements above the calculated REE in health. It is therefore common for the calculated REE to be increased by a 'stress factor' which is determined based on the diagnosis. For example, surgical intervention can increase requirements by 10%, severe trauma up to 30%, sepsis 20-50% and severe burns 100% (Long et al., 1979). Individual variability of REE is, however, high and calculated nutritional requirements may, accordingly, be inaccurate (both high and low) by as much as 20-30% (Weissman et al., 1986). It is, however, uncertain whether this has clinical significance. The Harris Benedict equation with 'stress factors' is the technique used to determine calorific requirements of the patients in the Royal Adelaide Hospital ICU and this technique was therefore used in the studies described in this thesis which is of particular relevance to that described in chapter 10

In 1997, consensus conference guidelines were published by the American College of Chest Physicians (ACCP) based on best evidence relating to the optimisation of nutrition in the critically ill. These guidelines recommended a standard goal of 25 kcal/kg/day for all critically ill patients (Cerra et al., 1997). Following publication of the guidelines a descriptive study on their use was performed (Krishnan et al., 2003). These data indicated that, the best patient outcome was associated with delivery of 33 to 65% of ACCP targets; approximately 9 to 18 kcal/kg/day; and this was unrelated to illness severity and nutritional status (Krishnan et al., 2003). This was associated with a higher likelihood of survival to hospital discharge (odds ratio (OR), 1.22; 95% CI, 1.15 to 1.29) than with a lower delivery of nutrition. In contrast, delivery of $\geq 66\%$ of ACCP guidelines was associated with a significantly *lower* likelihood of survival to hospital discharge (OR, 0.82; 95% CI, 0.70 to 0.94) (see figure).

NOTE:

This figure is included on page 35 of the print copy of the thesis held in the University of Adelaide Library.

*Figure 2.3 The outcome of patients at various levels of nutritional delivery (A survival, B time requiring spontaneous ventilation & C sepsis complications). Tertile II comprises patients fed 33-65% of ACCP recommendations: tertile III comprises patients fed $\geq 66\%$ ACCP recommendations. Data are odds ratios and 95% confidence intervals and are compared to tertile I 0-32% ACCP recommended intake. An odds ration >1 indicates a greater likelihood of outcome compared to tertile I. * = data adjusted for SAPS II score, serum albumin, body mass index, gastric residuals and route of feeding in a multivariate regression model. All outcome measures appear to be improved in patients fed 33-65% ACCP recommendations even when other factors are taken into account. Reproduced with permission (Krishnan et al., 2003).*

While this study suggests that mild underfeeding is optimal for survival, other descriptive studies have suggested that underfeeding in the critically ill is associated with an inability to wean from mechanical ventilation (Bassili and Deitel, 1981) and an increase in complications, particularly infections (Villet et al., 2005). Severe underfeeding (less than 25% requirements) increases the risk of nosocomial blood stream infections independent of illness severity compared with feeding >25% requirements which was associated with a relative risk of death of 0.27 (95% CI, 0.11-0.68). (Rubinson et al., 2004). The descriptive nature of these studies means that a causal association cannot be established between underfeeding and outcome. However the weight of evidence at present would suggest that mild underfeeding may be optimal, but severe underfeeding leads to malnutrition and reduced ability to overcome infections which are a leading cause of death in the ICU population.

2.4.1 Delivery of Nutritional Goals

A number of observational studies have been performed in various sites world wide, in an effort to define the factors which determine the capacity to successfully feed the critically ill (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). The results of these surveys (from USA, Canada, UK, and France) demonstrate that EN is less effective than TPN in achieving nutritional goals. Success rates of EN vary from 26 to 86% depending on the definition of successful feeding and the subgroup studied. Importantly, all these studies demonstrated the dominant problem limiting the success of enteral administration of nutrition to be upper gastrointestinal dysfunction (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). Success of feeding was examined comparing nutritional delivery to calculated nutritional goals. These data, however, need to be interpreted carefully with an awareness that nutritional goals are arbitrary and not based on clinical outcome studies. The success of feeding and factors that limit it have not been examined in an Australasian intensive care unit (see chapter 10). If it is accepted that care of the critically ill can be improved by better delivery of nutrition, an improved understanding of the underlying pathophysiology is fundamental to the achievement of more effective therapy. This issue represents the primary focus of the work reported in this thesis.

2.5 Composition of Feed

Enteral feed formulae are liquids typically comprised of protein, carbohydrate and fat in similar proportions to those found in the normal Western diet. The ACCP guidelines recommend that 30-70% of the daily caloric administration be made up of carbohydrate, and 10-30% fat (Cerra et al., 1997). Protein requirements are approximately 1.5gm/kg/day, although administration of 2gm/kg /day or greater is associated with improved mortality in patients on dialysis (Scheinkestel et al., 2003). There are no data on the effect of changing the proportions of individual components of the formulae on gastrointestinal function and patient metabolism. High carbohydrate feeds may increase blood glucose which is known to be deleterious in the critically ill (van den Berghe et al., 2001) and may also reduce gastric emptying and compromise further nutrient delivery (Fraser et al., 1991; Horowitz and Fraser, 1994; MacGregor et al., 1976). Fibre is sometimes added to the enteral feed formula in an effort to prevent diarrhoea however in one study this proved to be ineffective (Schultz et al., 2000).

There has been much interest in the use of what is termed 'immunonutrition', the addition of immune enhancing substances to formulae in an effort to modify the immune response and thereby to improve outcomes. Detailed discussion of this is outside the scope of this review. Substances added include specific amino acids (e.g. glutamine and arginine), long chain fatty

acids, and nucleic acids. Numerous studies have been performed and the results are conflicting. A recent review summarised the findings, confirming a likely benefit with the use of 'immunonutrition' for malnourished patients having major surgery but documenting insufficient and conflicting data to recommend its use in critically ill patients (Bistrian and McCowen, 2006).

2.6 Timing of initiation of feeding

There are several studies addressing the issue of timing of initiation of enteral feeding after admission to the ICU, however the results are as yet inconclusive. While commencing feeding early may appear beneficial in terms of improving the provision of nutritional goals over the whole of the ICU stay, proponents of delayed feeding suggest that during the resuscitation phase, blood flow is diverted away from the gut. Early feeding at this stage may redirect blood flow back to gut mucosa thus robbing other tissues of vital oxygen supply, or may result in gut mucosa that has an oxygen requirement not supported by the reduced flow rendering the mucosa prone to ischaemia. However, while the evidence from animal studies using physiological endpoints supports early feeding (Mochizuki et al., 1984; Zaloga et al., 1992), the studies in patients are inconsistent.

Three studies are summarised here that support the early initiation of enteral nutrition in critically ill patients, both in terms of clinically important outcomes and biochemical markers. Moore and Jones randomised 75 patients to receive jejunostomy feeds starting at either 18 h after operation for abdominal trauma (aiming for 3000kcal/day by 72h) or after 5 days. Infective complications were less ($P < 0.025$) in the early EN group and this was associated with improved nitrogen balance. This study demonstrates the feasibility of immediate postoperative EN via jejunostomy after major abdominal trauma, and suggests that early EN reduces septic complications in critically injured patients (Moore and Jones, 1986). However the study was not blinded and as the diagnosis of nosocomial sepsis can be subjective this is a significant limitation of the study. Another group reported that early initiation of EN (within 6 h of ICU admission after trauma) was associated with less organ failure (multi-organ failure score 1.84 versus 2.81; $p < 0.002$) and better small intestinal integrity (lactulose/mannitol ratio 0.02 versus 0.06) on day 4 when compared to starting feeding after 24h (Kompan et al., 1999). However, early EN had no influence on the length of ICU stay or the time of mechanical ventilation. A subsequent study where only 20 patients with burns were randomised to receive EN immediately, i.e., 4.4 ± 0.5 h after injury or after 48h (57.7 ± 2.6 h) was underpowered to demonstrate a difference in clinically important outcomes such as mortality or infective complications. However, several surrogate endpoints suggested a benefit from the early initiation of EN, including an earlier return to positive nitrogen balance, reduced urinary catecholamine excretion, reduced plasma glucagon concentrations and increased insulin concentrations (Chiarelli et al., 1990).

In contrast, 3 studies reported either no benefit or negative outcomes with the early introduction of enteral feeding. In one study, 52 patients with blunt trauma were randomized to receive early (< 24 h) or late (72 h) nasoduodenal EN. In this small study, early EN after blunt trauma neither attenuated the stress response, nor altered patient outcome. While it is likely to be underpowered to demonstrate an effect, the trend was for more, rather than less infections in the early EN group (Eyer et al., 1993). The inconsistencies between this and the other studies may be explained by the inclusion of different patient groups. The effects of the timing of initiation of feeding are likely to be subtle and may only make a difference in patient groups with high

sickness severity. Thus benefits may be observed in burns, head injuries and severe abdominal injuries but not in a less injured blunt trauma group.

A further study suggested that early enteral nutrition led to a worse outcome (Ibrahim et al., 2002). These authors randomised 150 mechanically ventilated, medical patients to early feeding (day 1) or late feeding (day 5). Whilst there was a greater nutrient delivery in the early group, there was an increased incidence of ventilator-associated pneumonia (49% versus 31%; $P = .02$), diarrhoea due to *Clostridium difficile* infection (13% versus 4%; $P = .04$), a longer length of stay in the ICU (14 ± 14 days versus 10 ± 7 days; $P = .04$) and in hospital (23 ± 20 days versus 17 ± 13 days; $P = .02$) compared to patients who commenced feeding on day 5. There was, however, no difference in hospital mortality (20% versus 27%; $P = .33$). Interpretation of these results is limited by the mode of feeding in this study. Intermittent bolus feeding may increase the risk of ventilator-associated pneumonia due to increased volumes in the stomach. Furthermore, the difference in results from previous positive studies may be due to patient selection as this study was performed in a medical group of critically ill patients. A third study failed to show a benefit following early initiation of feed at (<72 h) using an endoscopically placed postpyloric tube, on length of stay or infectious complications when compared to feed started when gastric ileus had resolved. In this case the lack of effect could be due to the fact that feeding in the early group was not initiated as early as in other studies (Minard et al., 2000). It is possible that certain subgroups may benefit while others may be harmed by this approach.

2.6.1 Meta-analyses examining the timing of initiation of feeding in critically ill patients

As the results of these studies are conflicting it may be useful to look at meta-analyses examining the combined data. Two recent meta-analyses suggested a trend towards improved mortality with early enteral nutrition of between 8 and 12% (Doig GS, 2005) (Perel et al., 2006) (see figure 2.4). However Doig et al only included 2 studies with mortality outcomes (Kompan et al., 1999; Minard et al., 2000). The study by Chiarelli et al was also included but had no deaths (Chiarelli et al., 1990). Studies mentioned above were excluded due to methodological issues (including significant loss to follow up and bolus instead of continuous feeding). However, a more recent meta-analysis performed for the Cochrane database included mortality data from 7 studies and 284 patients, and came up with the same conclusions (Perel et al., 2006). The relative risk of death with early nutritional support was 0.67 (95% CI 0.41 to 1.07) (Perel et al., 2006). Consistent with these meta-analyses, a large retrospective database analysis, examining outcome data from over 4000 patients, suggested a mortality benefit of 5% with the early initiation of enteral nutrition (Artinian et al., 2006). The benefit appeared greatest in those patients who were sickest. This study also reported an increased risk of ventilator-associated pneumonia with early introduction of EN. This study must be interpreted with caution due to the fact that it is retrospective and noninterventional, and while attempts have been made to correct for illness severity, the relationship between early initiation of EN and survival must be considered an association and not necessarily causative.

NOTE:
This figure is included on page 39
of the print copy of the thesis held in
the University of Adelaide Library.

Figure 2.4 Forest plot showing the result of a meta-analysis examining the effects of early vs. delayed EN on mortality. A trend to improved mortality with early initiation of EN was demonstrated. Reproduced with permission (Doig GS, 2005).

2.6.2 Conclusion on the timing of initiation of feeding

In summary, the effects of early administration of EN on outcomes in critically ill patients are unclear. In practice, most centres commence EN as early as practicable, and as soon as the initial resuscitation is complete, and the patient's condition has stabilised. However this practice could result in the under prescription of nutrition. In the study reported in chapter 10, the timing of initiation of feeding by intensivists in an Australian tertiary, mixed intensive care unit was assessed.

2.7 Summary

Many questions remain unanswered surrounding the administration of nutrition to critically ill patients. Current evidence supports enteral administration when possible but the optimal timing, amount and formulation is as yet unclear. Given this uncertainty, it would be of interest to examine the current practice of prescription of enteral nutrition by a group of Australian intensivists (see chapter 10). Also, while the enteral has advantages over the intravenous route in terms of reduced septic complications, the administration of enteral nutrition is frequently limited by upper gastrointestinal dysfunction. The success of enteral administration of nutrition in current Australasian practice is at present unclear and is examined in chapter 10. The pathophysiology underlying the upper gastrointestinal dysfunction which limits nutritional delivery is poorly understood and is explored in chapters 11. The overall aim of the work presented in this thesis is to establish the prevalence of problems with the delivery of enteral nutrition and explore the reasons underlying these so that the administration of nutrition can be optimised with the ultimate result of improved patient outcomes.

Chapter 3

Gastric and small intestinal structure and function in health

3.1 Introduction

One of the aims of the work performed for this thesis was to characterise aspects of gastric and small intestinal motor and absorptive function relevant to the optimal provision of enteral nutrition in the critically ill. An understanding of normal gastrointestinal anatomy and physiology is fundamental to interpretation of this work, and is outlined in this chapter. The aim is not to provide a comprehensive review of gastrointestinal structure and function, but to focus on information of major relevance to the studies described in this thesis.

The function of the stomach and small intestine is to store, break down, digest and absorb ingested nutrients, to supply the body with substrates for ongoing metabolic activity. These processes are frequently deranged in the critically ill, as evidenced by intolerance to nasogastric administration of nutrient. Furthermore, there is a high prevalence of marked cachexia in long stay patients leaving ICU, which may reflect limitations in nutrient delivery, but possibly also abnormalities in nutrient absorption. .

3.2 Anatomy of the antro-pyloro-duodenal region

3.2.1 Gross anatomy

The stomach is a muscular bag joining the oesophagus to the duodenum (figure 3.1). It varies greatly in size between individuals. It is comprised of the fundus, body, antrum and pylorus. The fundus extends up above the cardiac orifice and is in contact with the dome of the diaphragm. The body extends from the fundus to the incisura angularis which is a constant notch on the lower part of the lesser curvature. The thick muscular coat of the antrum terminates at the pylorus which forms the muscular junction between the stomach and the duodenum and is integral to the control of gastric emptying. The duodenum forms part of the small intestine and joins the stomach to the jejunum. It is divided into 4 parts all of which run in different directions. The first part runs backwards and sometimes upwards from the pylorus; the second part curves downwards around the head of the pancreas, receiving the common opening of the bile duct and main pancreatic duct at the papilla of Vater, halfway along; the third part curves forward around the pancreas and the fourth part ascends to the duodeno-jejunal flexure which is supported by a thin band of smooth muscle called the ligament of Treitz. This descends from the right crus of the diaphragm. The duodenum is retroperitoneal but empties into the jejunum which in turn empties into the ileum both of which lie in the margin of the mesentery (Last, 1984).

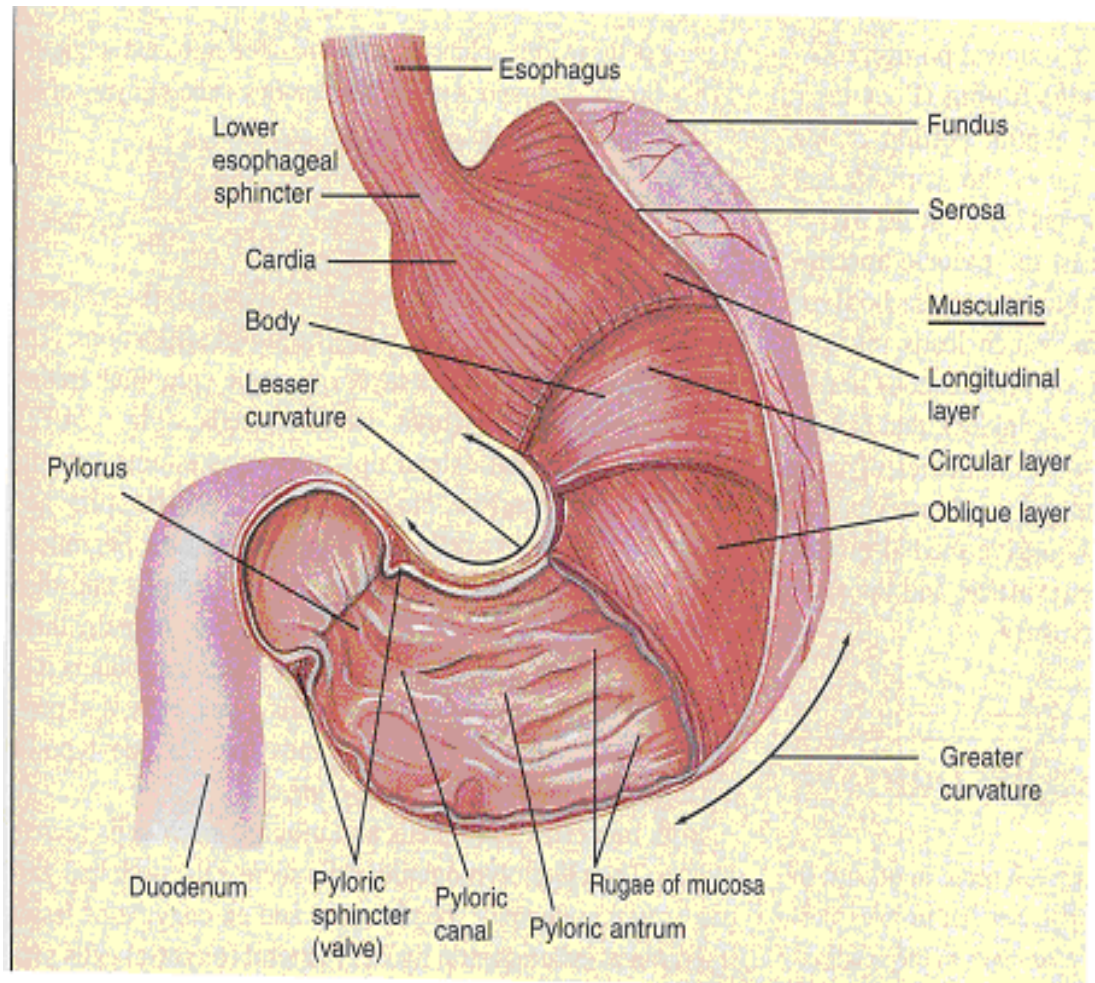


Figure 3.1 Gross anatomy of the stomach pylorus and proximal duodenum indicating muscular layers. Reprinted with permission of John Wiley & Sons, Inc.(Tortora, 2000)

3.2.2 Muscular anatomy

The smooth muscle coats of the gut are comprised of an outer, thin, longitudinal layer and an inner, thicker, densely innervated, circular coat. In the stomach both of these layers are complete. There is also an incomplete innermost oblique muscular coat which becomes vertical when the body is erect and supports the weight of the stomach contents (Last, 1984). Fibres in the outer longitudinal layer commence in the body of the stomach and interdigitate with the circular muscle fibres of the pylorus except for some of the more superficial muscle fibres on the lesser curvature of the stomach which extend across the pylorus. The muscle fibres of the circular inner coat become thicker as they approach the pylorus but are interrupted at the gastroduodenal junction. The circular layer is subdivided into inner and outer layers. The circular layer mediates the basic contractile patterns and segmentation (mixing and propulsion). The longitudinal muscle probably does not have potent propulsive capabilities, but shortens the gut length to accelerate transit.

3.2.2.1 The pylorus

The pylorus is a complex anatomical structure consisting of two distinct muscle loops that are closed over the lesser curvature and open over the greater curvature. All the circular, and the majority of the longitudinal muscle fibres converge on a relatively narrow area located on the lesser curvature of the stomach to form a muscular prominence known as the pyloric torus. This ring of muscle is reinforced by muscle fibres and connective tissue from the longitudinal muscle and mucosa. On the greater curvature, the circular muscle fibres form two distinct loops of muscle known as the intermediate and distal pyloric sphincters. Pyloric closure involves contraction of both proximal and distal muscle loops, and occlusion of the lumen by mucosal folds (Ramkumar and Schulze, 2005). The pyloric ring is not a separate anatomical structure, but can be viewed as part of a cylinder. Contraction of the cylinder narrows the diameter of the pyloric ring, and thus obstructs the pyloric aperture. The sphincteric cylinder is 3-5 cm in length when fully contracted. On the aboral side both the cylinder and the mucosal zone end at the ring. The entire cylinder is lined by pyloric mucosa, which extends a short distance orally beyond the confines of the cylinder.

Distal to the pylorus the thickness of the circular muscle decreases abruptly to form the relatively thin walled duodenum (Skandalakis et al., 1989).

3.2.3 Neural anatomy

3.2.3.1 Introduction

Neural control of the upper gastrointestinal tract is mediated by a combination of extrinsic nerves, primarily the vagus and sympathetic supply, and the enteric nervous system, made up of the myenteric and submucosal plexi which are interconnected by a multitude of interneurons.

3.2.3.2 Extrinsic neurological supply

Extrinsic neurological control of the gastrointestinal tract is from sympathetic and parasympathetic nerves. The sympathetic supply is derived from the 6th to 9th thoracic segments of the spinal cord. The cell bodies of the postganglionic neurons that supply the antro-pyloro-duodenal region are located in the coeliac plexus and travel via branches which accompany the gastric and gastroepiploic arteries (Last, 1984). The parasympathetic neural supply is from the

vagus nerve. The anterior vagal trunk supplies the terminal antrum, and sometimes the pylorus, often by a major branch called the nerve of Latarjet. The hepatic division of the vagus supplies the pylorus and proximal duodenum. The posterior aspect of the stomach, with the exception of the pylorus, is supplied by the posterior vagal trunk (Skandalakis et al., 1980; Skandalakis et al., 1986).

Extrinsic sensory innervation is important in feedback control of gastrointestinal motor function. Mechanoreceptors in the wall of the gastrointestinal tract are innervated by unmyelinated afferent sensory fibres in the vagus, and signal muscle tension generated passively by distension, or actively during contraction. These pathways also carry signals from chemoreceptors responding to intraluminal nutrient (Grundy, 1988). More vagal afferents arise from the antrum than the duodenum, suggesting that other mechanisms, such as the enteric nervous system, or humoral effects, may have a more important role on duodenal feedback (Carobi and Candio, 1990).

3.2.3.3 Enteric nervous system

More important in the neural control of the gastrointestinal tract is the enteric nervous system. This is made up of two plexi, the myenteric plexus and the submucosal plexus (Hansen, 2003) as well as a multitude of interneurons. The myenteric plexus, located between the longitudinal and circular muscle layers, mainly controls motility, while the submucosal plexus, located between the circular muscle layer and the mucosa, controls mucosal activity (electrolyte and fluid excretion, mucus secretion, mucosal blood flow, neuro-immune interactions). The enteric nervous system contains up to 100 million neurons, compared with only 2000 efferent fibres in the vagus (Hansen, 2003), suggesting that intrinsic nerves are more important in the control of gastrointestinal motility while the extrinsic innervation serves only a modulatory function (Hansen, 2003).

The pylorus has a high density of nerve fibres, which are quite distinct from the adjacent duodenum and distal stomach.

3.2.3.4 Interstitial cells of Cahal

The interstitial cells of Cahal are a network of specialised cells embedded in the tunica muscularis throughout the gut. They undergo fluctuations in resting membrane potential that generate electrical control activity or 'slow waves' (Husebye, 1999). The interstitial cells of Cahal thus serve as electrical pacemakers, and determine the underlying rhythm of electrical activity in the upper gastrointestinal tract. They also provide pathways for the active propagation of 'slow waves', and are mediators of enteric motor neurotransmission and play a role in afferent neural signalling (Ward and Sanders, 2006). Motor neurotransmission in the gastrointestinal tract occurs via specialized synapses that exist between enteric nerve terminals and the interstitial cells of Cahal. These are coupled to smooth muscle cells via gap junctions and post-junctional responses are conducted to neighbouring smooth muscle cells. This is important both for cholinergic excitatory and inhibitory nitroergic motor neurotransmission (Ward and Sanders, 2006).

3.3 Regulation of gastric and small intestinal motility

Gastric and small intestinal motility consists of an underlying regular intrinsic rhythm that is modulated by various factors. Control of intestinal motility is maintained by interaction

between the intestinal smooth muscle, the enteric nervous system, extrinsic nerves, and regulatory peptides.

3.3.1 Interstitial cells of Cahal

As described above, the interstitial cells of Cahal undergo regular fluctuations in resting membrane potential and act as pacemakers for the motor activity of the gut. Whether these fluctuations in resting membrane potential initiate mechanical contractions, and the amplitude of these, is determined by other neural (intrinsic and extrinsic) and humoral mechanisms (Hansen, 2003). These regular 'slow waves' occur at different frequencies, amplitudes, and durations in different regions of the gut. In humans, the frequency is approximately 3 /min in the antrum of the stomach, 12 /min in the duodenum, 8 /min in the ileum and 6-10 /min in the colon.

3.3.2 Neural Regulation

As outlined above, neural control of gastrointestinal function is mediated by extrinsic and intrinsic neurological systems.

3.3.2.1 Extrinsic Neurological Control

The autonomic nervous system is responsible for extrinsic neurological control of the upper gastrointestinal tract. Parasympathetic stimulation results in an increase in gastric and duodenal motility and emptying, whilst sympathetic innervation is inhibitory. Vagal stimulation at low frequencies results in pyloric contraction and at high frequencies results in relaxation, suggesting that both excitatory and inhibitory vagal pathways are present (Hansen, 2003). Extrinsic nerves influence smooth muscle indirectly by acting on the neurons in the myenteric plexus. Both sympathetic and parasympathetic function may be altered and therapeutically manipulated in critical illness.

3.3.2.2 Intrinsic Neurological Control

As noted above, the enteric nervous system is more important than extrinsic modulation in the minute by minute control of gastrointestinal activity. The smooth muscle cells of the gut form an electrical syncytium that is innervated by hundreds of excitatory and inhibitory neurons. Excitatory nerves in the myenteric plexus release a number of neurotransmitters including, tachykinins, acetylcholine, serotonin (5-HT) and substance P (Bornstein et al., 2004). Calcium ions induce recruitment in tachykinin, acetylcholine or serotonin-induced contractions (Bornstein et al., 2004). The effect of acetylcholine involves reduction of cAMP-levels in the smooth muscle cells. Inhibitory nerves act by releasing other neurotransmitters such as, adenosine triphosphate (ATP), neurotensin, bombesin – like substances and enkephalin (Bornstein et al., 2004).

3.3.3 Humoral

In addition to neurological control, circulatory hormones have an important influence on gastrointestinal motility. These may be excitatory or inhibitory, and are particularly important for feedback control of motility. Inhibition of gastrointestinal smooth muscle activity occurs with the release of cholecystokinin (CCK), endogenous opioids, glucagon, glucagon-like peptide-1 (GLP-1), nitric oxide (NO), somatostatin, peptide YY, vasoactive intestinal peptide,

and pituitary adenylyl cyclase activating peptide, (Holst, 1994). Stimulatory hormones include motilin, ghrelin (Masuda et al., 2000), 5HT and secretin. These hormones can all have variable actions in different parts of the gut. For example, while 5HT is, in general, an excitatory neurotransmitter, it has an inhibitory effect on the pylorus, and, while CCK is in general inhibitory, it has an excitatory effect on the pylorus (Katschinski et al., 1996). These differences are in keeping with the overall effect of the particular hormones. For example, the net effect of CCK is to reduce gastric emptying. This is achieved by decreasing antral contractility, and increasing pyloric activity, such that the stomach relaxes and the pylorus closes to prevent emptying.

3.3.3.1 Inhibitory hormones

Cholecystokinin (CCK)

CCK is the best characterised gastrointestinal humoral mediator in humans. It is a peptide hormone which occurs in a number of molecular forms. CCK is released from the duodenum and jejunum, in a dose-dependent fashion, in response to the presence of fat, protein and to a lesser extent carbohydrate, in the small intestinal lumen (Borovicka et al., 1996; Fried et al., 1991; Rayner et al., 2000). It acts by activating vagal and spinal afferent nerves controlling gastrointestinal motility (Raybould, 1991). It has a vital role in the control of the entero-gastric feed-back response, and also regulates appetite and energy homeostasis (Borovicka et al., 1996; Fraser and Davison, 1993; Fried et al., 1991; Liddle et al., 1986; Rayner et al., 2000; Stacher et al., 1982; Yamagishi and Debas, 1978). Exogenous administration of CCK slows gastric emptying in both animal and human studies (Borovicka et al., 1996; Fraser and Davison, 1993; Stacher et al., 1982; Yamagishi and Debas, 1978) by fundic relaxation, antral inhibition and stimulation of isolated pyloric contractions (Borovicka et al., 1996; Fraser and Davison, 1993; Fried et al., 1991; Liddle et al., 1986; Stacher et al., 1982; Yamagishi and Debas, 1978). Both central and peripheral routes appear to be important for these effects (Lopez et al., 1991).

Endogenous opioids

Endogenous opioids are peptidergic neurotransmitters that act on opioid receptors which are present throughout the enteric nervous system (Sternini et al., 2004). There are three distinct families of endogenous opioids, enkephalins, endorphins and dynorphins. There are 3 primary receptor types which mediate the effects of endogenous opioids and drugs that affect opioid receptors. These are the μ , κ and δ receptors. Suppression of neuronal excitability accounts for most of the actions of endogenously released opioid peptides and synthetic opioids on gastrointestinal motility and secretion. Opioids act to delay gastric emptying and intestinal transit by inhibiting cholinergic nerves. They also suppress intestinal secretion of water and electrolytes and inhibit transport of bile into the duodenum (Wood and Galligan, 2004). Delays in gastric emptying may occur due to increased antral, pyloric and upper duodenal tone as a result of reducing tonic NO mediated inhibition. Opioids also appear to be involved in the feedback response to the presence of nutrient. They exert a central stimulatory effect on pyloric motility, (Lopez et al., 1991) and abolish the delay in small bowel transit that occurs in response to the presence of fat (Kinsman and Read, 1984). These effects are of particular interest, not only because endogenous opioid levels are affected by critical illness, but also because exogenous administration of opioids is frequent in the critically ill and this may contribute significantly to the pathogenesis of abnormal gastrointestinal function. The importance of opioids in the gastrointestinal disturbance observed in critical illness is as yet uncertain, but if demonstrated there are therapeutic opportunities in terms of limiting use or administering local antagonists.

Glucagon-like peptide-1 (GLP-1)

As its name suggests, GLP-1 is similar in structure to glucagon. It is a peptide of 30 amino acids. It is secreted predominately from L cells located in the distal jejunum, ileum and colon in response to the presence of nutrients. GLP-1 has a number of important actions. Together with gastric inhibitory polypeptide, it is one of the incretin hormones, and potentiates glucose stimulated insulin secretion and inhibits glucagon secretion, thereby inhibiting hepatic glucose production and lowering blood glucose concentrations. Exogenous GLP-1 also slows gastric emptying (Dupre et al., 1995) and, at least in animals, modulates small intestinal motility (Tolessa et al., 1998) so that there is a reduction rather than an increase in postprandial insulin levels (Little et al., 2006). Suppression of gastric emptying appears to outweigh insulinotropic properties at least in health. The capacity of GLP-1 to normalise blood glucose levels has engendered an interest in its use in type 2 diabetics and stimulated the development of GLP-1 analogues such as exenatide (Anonymous, 2004) and liraglutide (VilSBoll, 2007) and inhibitors of its enzymatic breakdown (Ahren et al., 2007). The administration of GLP-1 to the critically ill is potentially attractive as it may contribute to better glucose control however the inhibitory effect on gastric emptying may limit its benefit.

Nitric oxide

Nitric oxide (NO) is an important inhibitory nonadrenergic, noncholinergic neurotransmitter throughout the gastrointestinal tract. It is produced by the action of inducible nitric oxide synthase, which activates guanylyl cyclase, leading to the production of cGMP, which causes smooth muscle relaxation. In the stomach, NO mediates proximal gastric relaxation (Desai et al., 1991) and reduces antral activity, thereby delaying gastric emptying (Konturek et al., 1999). It also has the conflicting effect of relaxing the pylorus which will facilitate gastric emptying. NO levels are frequently elevated in critical illness and NO may thus contribute to gastrointestinal dysmotility. Because of its widespread distribution, manipulation of NO release may have therapeutic potential. For example, NO synthase inhibitors can be administered to increase small intestinal motility (Fraser et al., 2005). However, in a study in critically ill patients with sepsis, NO inhibition was associated with an increase in myocardial events and death, so therapeutic options may be limited (Lopez et al., 2004).

Somatostatin

Somatostatin has a dose dependent effect to slow gastric emptying by inhibiting antral contractions and stimulating phase 3 activity (Soudah et al., 1991). It may facilitate movement of the activity front into the small intestine (Peeters et al., 1983). Octreotide, a somatostatin analogue, delays gastric emptying of solids (but not liquids), increases fasting gastric volume, reduces postprandial gastric relaxation, and decreases the sense of fullness after a meal (Fox-Orenstein et al., 2003).

PeptideYY

Peptide YY (PYY) is mainly released by endocrine cells in the lower bowel. It inhibits gut motility, gastric emptying and acid secretion, pancreatic exocrine secretion and is a potent vasoconstrictor. It has been suggested that PYY regulates gastrointestinal function by effects on blood flow, modulating neural control mechanisms, and/or direct effects on cells such as enterocytes (Sheikh, 1991). PYY levels have not been reported in ICU patients.

3.3.3.2 Excitatory hormones

Motilin

Motilin is a peptide released from enterochromaffin cells in the duodenum and jejunum, although the precise stimulus for motilin release remains unknown (Pandolfino et al., 2000). It acts on receptors which have been identified as a guanosine triphosphate protein binding receptor (Depoortere and Peeters, 1997; Feighner et al., 1999), which are found on enteric neurones in the antrum of the stomach (Tack, 1995), and throughout the enteric nervous system, and on gut smooth muscle, with decreasing density from the stomach to the lower intestinal tract. The motilin receptor has been cloned and has substantial structural homology with the growth hormone secretagogue receptor (Feighner et al., 1999). Motilin also appears to have a centrally mediated effect, since motilin and motilin binding sites can also be found in the cerebral cortex (Depoortere and Peeters, 1997; Pandolfino et al., 2000). Motilin acts in the gut as an excitatory hormone, It increases antroduodenal activity and thereby gastric emptying, and also initiates phase 3 activity (Vantrappen et al., 1979) (Bruley des Varannes et al., 1995). However, the initiation and aboral migration of the migrating motor complex (MMC) in the small bowel is also under extrinsic neurologic control and the presence of motilin is not an absolute requirement (Chung et al., 1994; Sarna, 1985). Motilin also stimulates the pylorus which will paradoxically reduce gastric emptying. Erythromycin and its derivatives act as motilin agonists and thereby stimulate gastric emptying and small intestinal transit (Sarna et al., 1991). Erythromycin has been demonstrated to have clinically useful prokinetic effects in several patient groups (chapter 7) (Chryso et al., 2001; Janssens et al., 1990; Smith et al., 2000). It increases gastric motility and emptying in the critically ill, but its effect on the success of feeding is as yet unknown (see chapter 13).

Ghrelin

Ghrelin is a peptide, structurally similar to motilin, which was discovered in 1999 by Kojima et al (Kojima et al., 1999). Ghrelin is produced primarily in the stomach, but also in the hypothalamus, and pituitary gland. It is an antagonist of somatostatin and activates the release of growth hormone from the pituitary gland. It participates in the regulation of energy homeostasis, increases food intake, decreases energy output and exerts a lipogenic effect (Rosicka et al., 2002). Administration of ghrelin increases gastric emptying in healthy humans (Levin et al., 2006), and in patients with gastroparesis (Murray et al., 2005; Tack et al., 2005) but not in those with obesity (Valera Mora et al., 2005). It also induces phase III activity, (although not through the release of motilin), and causes prolonged increased tone of the proximal stomach (Tack et al., 2006). Ghrelin may have potential as a prokinetic in the critically ill. However, its effect on growth hormone release may limit its use, as the administration of growth hormone to critically ill patients has previously been demonstrated to increase the mortality rate (Takala et al., 1999).

Serotonin

The precise role of serotonin in the control of gastrointestinal motility is as yet unclear because there are many receptor subtypes with differing locations and variable, sometimes opposing effects. Overall exogenous serotonin has an excitatory action on enteric neurones and plays a part in the initiation of peristalsis (Galligan and Vanner, 2005). It also increases gastric emptying and hastens small intestinal transit.

In summary, there are a number of neural and humoral mediators involved in regulation of gastrointestinal motility and other gastrointestinal functions in health. An understanding of their

role in abnormalities of gastrointestinal function in the critically ill has implications for both pathogenesis, and therapies to optimise nutritional status.

3.3.4 Small intestinal nutrient feedback

Small intestinal feedback is an important determinant of gastric emptying (Brener et al., 1983). While it is likely that all macronutrients have similar effects, these may differ in intensity. The effects listed here represent those that have been demonstrated to date. Intraduodenal infusion of lipid is associated with inhibition of antral and duodenal activity and stimulation of pyloric phasic and tonic pressures, as well as a reduction in antegrade propagating pressure waves (Andrews et al., 2001; Heddle et al., 1989; Heddle et al., 1988a; Tougas et al., 1992). Intraduodenal glucose also reduces antral activity (Verghagen et al., 1998) and stimulates pyloric activity (Heddle et al., 1988c). Amino acid infusions relax the proximal stomach (Mearadji et al., 2001) and stimulate pyloric activity (Edelbroek et al., 1992; Edelbroek et al., 1994) (see figure). Increased pyloric motility is associated with slowing of gastric emptying (Heddle et al., 1989) as a consequence of occlusion of the pylorus (Tougas et al., 1992). Animal studies indicate that the degree of inhibition of gastric emptying is proportional to the load and type of nutrient and the area and length of small intestinal exposure (Lin, 1994; Lin et al., 1989, 1990).

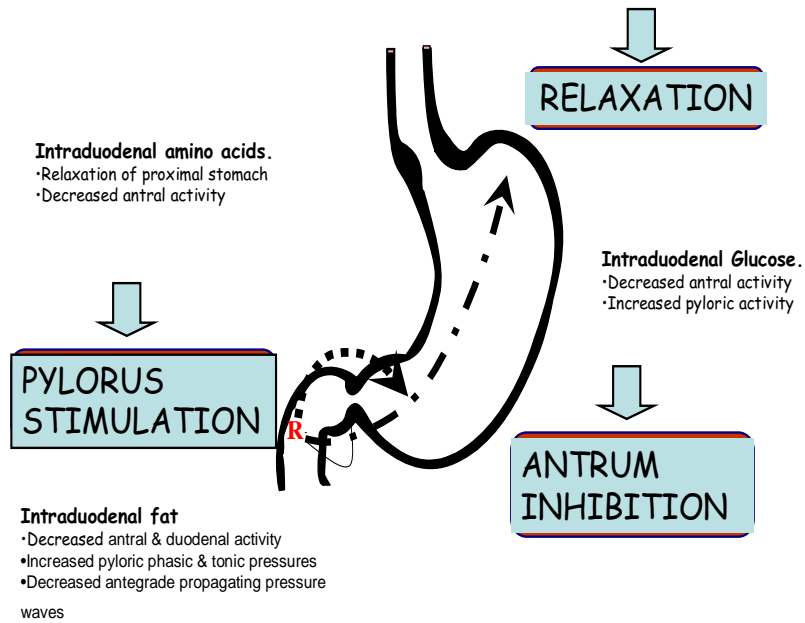


Figure 3.2 Effect of small intestinal feedback on different components of gastric motor responses.

3.3.4.1 Effect of nutrient type on enterogastric feedback

In both animals and humans, the mechanisms underlying small intestinal feedback on gastric motility, and thus emptying, are dependent on the type of nutrient administered (Lin, 1994). For instance, feedback in response to the presence of dextrose is mediated by cholinergic (Fone et al., 1989; Raybould, 1991), and serotonergic mechanisms (Raybould et al., 2003). Feedback from fat and protein is mediated by the release of CCK acting on CCK₁ receptors (Raybould, 1991). Cholinergic mechanisms provide a minor contribution to feedback in response to lipid. (Fraser et al., 1992a; Zittel et al., 1994).

Gastric emptying can be viewed either in terms of the rate of volume emptied or the rate of energy delivery from the stomach to the duodenum (Hunt and Stubbs, 1975). The rate of volume emptied is dependant on the volume in the stomach (Doran et al., 1998; McHugh and Moran, 1979; Moran et al., 1999), the caloric density of the nutrient (Calbet and MacLean, 1997), and the type of nutrient emptied. The type of nutrient involved is a major determinant of GE, with both lipid and protein producing slower emptying than glucose (Mossi et al., 1994). For example, dextrose (5%) empties faster than either an amino acid-glucose mixture (12%/8%) or Ensure (1 kcal/ml; 37.2 g/l fat (corn oil); 37.2 g/l protein (sodium and calcium caseinates); 145 g/l carbohydrate (corn syrup/sucrose)) which empty at the same rate (Mossi et al., 1994). Intralipid (20% soy bean emulsion; 20gm fat/100ml) empties even more slowly, such that even in healthy humans, 20% of a 300ml meal remained in the stomach at 3 hours (Mossi et al., 1994). In a group of (non-critically ill) patients with COPD a highly concentrated fat feed (55% lipid) was associated with reduced volume of gastric emptying compared to a medium fat feed (41% lipid) (scintigraphic t_{1/2} 134 vs. 109 min) (Akrobawi et al., 1996). Thus the effect of varying macronutrient composition may be of relevance to the success of feeding the critically ill as manipulation of this may affect gastric emptying.

A number of animal studies have demonstrated that the delivery of calories from the stomach to the duodenum remains stable despite differing nutrient concentrations and compositions (Hunt and Stubbs, 1975; Maerz et al., 1994; McHugh and Moran, 1979; Weber and Ehrlein, 1998). In humans glucose delivery from the stomach to the small intestine is tightly regulated at an overall rate of approximately 2-3 kcal/min (Brener et al., 1983). Lipid emptying has not been quantified precisely in healthy humans. However, once macronutrients are broken down to their constituents, such as medium chain triglycerides or free fatty acids, they exert a much lesser feedback effect and these can then empty faster than carbohydrates (Beckers et al., 1992).

Varying the type of lipid may also have an effect on the rate of gastric emptying. Animal studies do not support this premise (Porsgaard et al., 2003) but studies in humans have demonstrated that the effect of fat on proximal gastric relaxation, antral and pyloric activity, and gastric emptying is dependent on fatty acid chain length (Hunt and Knox, 1968). For example, dodecanoic acid (C12) induces greater effects on these parameters (acting to slow GE) than decanoic acid (C10) (Feltrin et al., 2004; Lal et al., 2004). This is mediated by CCK acting on CCK₁ receptors (Lal et al., 2004). Emptying rate is also affected by the physical characteristics of the fat. For example, while subsequent digestion of fat is not affected by intragastric layering of fat on water (Jian et al., 1982), it is affected by droplet size and emulsification (Borel et al., 1994). Studies examining the effects of manipulation of types of lipid and the physical properties of lipids with the aim of enhancing gastric emptying and nutrient absorption in patients in ICU would be of interest.

Gastrointestinal responses to nutrients have the capacity to adapt in response to chronic

changes in exposure to a particular nutrient. For example, in healthy subjects, chronic high fat intake for 14 days reduces the inhibitory effect of fat on gastric emptying (Cunningham et al., 1991a). Similarly, high intake of glucose for several days prior to gastric emptying measurement also leads to faster emptying of a glucose drink (20 vs. 30 min) (Cunningham et al., 1991b). In contrast, prior nutrient deprivation slows gastric emptying (Beckoff et al., 2001; Corvilain et al., 1995). This may be of particular relevance to critical illness where fasting is frequent prior to and in the early stages of ICU admission. Furthermore, standard nutrient formulations have a high lipid composition potentially affecting enterogastric feedback and subsequent emptying. The effect of macronutrient modification on subsequent gastrointestinal function may thus provide a strategy for managing enteral nutrition more successfully.

3.3.4.2 Effect of nutrient blood concentrations on enterogastric feedback

Increased nutrient levels in blood also slow gastric emptying. In health, intravenous nutrient infusions delay gastric emptying. As gastric emptying is directly affected by blood glucose levels (see section 5.5), the slowing of gastric emptying during intravenous feeding could potentially be related to hyperglycaemia (MacGregor et al., 1979). However, similar responses are seen with pure lipid administration (Casaubon et al., 1989). This effect is attenuated if the intravenous feed contains branched chain amino acids (Bursztein-De Myttenaere et al., 1994). This may be of importance when contemplating attempts to influence gastric emptying in the critically ill patients particularly in the context of TPN or intravenous supplementation of enteral administration.

3.3.4.3 Small intestinal feedback

Optimal absorption of fat requires adequate time of contact with the absorptive sites of the small intestine. To facilitate this, intestinal transit must be slowed in response to the fat that has emptied into the small intestine. Intestinal transit is known to be inhibited by the presence of fat throughout the small intestine (Lin et al., 1996). In humans, this appears to be mediated by NO (Fraser et al., 2005) and/or endogenous opioids (Kinsman and Read, 1984). Animal studies suggest that CCK, insulin, gastrin, neurotensin (Siegle and Ehrlein, 1989b) and calcitonin (Hamada et al., 1999) may also play a role (Bueno and Fioramonti, 1994). As NO and endogenous opioids levels are elevated in critical illness it is likely that small intestinal transit will be delayed but this has not been measured.

3.4 Motility of the stomach & small intestine in health

Gastrointestinal motor activity is broadly divided into fasting and postprandial patterns. The postprandial period is initiated by nutrient intake and, by definition, ends with the recurrence of fasting motility, which is characterised by phase III of the migrating motor complex in the upper small bowel (Weisbrodt, 1987). There is rapid conversion of fasting to fed activity following exposure to nutrient. Postprandial activity results in breakdown, digestion and distal transfer of nutrients. Fasting activity leads to the expulsion of undigested food, and cellular debris including bacteria.

3.4.1 *Fasting motility*

Fasting motility patterns are cyclical in nature, and are typified by the 'migrating motor complex' (MMC). This is divided into three phases. Phase I is a period of motor quiescence. This is followed by phase II, characterised by irregular duodenal contractions at a rate of more

than two per 10 min. Phase III, is a burst of rhythmic contractile activity occurring at the maximum frequency (three contractions min^{-1} in the antrum and 10-12 min^{-1} in the duodenum). During this phase, each slow wave of electrical activity from the interstitial cells of Cahal (see above section 3.3.1) results in a contraction. The duration of a phase III episode varies from 2 to 10 minutes in the duodenum (Kellow et al., 1986). It is initiated proximally and migrates distally through the duodenum into the small intestine, and is followed by motor quiescence (phase I). Phase III activity usually occurs every 85 to 110 minutes (Kellow et al., 1986; Kellow et al., 1990; Vantrappen et al., 1977), however there is a substantial variability in, as well as between, individuals. The majority of the migrating motor complex is comprised of phase 2 activity (75%) while phase 1 comprises about 20%, and phase 3 the remaining 5% (Dive et al., 1994b). The antrum is involved in about 60% of episodes and the duodenum in about 85% (Kellow et al., 1986) and many of the episodes commence in the antrum and move distally as far as the small intestine. The pylorus is open during phase 3 activity to allow emptying of the stomach into the duodenum. MMC activity moves undigested solids and bacteria distally from the gastrointestinal tract to the colon (Husebye, 1999).

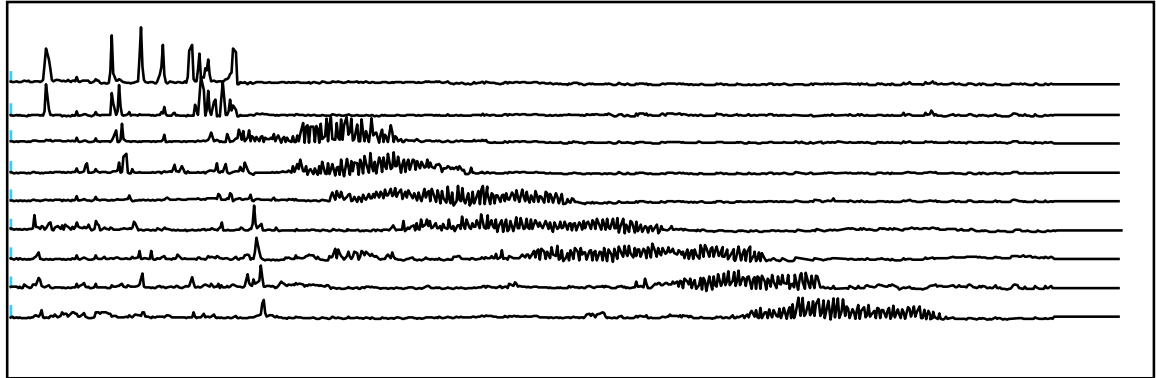


Figure 3.3 Manometric example of a migrating motor complex in the stomach and proximal small intestine. High frequency pressure waves indicative of phase 3 activity are shown migrating distally followed by motor quiescence (phase 1) and preceded by irregular activity typical of phase 2.

MMC activity is frequently abnormal in the critically ill, in terms of frequency, percentage of time in the 3 phases and presence or absence during feeding (see chapter 4). The causes and significance of these abnormalities are uncertain. The effect of enteral nutrient administration on MMC activity in the critically ill was evaluated in the study reported in chapter 11. The relationship between gastric emptying and MMC activity and its organisation is also reported in chapter 11.

3.4.2 Control of MMC activity

MMC activity is influenced by both neural and humoral mechanisms.

3.4.2.1 Neural mechanisms

Intrinsic

The initiation and migration of the MMC is mainly controlled by the enteric nervous system with modulation from extrinsic neurological control and hormonal influences. Although extrinsic neural control is important, MMC activity can occur in gut which has been externally denervated (Sarna, 1985).

Extrinsic

As with the extrinsic neurological control of other aspects of gastrointestinal motility, the extrinsic neurological control of fasting motility is mediated primarily by the vagus and sympathetic supply. Abolition of fasting motility by food intake requires an intact vagus (Hall et al., 1986). Consistent with this observation, persistence of MMC activity with eating suggests abnormal extrinsic neural control (Thompson et al., 1982). This is of relevance to the critically ill because (see chapter 4) there is failure of abolition of fasting motility patterns by feeding in some patients, perhaps indicative of reduced vagal activity.

3.4.2.2 Hormonal mechanisms

Motilin.

The hormone that appears of most importance in the control of the MMC is motilin. Intravenous administration of motilin (Vantrappen et al., 1979), or 1-3mg/kg/h of the motilin agonist erythromycin (Tomomasa et al., 1986), induces 'phase III-like' activity in the antroduodenal region. Motilin levels peak during MMC activity. The effect of erythromycin on MMC activity is highly relevant to critically ill patients as erythromycin is used as a prokinetic (see chapter 13).

Other hormones and drugs.

Somatostatin (Peeters et al., 1983), opioids (Benson et al., 1994; Waterfall, 1983), sumatriptan (Tack et al., 1998) and paroxetine (Gorard et al., 1994) can also initiate phase III-like activity in the duodenum and the small bowel, suggesting that circuits of the enteric nervous system with both peptidergic and serotonergic transmission are involved.

3.4.2.3 Intestinal microflora

Normal intestinal microflora also stimulate the initiation and aboral migration of physiological phase III activity (Caenepeel et al., 1989; Husebye et al., 1994).

Abnormalities of upper gastrointestinal motility in the critically ill are described in chapter 4 and the authors studies on this topic are described in chapter 11.

3.4.3 Postprandial motility

Normal gastroduodenal function involves the receipt of food into the proximal stomach following transit down the oesophagus. This ingesta may be non-nutrient liquid, nutrient liquid or solid. These are handled in different ways:

- I. Non-nutrient liquids move rapidly from the proximal to the distal stomach, and flow through the pylorus occurs in an exponential pattern which is dependent on volume (Brener et al., 1983).
- II. Nutrient liquid flow through the pylorus is controlled by small intestinal feedback (see 3.3.4) so that the rate of delivery of calories to the duodenum is relatively constant (Brener et al., 1983).
- III. Digestible solids are broken down into smaller particles by intermittent motor activity of the stomach to a size of 1mm or less before movement through the pylorus. Non-digestible solids are also broken down, but are eventually cleared from the gut when fasting motility (phase 3 activity) resumes.

The gastrointestinal handling of nutrient liquid is of most relevance to the studies in this thesis as this is the formulation used in enteral nutrition. The following description of postprandial motility therefore concentrates primarily on activity following liquid nutrient ingestion.

3.4.3.1 Proximal gastric postprandial motility

Proximal gastric receptive relaxation is an enteric reflex mediated via nitrergic fibres in the vagus nerve (Takahashi and Owyang, 1997). Ingestion of food results in inhibition of tonic contraction of the gastric smooth muscle. The resulting relaxation of the proximal stomach allows filling with ingesta with only minor increases in pressure. Gastric accommodation is prolonged (up to 3 hours) and persists until nearly complete emptying has occurred (Simonian et al., 2004). The mechanisms leading to distal movement of food are not well characterised. Fundic volume waves are intermittent contractions, which may be important in the redistribution of proximal gastric content distally and increased fundic wave activity has been associated with relatively accelerated gastric emptying of liquid (Frank et al., 1995).

3.4.3.2 Distal gastric postprandial motility

The coordinated motility of the antrum and pylorus facilitates and controls emptying of ingesta into the proximal duodenum. The presence of nutrient in the stomach (Houghton et al., 1988a) stimulates antral contractions which are important for transpyloric flow. This action is nutrient and volume dependent. Antro-pyloro-duodenal (APD) activity is characterised by either intermittent isolated pressures which vary in frequency and amplitude, or coordinated propagated (peristaltic) pressure waves which move varying distances through the antrum, across the pylorus and into the duodenum (White et al., 1981). Intermittent, isolated pressures appear to be primarily responsible for the mixing and breakdown of food boluses (White et al., 1981). Under fed conditions, the pylorus exhibits a complex motor response of prolonged periods of closure, with duodenal mixing and retropulsion. Pyloric relaxation is produced by strong inhibitory inputs received during gastric emptying via descending pathways from the gastric antrum. This action is also influenced by vagal activity. Distension, chemical and

osmolar stimulation of the duodenum activates ascending excitatory motor pathways to the pylorus and thereby slows gastric emptying by a feedback mechanism (Yuan et al., 2001).

3.4.3.3 Gastric emptying

Gastric emptying occurs predominantly in a pulsatile fashion, and is dependent on the integration of motor activities in the proximal and distal stomach as well as the proximal small intestine (Anvari et al., 1995a; Horowitz et al., 1994; Paterson et al., 2000). Transpyloric flow occurs when an APD pressure gradient is generated. This can occur with peristaltic and non-peristaltic motor activity (Hausken et al., 2002; Indireskumar et al., 2000). Non peristaltic gradients are due to changes in overall basal antral, relative to duodenal, pressure. Peristaltic activity is thought to be responsible for the majority of gastric emptying episodes (Hausken et al., 2002).

Duodenal motility also influences gastric emptying (Haba and Sarna, 1993). Retrograde peristaltic activity occurs frequently in the proximal duodenum, both as a component of phase 3 activity (Haba and Sarna, 1993), and post-prandially. Retrograde contractions move chyme back into the distal antrum slowing gastric emptying (Haba and Sarna, 1993). Uncoordinated peristaltic activity may contribute to slow gastric emptying in the critically ill and this issue is the focus of the study that is described in chapter 11.

3.4.3.4 Small intestinal transit

After nutrients enter the small bowel, initial transit is rapid with chyme spread along the bowel (Johansson and Ekelund, 1976). Further movement of digesta then slows, as a result of the interaction between nutrients and receptors in the small intestine (Schmid and Ehrlein, 1993). Stimuli from mechano- and chemoreceptors, mediated by vagal afferent fibres, result in promotion of absorption by increasing contact time of nutrients and the small intestinal mucosa.

Postprandial small intestinal motility mixes chyme with exocrine and intestinal secretions, so that luminal contents are uniformly and evenly exposed to the mucosal surface (Sarna and Otterson, 1989). As with gastric motility (3.4.3.2), small intestinal motility can also be divided into isolated contractions whose function is mainly to mix digesta, and coordinated propulsive contractions which propel chyme distally at a rate that allows optimal absorption of food components, and reabsorption of bile (Huge et al., 1995; Sarna and Otterson, 1989; Sarna et al., 1989). These propulsive single pressure waves propel chyme several centimetres aborally. Their occurrence is unpredictable and varies considerably between individuals (Sarna and Otterson, 1989). Occasionally, a contraction of large amplitude and long duration migrates over many centimetres and may rapidly propel the contents over this distance (Sarna et al., 1989). In general, the spatial and temporal relationships of individual phasic contractions become disorganized distally, resulting in a slower propulsion rate in the distal rather than in the proximal, small intestine. The length of spread of contraction waves is the most important factor that influences the rate of transit (Schemann and Ehrlein, 1986). Lengths of contraction and transit rate are generally greater in the jejunum than the ileum (Siegle and Ehrlein, 1989a). Slowing of transit may increase the rate of absorption (Huge et al., 1995).

Small intestinal transit and motility is yet to be investigated in the critically ill and has also not been studied for this thesis.

3.5 Factors affecting GE in health

An understanding of the factors affecting gastroduodenal function in health are of relevance to the studies reported in this thesis. Healthy subjects have provided control data for several studies (see chapters 10,11 and 12). Care must be taken in the choice of subjects to make up a healthy cohort given that many factors such as age and gender may affect the data.

The rate of GE in health is variable. A number of factors may have a substantial influence on it—including gender, age, posture, smoking and alcohol history, exercise levels, usual diet and anxiety (Anvari et al., 1995b; Beckoff et al., 2001; Burn-Murdoch et al., 1980; Clarkston et al., 1997; Datz et al., 1987; Divoll et al., 1982; Fone et al., 1990b; Gainsborough et al., 1993; Hermansson and Sivertsson, 1996; Hutson et al., 1989; Johnson et al., 1991; Marzio et al., 1991; Moore et al., 1983; Nakae et al., 1999; Roland et al., 1990; Shimamoto et al., 2002; Wallden et al., 2004; Wegener et al., 1991).

3.5.1 Gender

GE is probably slightly slower in pre-menopausal women than in age matched men (Datz et al., 1987; Hermansson and Sivertsson, 1996; Hutson et al., 1989). In one study, scintigraphic $t_{1/2}$ for solids was 60 min in males and 90 min in women, and for liquids was 30 min in men, and 50 min in women; $P < 0.001$ for both (Datz et al., 1987). A further study reported scintigraphic half emptying times for solids in males of 111 minutes and in women 158 min; $P < 0.001$ (Hermansson and Sivertsson, 1996). In another study, examining the emptying of a mixed meal, scintigraphic $t_{1/2}$ for liquid nutrient (milk) was 48 min in premenopausal women, compared with 30 min in the men ($P < 0.025$) and the emptying of solids was also slowed. In other studies the difference has been less marked. Antral motor activity has been reported to be similar in men and women, suggesting that a reduction in antral activity is not the cause of slower GE in women (Hutson et al., 1989). Furthermore, although it has been suggested that GE may be slower in the luteal phase of the menstrual cycle (Gill et al., 1987), this effect is debated (Horowitz et al., 1985). It may thus be prudent to ensure that the proportion of premenopausal women in the control group is similar to the group to be studied. Interestingly, the largest study examining GE in the critically ill suggests that gender has the opposite effect i.e. women had a faster emptying (Heyland et al., 1996b), although this is not a consistent finding (Kao et al., 1998; Kao et al., 1999). It is possible that normal hormonal effects are less evident in the critically ill, as critical illness causes marked aberrations in hormonal activity so the gender effect on GE may be less important. It is also likely that other factors have a stronger influence on GE causing marked slowing in some cases and obscuring the more subtle hormonal effects.

3.5.2 Effect of aging on emptying and transit

The effect of age on GE is uncertain with inconsistent observations (Beckoff et al., 2001; Clarkston et al., 1997; Divoll et al., 1982; Gainsborough et al., 1993; Moore et al., 1983; Nakae et al., 1999; Shimamoto et al., 2002). Extreme aging is associated with a decrease in appetite and a probable slowing of GE. This may reflect an increase in small intestinal nutrient feedback (Cook et al., 1997). Older people also have increased basal and nutrient stimulated CCK levels, which may contribute to slower GE and increased pyloric motility (MacIntosh et al., 1999). Studies on the elderly usually evaluate subjects in the age range 65-80. There is a great age range in critically ill patients, however, in the author's unit the median age is approximately 48 yrs, as there are many younger trauma patients. Heyland et al reported a

small, but significant slowing of GE with increasing age in a mixed critically ill cohort (Heyland et al., 1996b). It is possible that age may contribute to the delays in GE observed in the critically ill but its importance is as yet unclear and any effect is likely to be small. Factors associated with slow GE in the critically ill are examined in chapter 9.

3.5.3 Posture

A number of other factors should also be considered when examining GE in healthy subjects. The effect of posture is disputed and may be dependent on meal composition and volume. In health, non-nutrient liquid emptying appears to be moderately affected by posture (gravity) (Anvari et al., 1995b; Burn-Murdoch et al., 1980; Wallden et al., 2004) while nutrient liquid emptying is not or only marginally so (Burn-Murdoch et al., 1980; Jones et al., 2006). This presumably indicates the dominant effects of small intestinal feedback in regulating GE of nutrients (see section 3.3.4). Posture also has no effect on nutrient liquid emptying in patients with spinal cord injuries (Segal et al., 1995), although this study was underpowered to detect a small changes in GE between seated and supine positions. The effect of posture on the emptying of solids is disputed. When solid was mixed with nutrient liquid, GE was reported to be much more rapid when subjects were sitting compared to lying (76 min sitting vs. 117min lying; $P=0.012$) (Moore et al., 1988). However, when the emptying of solid alone was measured it was unaffected by posture (Doran et al., 1998). Despite the controversy, and the apparent lack of effect of posture on GE of nutrient liquids, it would appear prudent to standardise posture in measurements of GE. As patients in ICU are nursed supine with head elevated to 30°, all studies, both in control subjects and patients, reported in this thesis were performed in that position.

3.5.4 Exercise, diet, smoking, alcohol

Mild exercise may accelerate, while severe exercise delays GE (Marzio et al., 1991). Control subjects were therefore instructed not to exercise for 24h prior to a study. Also the gut may become 'sensitized' to chronic dietary exposure to particular nutrients. For example, a chronic very high fat diet results in faster GE of a high fat meal compared to a low fat diet (scintigraphic $t_{1/2}$; 100min vs. 150 min; $P<0.05$) (Cunningham et al., 1991a). Similarly, high intake of glucose for several days prior to GE measurement results in faster emptying of a glucose drink in healthy subjects (Cunningham et al., 1991b). Documentation of diet was, accordingly, included in data collection in all the healthy subjects studied and subjects with unusual diets were excluded (vegetarians). Cigarette smoking slows emptying (scintigraphic $t_{1/2}$; 37 min vs. 56 min; P value not given) (Johnson et al., 1991), as may acute and chronic alcohol ingestion (Franke et al., 2004; Wegener et al., 1991). Healthy subjects were accordingly, requested not to drink alcohol or smoke for 24 h prior to their studies.

3.5.5 Pain, stress, discomfort, anxiety

Discomfort and stress are frequent accompaniments of an ICU admission. These factors may also be important in healthy subjects undergoing physiological studies. The effect of discomfort and stress on GE has been demonstrated in healthy subjects under a number of conditions. For example, the stress of mental arithmetic increased the length of the lag phase of gastric emptying (Roland et al., 1990) and pain, caused by either ice water hand immersion (Fone et al., 1990b), or ischaemia (Petring and Sloth Madsen, 1991) also slows GE markedly. The healthy subjects included in studies reported in this thesis had participated in previous clinical studies, to minimise the effects of stress and anxiety.

3.6 Nutrient absorption

The most important function of the gastrointestinal tract is the absorption of food for fuel. As there is considerable redundancy in the system, severe derangements are required before abnormalities become apparent. Digestion involves the breakdown of complex food constituents (starch, triglycerides and protein) to their monomeric forms (sugar, free fatty acids, amino acids) for subsequent absorption from the intestinal lumen through the mucosal epithelial cells to the blood or lymphatic system. The most important site for absorption is the small intestine. Absorption is maximised by the increased surface area due to the presence of Kerkring's folds, villi and microvilli (Caspary, 1992) and factors such as the contact time between chyme and mucosa which is dependent on small intestinal motility. Other mucosal properties including the presence of enzymes, carrier proteins and perfusion are also important.

3.6.1 Glucose and other carbohydrates

Carbohydrates are ingested as polysaccharides (e.g. starch), oligosaccharides (e.g. sucrose) and monosaccharides (glucose). Poly- and oligosaccharides must be broken down to monosaccharides to be absorbed. Starch is cleaved by pancreatic α amylase at the surface of the mucosal membrane. There is further cleavage of short chain poly- and oligosaccharides by enzymes in the membrane of the small intestine. The end products of this process are primarily glucose, galactose and fructose (Caspary, 1992). Absorption then occurs by multiple mechanisms including sodium dependent active transport, facilitated diffusion, and passive diffusion.

Factors which potentially affect the rate and completeness of intestinal sugar absorption include: mode of ingestion, digestibility, gastric emptying, α amylase activity, transit time, contact surface (intestinal length, surface villi, enzyme content of brush border, carrier function), and thickness of diffusion barrier of the absorptive epithelium (unstirred layer).

There are limited data on carbohydrate absorption in critical illness (see chapter 4), but it is likely to be abnormal. This may contribute to the weight loss that occurs with prolonged admissions to the ICU. Potential limitations of glucose absorption in the critically ill may reflect aberrant motility, mucosal abnormalities including reduced perfusion, atrophy and abnormal enzymatic activity. As a major focus of this thesis was the optimisation of nutrient delivery in critical illness, the impact of gastrointestinal motility on subsequent absorption is reported in chapter 12.

3.6.2 Lipid

The majority of ingested fat is in the form of triglycerides. The remainder is comprised of phospholipids, cholesterol and fatty acids. Fat absorption is normally highly efficient so that less than 5% of ingested fat is excreted in the faeces. In the small intestinal lumen, fat must be solubilised to be absorbed, and this occurs by the formation of micellar dispersions. Mechanical dispersion converts fat droplets to finely dispersed particles and subsequent enzymatic hydrolysis (lipolysis) by the action of lipase breaks the triglycerides down to free fatty acids. This process starts in the mouth (salivary lipase) and continues through the stomach and in the small intestine (pancreatic lipase). The presence of free fatty acids in the proximal small intestine (Liddle, 1995) stimulates the release of CCK which triggers bile secretion. Bile contains bile salts and phospholipids which combine with the micelles of fat to form mixed

micelles with increased surface area of the fat droplets, allowing more effective enzymatic hydrolysis (Stremmel, 1987). Fatty acids are moved through the micro villous membrane in the upper jejunum via a specific carrier mediated, energy dependent, transport process driven by a transmembrane sodium gradient (Stremmel, 1987).

Limited data suggest that fat absorption is reduced in the critically ill (see chapter 4) (Fraser et al., 2006).

3.6.3 Protein

The majority of protein absorption occurs in the upper jejunum. Protein digestion occurs in three phases 1) in the intestinal lumen, 2) in the brush border, and 3) in the cytoplasm. In the luminal phase, breakdown of proteins to oligopeptides of 2-8 amino acids occurs by the actions of enzymes released in an inactive form from the pancreas, and activated by enzymes present in the small intestinal mucosa (e.g. trypsin). Brush border enzymes further hydrolyse these oligopeptides to amino acids which are transported by specific mucosal carriers.

3.7 Summary

In summary, it is important to have a complete understanding of the function of the gastrointestinal tract in health prior to an examination of the pathophysiology in disease. This allows a full insight into the relevance of any abnormalities demonstrated, likely underlying causes and therapeutic possibilities. The main function of the gastrointestinal tract is to break down, digest and absorb ingested nutrients. An important component of this is the motility of the gastrointestinal tract which breaks down the constituents of nutrition and moves them distally allowing digestion and absorption. Both motility and absorption are likely to be abnormal in critical illness. In health, the motor functions of the upper gastrointestinal tract are tightly regulated by neural and humoral mechanisms. Feedback from the small intestine controls movement of nutrient from the stomach and along the small intestine, to optimise absorption. This is mediated by neural and humoral responses to the presence of nutrient in the small intestine. Disturbances in these regulatory pathways are likely to be important in the motor dysfunctions that occur in critical illness. Absorption depends on mucosal surface area, blood flow and enzymatic activity. Little is known about motility and absorption in the critically ill and these aspects are examined in chapters 11 and 12.

Chapter 4

Pathophysiology of gastric and small intestinal function in the critically ill

4.1 Introduction

Despite the enteral administration of nutrient being the preferred route in the critically ill, it is frequently unsuccessful (see chapter 2). This is primarily due to delayed GE, which has been demonstrated to exist in a substantial proportion of critically ill patients. In this chapter, previous work relating to the prevalence, risk factors and pathophysiology of delayed GE in the critically ill is reviewed. The abnormalities in upper gastrointestinal motility underlying disordered GE in the critically ill have hitherto received little attention and the effects on absorption are even less well characterised. The aberrations in gastroduodenal function demonstrated in other disorders, are also discussed, given that these insights may be of relevance to the critically ill.

4.2 Gastric and small intestinal function in the critically ill

4.2.1 Gastric emptying

The term gastroparesis describes abnormally slow emptying of a meal from the stomach into the duodenum, resulting from disordered gastro-duodenal motility. It may result from neuropathic and/or myopathic abnormalities or may be 'idiopathic'. In addition to its occurrence in association with critical illness, slow GE occurs in diabetes mellitus, postvagotomy, postviral infection, and progressive systemic sclerosis. Delayed GE may also be associated with functional dyspepsia and anorexia nervosa. In ambulant patients, it may result in upper gastrointestinal symptoms, such as decreased appetite, early satiety, postprandial fullness and vomiting. In the critically ill, slow GE is usually identified by the presence of large volumes of gastric aspirate (see chapter 8), which may also result in reflux of gastric contents into the pharynx and mouth. The latter can result in the aspiration of gastric contents into the lungs, with subsequent deterioration in ventilatory function, aspiration pneumonitis, and/or ventilator-associated pneumonia.

4.2.1.1 GE in the critically ill

Gastric emptying has been examined in the critically ill using a variety of techniques (see chapter 6 for a description of these techniques). However, a number of factors limit the applicability of these studies to the overall understanding of GE and feed intolerance in intensive care patients. These include;

- i. Differing definitions of critical illness
- ii. Heterogeneity or otherwise of the group studied
- iii. Limited numbers recruited
- iv. Variability in the measurement techniques hampering comparisons between studies.
- v. Variability in the conditions under which measurements of GE are made between patients and controls (e.g. posture, presence or absence of nasogastric tube etc)

vi. Selection of controls.

Definitions of critical illness

The first issue is the patient population studied. Patients may not be 'critically ill' even though the diagnosis would suggest critical illness. For example, Power *et al*, measured GE in a group of patients with traumatic brain injury. However, as all patients were at a stage of recovery when they were able to swallow the paracetamol, which was administered orally, they would not be considered critically ill. The reported prevalence of delayed GE of 12% is, thus, likely to underestimate the prevalence in a more acute patient group (Power *et al.*, 1989). A similar problem occurs with a subsequent study examining GE in 10 patients with >20% burns (Hu *et al.*, 1993). This study failed to demonstrate reduced GE in this group of patients (area under curve (AUC)₁₂₀ 556 +/- 190; burns vs. 539 +/- 131 µg/ml/min; healthy; not significant (NS)). However, it is unlikely that these patients were critically ill. They were in a burn centre not in an ICU, and they also ingested the paracetamol orally. Furthermore the patients were not receiving opiates, which suggests their burns were neither severe nor acute. Another possible explanation for the failure of this study to demonstrate slower GE in the patients with burns is that it may have been underpowered to demonstrate a difference (see below). For the purpose of the studies described in this thesis the author defined critical illness as patients who were treated in the intensive care unit and requiring mechanical ventilatory support.

The population of patients studied must also be taken into consideration when extrapolating results into clinical practice. Some investigators have examined specific diagnostic groups, such as traumatic brain injury, while others have studied heterogeneous groups of patients in the ICU. Although mixed groups are relevant as they reflect the day to day work load of the intensivist, their interpretation is sometimes difficult because ICUs can have disparate patient populations. Traumatic brain injury and burns have been traditionally considered specific risk factors for feed intolerance. Data regarding traumatic brain injury are however conflicting. There are also insufficient data on burns to enable the prevalence to be determined. Thus the prevalence of delayed GE and risk factors in the critically ill population as a whole have not yet been fully described (see below).

Limited numbers

The small numbers enrolled in most published studies reflect the difficulties in recruiting critically ill patients. There is significant variability in GE in health and this variability may be exaggerated in critical illness. Therefore, in small studies, the failure to observe differences in GE measurements between ICU patients and healthy subjects may be due to the low statistical power of the studies (Heyland *et al.*, 1996b; Hu *et al.*, 1993).

Variability in measurement techniques

Even when the same method is used, the techniques for measurement of GE can vary considerably between centres, making comparisons virtually impossible. This particularly applies to paracetamol absorption measurements, where there is substantial variability in both the doses administered and the parameters reported. In the studies reported below (see table 4.1) the dose of paracetamol varied from 0.5 to 1.6 g and the AUC was reported for different time periods i.e. 60 or 120 minutes.

Variability in conditions of measurement

GE may be affected by the presence or absence of a nasogastric tube (Read *et al.*, 1983), and the volume and composition of feed administered (Hunt and Stubbs, 1975). Furthermore, studies frequently fail to provide sufficient details of the conditions under which healthy

subjects were studied, making interpretation of the results difficult and comparison between studies invalid. For example, historical controls studied under different conditions are not suitable for comparison (Ott et al., 1991). Rather than directly comparing GE between the patients and healthy cohorts, it may be more useful to document the number of patients in whom GE rates fall outside the normal range, provided this is determined in a healthy cohort studied under identical conditions to the patients. A common practice is to infuse the marker into the stomach via a nasogastric tube in the patient group, but allow the control group to swallow the marker (Kao et al., 1998; Ott et al., 1991; Spapen et al., 1995). This difference in technique is likely to affect GE measurement and limit the capacity to compare the groups. Only one study has hitherto used nasogastric tubes to place marker in the both patients and healthy subjects (Weekes and Elia, 1996). When measuring GE in a healthy cohort, it is also important that subjects have been accustomed to the positioning of a nasogastric tube prior to the study, as GE may be substantially slowed by stress or discomfort (Roland et al., 1990).

GE in the critically ill compared to healthy subjects

Three studies have used paracetamol absorption to compare GE in critically ill patients to that in healthy subjects (see table 4.1) (Goldhill et al., 1995; Heyland et al., 1996b; Tarling et al., 1997). The study by Tarling *et al* reported a prevalence of delayed GE of 60% in a mixed group of 27 ICU patients (Tarling et al., 1997). Goldhill *et al* reported that GE was markedly delayed in 14 patients on the day after, when compared to before cardiac surgery (AUC₆₀ 892 mg min.l⁻¹ (SEM 57) vs. 131 mg min.l⁻¹ (SEM 25)) (Goldhill et al., 1995). The study by Heyland *et al* reported reduced GE in a mixed group of 72 ICU patients, as measured by time to maximal concentration (T_{max}), and maximal concentration (C_{max}), of paracetamol, compared to controls (T_{max} 105 min (60-180) vs. 30 min (15-90); P < 0.001; C_{max} 94.1 (75.3) μmol/l vs. 208.4 (33.1) μmol/l; P < 0.001), however, when examining the more traditionally used AUC measurement there was no difference (AUC₁₂₀ 9301 (7343) μmol/min per l vs. 11644 (1336) μmol/min per l (p = 0.28)) (Heyland et al., 1996b). These studies suggest that there is great variability in GE in critically ill patients and that a proportion of patients may have marked slowing of GE, but the true prevalence remains uncertain. A high variability of GE measurements, with a proportion of patients having normal GE, may necessitate that studies include relatively large numbers of subjects to demonstrate a difference in GE.

In the study by Tarling *et al*, it was reported that slow GE was associated with reduced illness severity, which is unexpected and appears intuitively unlikely. The patients who demonstrated reduced illness severity and GE included those who had head and neck surgery. As these patients tend to stay a short time in ICU post operatively, it is likely that they were studied soon after their admission and at this time the residual effects of general anaesthesia might have affected GE. This suggestion is in keeping with the findings of an earlier study from the same group in which GE was markedly delayed one day after cardiac surgery (Goldhill et al., 1995). In the study by Heyland *et al* GE was slower in men, which was unexpected given that in healthy subjects GE is slightly slower in women (Datz et al., 1987; Hermansson and Sivertsson, 1996; Hutson et al., 1989). However, men tend to be more unwell in ICU and have a worse outcome (Moran et al., 2008). Hence, the finding of slower GE in males may relate to increased illness severity.

Authors	No	Type of patients	Dose (g) paracetamol	GE	Factors associated with slow GE
(Goldhill et al., 1995)	13	Pre and post cardiac surgery, Cross over study	1	GE reduced post op AUC ₆₀ 892 mg min.l-1 (SEM 57) vs. 131 mg min.l-1 (SEM 25)	
(Heyland et al., 1996b)	72	Mixed ICU patients vs. 10 healthy men	1.6	Reduced GE in ICU Pts. Tmax 105 min (60-180) vs. 30 min (15-90); P < 0.0001 Cmax 94.1 (75.3) µmol/l vs. 208.4 (33.1) µmol/l; P < 0.0001	Age, <i>male</i> gender, use of opiates.
(Tarling et al., 1997)	27	Mixed ICU patients vs. 13 pre op cardiac pts (see Goldhill et al 1995)	1	60% ICU pts had GE > 2SDs < healthy mean. AUC ₆₀ ICU Pts 573 mg.min/l vs. 892 mg min.l-1 (SEM 57). P value not given.	<i>Reduced</i> illness severity, Use of Dopamine.

Table 4.1 Previous studies (n=3) using paracetamol absorption to examine the prevalence and risk factors of disordered GE in the critically ill. TBI = traumatic brain injury, ICP= intracranial pressure, GE = gastric emptying, op = operative.

Authors	n	Type of patients	Dose (g) paracetamol	GE	Factors affecting GE
(McArthur et al., 1995)	21	TBI pts RCT ; Morphine (M) vs. propofol (P)	1	No difference in GE Cmax M 18.5 vs. P 20.8 mg/l, NS Tmax M 20 versus P 25 min NS AUC ₃₀ 354 (22-858) vs. 330 (35-841); NS	No effect of opiates. ICP
(Dive et al., 1995)	10	Mixed ICU pts Erythromycin vs. placebo Crossover trial	1	Tmax 171 ± 93 mins; Cmax 5.38 ± 3.80 µ/mL; AUC ₆₀ 72 ± 42 µ/min/mL	Erythromycin accelerated GE
(Jooste et al., 1999)	10	Mixed ICU pts Metoclopramide vs. placebo Crossover trial	1.2	Cmax 7.1 ± 2.6 mg/l AUC ₁₂₀ 994±624 mg.min/l	Metoclopramide increased GE but had no effect on GRV
(Tamion et al., 2003)	20	Mixed ICU pts NMB vs. placebo Crossover trial	1	Cmax 6.5±3.8 mg/l Tmax 102±75 min AUC ₆₀ 82±42 mg min ⁻¹ l ⁻¹ AUC ₁₂₀ 360±262 mg min ⁻¹ l ⁻¹	No effect of NMB
(Marino et al., 2003)	21	TBI Pts Cross over trial metoclopramide vs. placebo	1	AUC ₁₂₀ 418± 594 mg min ⁻¹ l ⁻¹ , Day 0 AUC ₁₂₀ 149± 161 mg min ⁻¹ l ⁻¹ , Day 2	No effect of metoclopramide. GE worse on day 2
(Memis et al., 2006)	24	Mixed ICU pts RCT; propofol (P) vs. dexmedetomidine (D).	1.5	No difference in GE Increased GRV with propofol AUC ₁₂₀ P 894.53 ± 499.39 vs. D 1113.46 +/- 598.09	?propofol

Table 4.2 Additional studies which have quantified GE in the critically ill using the paracetamol absorption technique (only placebo data are given to indicate range of GE measurements in ICU population). TBI = traumatic brain injury, pts = patients, RCT = randomised controlled trial, GE = gastric emptying, Cmax = maximal concentration, Tmax = time to maximal concentration, ICP = intracranial pressure, NMB = neuromuscular blocking agents, GRV gastric residual volume.

Authors	No.	Type of patients	GE	Factors affecting GE
(Ott et al., 1991)	12	TBI. Not clear if TBI pts ventilated or ICU. Full range of ICP.	Non nutrient liquid, route not stated, No control group 50% delayed (previously determined normal range) T½ not given.	Time from injury
(Spapen et al., 1995)	10	Mixed ICU vs. 10 healthy	Liquid nutrient via NGT in pts & by oral route in healthy. T ½ healthy, 31 ±15 mins; patients, 78 ±40 mins; p < .002 Prevalence of delayed GE not given	Not given
(Kao et al., 1998)	35	TBI vs. 16 healthy. Not clear if TBI pts ventilated or in ICU. Full range of ICP.	Non nutrient liquid administered by NGT to pts. Route not stated in healthy group. Healthy, 29 ± 4 mins, patients, 57 ± 21 min, p < 0.05 abnormal in 80% TBI	Gender (F slower), age, GCS, time from injury

Table 4.3 Studies using scintigraphy to evaluate the prevalence of delayed GE in the critically ill. TBI=traumatic brain injury, pts = patients, ICP =intracranial pressure, SCI = spinal cord injury, T½ = scintigraphic half emptying time, NGT = nasogastric tube.

Authors	No	Type of patients	GE	Factors affecting GE
(Weekes and Elia, 1996)	6	TBI (mechanically ventilated) vs. 4 controls	Liquid nutrient emptying <50% emptied at 120m vs. 100% in controls	

Table 4.4 Study using phenol red technique to measure GE in critically ill patients.

Scintigraphy is considered the most accurate method for measurement of GE (see chapter 6). As shown in table 4.3 above, scintigraphy has been used to compare GE in critically ill patients to normal subjects in three studies. However, in 2 of these it is unclear what proportion of the patient group was critically ill. Both Ott *et al* and Kao *et al* measured GE in a cohort of patients over a period of time after traumatic brain injury. Neither study states how many, if any, of the patients were mechanically ventilated, or in an intensive care unit, although as both groups recruited patients with Glasgow Coma Scores as low as 3 it is likely that some were. In these studies GE of non-nutrient liquid was quantified, while the emptying of nutrient liquids is of primary interest. Thus the study by Spapen *et al* is the only one to date which has formally examined GE of liquid nutrient using scintigraphy in a mechanically ventilated ICU population. This was a study comparing the effects of cisapride to placebo. They reported that GE of 50 ml of Sondalis Iso (an enteral feed formula) was delayed in a mixed group of only 10 ICU patients compared to healthy humans (Spapen *et al.*, 1995). There are, however, substantial methodological problems with the study. The test meal was swallowed by the healthy subjects and infused via a nasogastric tube into the patients (see above). Only the half emptying time was provided (controls 31 ± 15 min vs. patients 78 ± 40 min; $P < 0.002$). Finally, the sample size was clearly insufficient to evaluate the prevalence, or risk factors of disordered GE.

Weekes *et al* reported a marked reduction in GE in 6 patients after severe head injury using the phenol red technique when compared to 4 healthy male subjects who also had nasogastric tubes (Weekes and Elia, 1996).

In summary, although GE has been measured in a variety of critically ill patient groups and compared to healthy cohorts in a number of studies, there are substantial limitations to these data (including the definition of critical illness, the power of the study, variability in measurement techniques, and in the conditions under which measurements of GE were undertaken between patients and controls, including the use of historical controls). Hence, both the prevalence of delayed GE and the factors that determine this in critical illness remain poorly defined. The study described in chapter 10 was designed to examine the prevalence of slow GE using scintigraphy in a mixed group of critically ill subjects. These data are compared to a group of healthy controls who were studied under exactly the same conditions.

4.2.2 Gastroduodenal motor dysfunctions

In health, GE depends on a balance between propulsive forces generated by the fundus and antrum and resistance provided by the pylorus and proximal duodenum (see chapter 3). It has hitherto been assumed that delayed GE observed in critically ill patients is due to “pump failure”, characterized by antral hypomotility (Mutlu *et al.*, 2001). However, information relating to the motor dysfunctions responsible for slow GE in the critically ill is limited (Bosscha *et al.*, 1998; Dive *et al.*, 2000; Dive *et al.*, 1994a; Dive *et al.*, 1994b; Toumadre *et al.*, 2001). As discussed in chapter 3, in healthy humans, retardation of GE is associated with the suppression of pressure waves in the distal antrum and proximal duodenum and the stimulation of pressure waves localised to the pylorus (Heddle *et al.*, 1989). There is also a redistribution of ingesta from the distal to proximal stomach (Heddle *et al.*, 1989). In healthy subjects, the slowing of GE induced by cold stress, or acute hyperglycaemia is associated with similar motor patterns, as well as a reduction in antro-pyloro-duodenal propagated waves (Fone *et al.*, 1990b; Fraser *et al.*, 1994). Patients in ICU are frequently in discomfort, and hyperglycaemia is extremely common. Thus it would not be surprising if similar motor changes underlying delays in GE occurred. However, there are many other factors which are also likely to affect GE in critical illness (see chapter 5). While motor activity in the antrum and proximal duodenum has

been examined in the critically ill (see below), pyloric activity, the coordination of waves in the antropyloroduodenal region and the relative contributions of the proximal and distal stomach have not.

4.2.2.1 Proximal gastric function

Fundic tone is important for gastric emptying of liquids (Kelly, 1980) (see chapter 3). Proximal gastric relaxation occurs in response to the presence of duodenal nutrient. Abnormal relaxation and retention in the proximal stomach in the context of delayed GE is associated with cold stress (Fone et al., 1990b). Increased retention of solids in the proximal stomach has been reported in diabetics with gastroparesis (Jones et al., 1995). Proximal gastric function has not been examined in the critically ill; however, dysmotility of the fundus could contribute to prolonged proximal gastric relaxation which could, in turn, cause delays in GE, particularly of liquid nutrient.

4.2.2.2 Antral dysfunction

Fasting antral motility

Reduced antral motility is characterised by the absence, or reduction of the antral component of phase 3 of the interdigestive migrating motor complex (MMC). Reduced fasting antral motility, with an absence of antral phase 3 activity, has been reported in critical illness (Dive et al., 1994b). As discussed (chapter 3), antral phase 3 activity is associated with the expulsion of non-digestible food residues and cellular debris into the intestine. An absence or reduction of antral phase 3 activity may predispose to increased bacterial colonisation of the stomach. In critically ill patients this may have serious consequences as it can be a precursor for ventilator-associated pneumonia (Inglis et al., 1993). Fasting antral motility is reduced in many cases of idiopathic gastroparesis (Labo et al., 1986; Narducci et al., 1986), and gastroparesis associated with progressive systemic sclerosis (Bortolotti et al., 1991), diabetes mellitus (Malagelada et al., 1980) and following truncal vagotomy (Malagelada et al., 1980).

Postprandial antral motility

During, and after, feeding, antral contraction results in trituration of solids and movement of nutrients through the pylorus (chapter 3). The rate of GE is related to antral activity (Houghton et al., 1988a). Delayed GE may be associated with weak and/or disordered antroduodenal contractions (Fone et al., 1990b). Reduced postprandial antral activity has been reported in critically ill patients (Dive et al., 1994b). The same group demonstrated that increased antral activity, induced by the administration of erythromycin, was associated with more rapid GE (mean number of contractions, erythromycin $104 \pm 34/h$ vs. placebo $5 \pm 8/h$; $P = .003$, mean amplitude of contractions 52 ± 16 vs. 20 ± 17 mm Hg; $P = .005$, paracetamol AUC₆₀ 730 ± 269 vs. 72 ± 42 $\mu\text{g}/\text{min}/\text{mL}$; $P = .002$) (Dive et al., 1995). Thus a direct relationship between GE and antral activity in the critically ill has been established.

4.2.2.3 Pyloric motility

Pyloric activity (phasic and tonic) is integral to the regulation of GE (chapter 3). However, technical challenges associated with its measurement have resulted in a reduced appreciation of its role in gastrointestinal physiology (Heddle et al., 1988b) (see chapter 6). Increased basal pyloric pressure and/or an increased frequency of phasic contractions result in a slowing of GE. Thus Fone *et al* reported that increased pyloric activity was associated with reduced GE induced by cold stress in healthy subjects (Fone et al., 1990b). Pyloric activity has not

previously been formally examined in the critically ill. Pyloric motility and the relationship between pyloric activity and GE in the critically ill is reported in this thesis (see chapter 11).

4.2.2.4 Duodenal motility

Duodenal motility can potentially affect the rate of GE via a number of pathways. A reduction in duodenal contractions may delay the aboral movement of chyme, allowing pooling of duodenal content and reducing the gastroduodenal pressure gradient. Distension of the proximal duodenum may also inhibit both proximal and distal gastric motility (Treacy et al., 1996). Furthermore duodenal contractions can be retrograde both as a component of phase 3 activity (Haba and Sarna, 1993), and post-prandially. Retrograde contractions move chyme back into the distal antrum slowing gastric emptying (Haba and Sarna, 1993).

Fasting duodenal motility

The MMC, characterised by the intermittent appearance of phase III activity, is the hallmark of fasting duodenal motility (see chapter 3). Abnormalities in MMC activity may be characterised by changes in the proportion of time spent in the three phases, the coordination of contractions during the phases, and/or the direction of migration of phase III activity. Persistence of MMC activity during feeding is considered pathological although its implications are unclear. Paradoxically, more frequent MMC activity may be associated with slower small bowel transit presumably because of uncoordinated motor function with increased retrograde activity. Both more frequent MMC activity and delayed transit have been demonstrated following the administration of opioids (Powell, 1981) and postoperatively (Benson et al., 1994; Miedema et al., 2002; Noer, 1968). These are relevant to critical illness. Reduced motor activity may predispose to increased bacterial load, while increased transit will allow less time for nutrient absorption.

In critical illness, during fasting, the number of contractions and the occurrence of activity fronts in the duodenum (proximal and distal), have been reported to be comparable to health (Dive et al., 1994b). Although the duration of the duodenal migrating motor complex is also similar, the relative contribution of the quiescent period (phase 1) to the total cycle length has been reported to be increased. Conversely, the contribution of phase 2 activity is reduced (Dive et al., 1994b; Miedema et al., 2002). Abnormally propagated (retrograde or stationary) activity fronts in the duodenum also occur (Dive et al., 1994b) (Miedema et al., 2002; Toumadre et al., 2001). Furthermore, fasting activity has been reported to persist in some critically ill patients during feeding (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Moore et al., 2001; Toumadre et al., 2001).

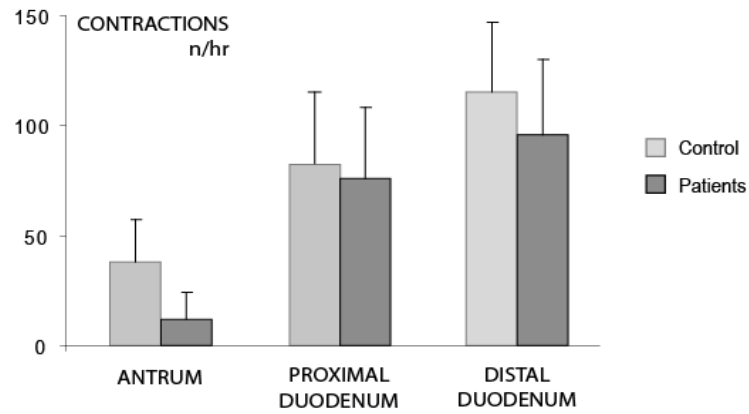


Figure 4.1 Contractions recorded in antrum, proximal duodenum and distal duodenum in 12 healthy subjects (shaded columns) and 12 critically ill patients (unshaded columns). Data are number of contractions per hour. In the antrum the ICU patients had significantly less contractions compared to the healthy subjects ($P=0.002$). By contrast the small differences in numbers of contractions in both proximal and distal duodenum did not reach statistical significance. Reproduced with permission. (Dive et al., 1994b)

Normal intestinal microflora stimulate the initiation and aboral migration of physiological phase III activity (Caenepeel et al., 1989; Husebye et al., 1994). The microflora in critical illness are unlikely to be normal and the effect of this on motility is unclear. Conversely, loss of normal MMC activity is associated with intestinal bacterial overgrowth (Svenberg et al., 1982). Abnormal motility may facilitate bacterial overgrowth and subsequent blood stream contamination, added to by the failure of the hepatic reticulo-endothelial system to control the movement of gut bacteria into the systemic circulation. Thus small intestinal dysmotility may have a role in the perpetuation of sepsis in critical illness.

The significance of abnormal duodenal motility in critical illness remains uncertain. In a small group of patients with very severe trauma, the presence of the fasting MMC predicted subsequent successful enteral feeding by jejunostomy (Moore et al., 2001). However, as only 5 (of 10) patients had fasting MMC activity, this hypothesis needs confirmation in a larger study. This premise is supported by a similar finding in a group of children with chronic idiopathic intestinal pseudo-obstruction (Di Lorenzo et al., 1995), where the presence of fasting MMC activity also predicted those who could be successfully fed with a jejunal tube. The presence of fasting MMC is also predictive of ability to take oral nutrient with the administration of prokinetics in both children and adults with this condition (Di Lorenzo et al., 1995; Hyman et al., 1993; Verne et al., 1995). Thus the presence of fasting MMC activity appears to have clinical importance, but this requires further study in critical illness.

The impact of the persistence of fasting motor activity during nutrient administration on GE and feed tolerance in the critically ill is unclear. Given that the coordination of waves during phase III activity, and the migration of phase III activity may be abnormal in the critically ill, persistent phase III activity may hinder effective nasogastric or jejunal feeding, by reducing small intestinal absorption. Assessing the impact of persistent MMC activity on GE, the success of feeding, absorption and the incidence of complications such as diarrhoea is relevant to the ICU population as it may offer the potential for therapeutic intervention. The relationship between persistent MMC activity and GE is explored in chapter 11.

4.2.7 Organisation of gastroduodenal motility

The temporal and spatial organisation of antral, pyloric and duodenal contractile activity is important in the regulation of GE (chapter 3). The organisation of gastroduodenal contractions may be disordered in several ways, including direction and length of propagation and the frequency of propagated waves. The organisation of antropyloroduodenal contractions has not been previously examined in the critically ill. The organisation of antroduodenal waves in the critically ill and the relationship between these and GE is addressed in chapter 11.

4.3 Pathogenesis of abnormal motility

GE in health is controlled by myogenic, neural and hormonal mechanisms, modulated by feedback arising from small intestinal receptors (see chapter 3). Abnormally slow GE may potentially result from, primary motor dysfunction (“pump failure”), disproportionate activation of normal motor mechanisms by increased intestinal feedback triggered by the presence of nutrients in the small intestine (“excessive feedback”) (Horowitz and Dent, 1991; Lin, 1994), or a combination of the two. Abnormal feedback could be mediated by neural or hormonal mechanisms. The pathogenesis of delayed GE in the critically ill is poorly defined. In particular, the possibility that increased small intestinal nutrient feedback contributes to delayed GE in the critically ill has not been assessed. The study described in chapter 11 focuses on the

nature of the disturbance in control underlying delayed gastric emptying in the critically ill, specifically small intestinal nutrient feedback.

4.3.1 Myogenic abnormalities

Myogenic causes of gastroparesis are uncommon. However they include Duchene's muscular dystrophy and dystrophia myotonica (Barohn et al., 1988; Horowitz et al., 1987), polymyositis and dermatomyositis (Horowitz et al., 1986), amyloidosis (Chokhavatia and Anuras, 1991) and in the late phases of progressive systemic sclerosis (Chokhavatia and Anuras, 1991; Greydanus and Camilleri, 1989). In the critically ill, muscle function may be affected by electrolyte disturbance. Skeletal muscle bulk is reduced over time due to nutritional factors, but it is not known whether this also affects smooth muscle. These factors are unlikely to fully account for the observed delays in GE.

4.3.2 Neural abnormalities

Abnormalities in intrinsic or extrinsic neural innervation may result in gastroparesis. Although it is not known if the myenteric plexus is affected in critical illness, degeneration of the myenteric plexus has been demonstrated in other conditions such as intestinal pseudo-obstruction (Krishnamurthy and Schuffler, 1987). Also, a lymphocytic infiltration of the myenteric plexus has been demonstrated in the paraneoplastic syndrome associated with small cell carcinoma of the lung (Schuffler et al., 1983). Hence, it is possible that abnormalities could occur in the critically ill. However, abnormalities of extrinsic neural control are more likely to be important. Vagal activity increases GE (see chapter 3), so factors that interfere with vagal control, will be inhibitory. Sympathetic activity is inhibitory and sympathetic overactivity is a feature of critical illness. Thus, although the causes of abnormal gastrointestinal motility in critical illness are unclear, it is possible that sympathetic neural stimulation may have a role.

4.3.3 Abnormal hormonal regulation

Numerous hormones are involved in the regulation of gastrointestinal motility (chapter 3). The best characterised is CCK, which is an important humoral mediator of the entero-gastric feedback response (see section 3.3.3.1) (Borovicka et al., 1996; Fraser and Davison, 1993; Fried et al., 1991; Liddle et al., 1986; Rayner et al., 2000; Stacher et al., 1982; Yamagishi and Debas, 1978). Plasma CCK concentrations are elevated in people with abnormally delayed gastric emptying. This has been demonstrated in association with reduced oral intake (Sturm et al., 2004), malnutrition (Aguilera et al., 2003; Suzuki et al., 2005) and eating disorders such as anorexia nervosa (Baranowska et al., 2000; Chance et al., 1984; Shulkes et al., 1983; Suzuki et al., 2005). More recently, healthy ageing has also been reported to be associated with a modest increase in basal and nutrient stimulated plasma CCK, suggesting a possible contribution to anorexia and weight loss in the elderly (MacIntosh et al., 2001). It would thus seem reasonable to consider CCK as a possible mediator when gastric emptying is pathologically reduced, as it is in critical illness.

Reduced motilin release has been demonstrated in dyspeptic patients with idiopathic delay in GE characterized by a lack of gastric activity fronts (Labo et al., 1986), suggesting that reduced motilin may be implicated in the cause of delayed GE and raising the possibility that motilin agonists may have a place in treatment.

Low ghrelin levels and high PYY levels have been measured in ICU patients (Nematy et al., 2006) however, the potential contribution of gastrointestinal hormones to the rate of GE in the critically ill has not been studied.

4.3.4 Abnormal enterogastric feedback

It is possible that an exaggerated feedback response could result in delayed GE. This is suggested by the similarity between patterns of motility associated with normal slowing of GE in response to the presence of nutrient in the small intestine (Fone et al., 1989; Heddle et al., 1988a; Heddle et al., 1988c; Tougas et al., 1992) and the gastroduodenal motor dysfunction reported in patients with gastroparesis. This hypothesis has not been studied in the critically ill and forms the focus of the study described in chapter 11.

4.4 Nutrient absorption

Nutrient absorption has rarely been measured in the critically ill. However, as small intestinal mucosa is abnormal during critical illness (Hernandez et al., 1999), it is likely to be abnormal and contribute to the weight loss that occurs with prolonged ICU stay. The distinction between 'rate' of absorption which may be modified by delayed GE, and 'total' absorption which is influenced primarily by small intestinal mucosal/pancreatic function, is important. In critically ill patients nutrient is delivered continuously into the gut. Ideally delivery should be at a rate where absorption can be maximised while minimising the possibility of adverse events such as diarrhoea.

Animal studies indicate that inflammatory mediators may affect gut absorptive function. In a rodent study, the endotoxin-induced reduction in glucose absorption was explained solely by an effect on GE (Hurwitz et al., 1975) and a subsequent study suggested this may be mediated by tumour necrosis factor- α (TNF- α) (Singh et al., 1993). In contrast, in rats, administration of interleukin-15 has been reported to reduce fat (triolein) absorption (Almendro et al., 2005), an effect apparently unrelated to changes in GE or intestinal motility. Furthermore, in rats 18 hours after a burn injury, absorption of enterally administered ^{14}C -palmitate triglyceride was reduced by 50%, in association with a 50% reduction in brush border lipase activity (Carter and Tompkins, 1994). Inflammatory mediators, including TNF- α and interleukin-15, are frequently elevated in critically ill patients with trauma and sepsis (Brauner et al., 2000) and these data suggest a role in reduced nutrient absorption.

Absorption has been measured in critically ill humans. Singh et al reported reduced D-xylose absorption in 11 septic and 8 trauma patients in intensive care (Singh et al., 1994). In patients 24–48 hrs and 72–96 hrs after injury, D-xylose plasma levels were reduced. These reverted to normal approximately 12 days after injury. Similarly septic patients also had impaired D-xylose absorption, but this did not normalise for 23 days. Interestingly, oral feeding could be resumed before normalization of absorption. However incomplete absorption may have resulted in diarrhoea and limited weight gain although these parameters were not reported. Glucose absorption has also been examined in critically ill subjects (Hadfield et al., 1995) by measuring urinary recovery of d-xylose and 3-O-Methyl-Glucose (3-OMG). Glucose absorption was reported to be markedly reduced in the critically ill compared to healthy subjects (6 % recovery of d-xylose compared to 35% in healthy subjects; 8-12% recovery of 3-OMG compared to about 50% in the healthy) (Hadfield et al., 1995). Both these studies infused the glucose into the stomach and, accordingly, did not determine if the reduced absorption reflected decreased glucose delivery to the small intestine and/or diminished small intestinal mucosal absorption.

Chioléro *et al* also demonstrated reduced xylose absorption in a mixed group of critically ill patients (Chiolero et al., 2003). The magnitude of the reduction was similar whether the xylose was infused intra gastrically, or intraduodenally suggesting that delayed GE was not the primary cause. However, as the study was descriptive only, and not randomised – with patients studied according to the method of nutritional support that was indicated clinically, it is likely that the patients who received small intestinal nutrition were sicker than those who received gastric nutrition. Thus the conclusion that GE was not responsible for abnormal glucose absorption requires confirmation. However, the study does support the argument that small intestinal glucose absorption is abnormal in the critically ill.

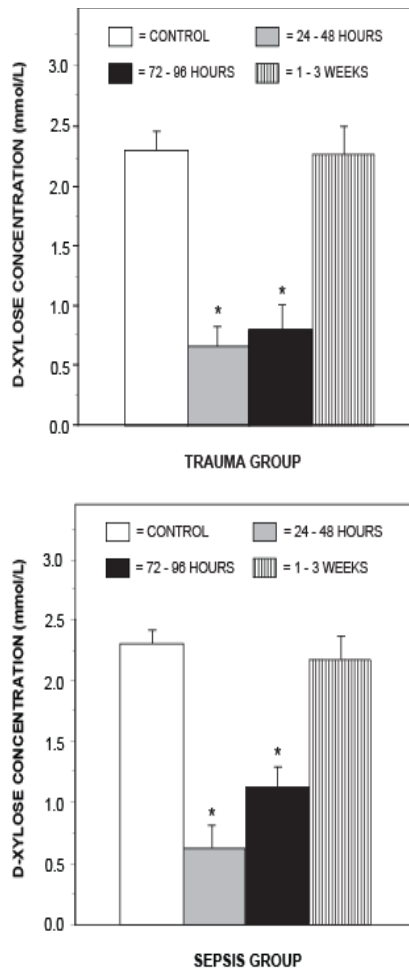


Figure 4.2 Effects of trauma (graph 1) and sepsis (graph 2) on D-xylose absorption over time in critically ill subjects. Concentration of D-xylose in peripheral blood 1 h after gastric administration. * $P < 0.05$ vs. controls ANOVA & Newman Keuls test. Reproduced with permission (Singh et al., 1994).

A subsequent study examined fat absorption in 7 patients after abdominal aortic aneurysm repair. The fat was instilled directly into the small intestine so GE was not a factor. Absorption of triolein was found to be reduced by about 50% on day one. This study also suggested that there was further deterioration in fat absorption by day 3, such that it was reduced to 20% of normal values. However, on day 3 only 4 patients were studied and as these were likely to be the sickest patients it is unclear whether there was a deterioration, or this small group had reduced fat absorption from day 1 (Fraser et al., 2006). Reduced fat absorption has also been reported to be associated with increased phase 3 like activity in the small intestine (Fraser et al., 2006). Increased activity fronts could reduce absorption by reducing the time of exposure of chyme to small intestinal mucosa. Thus fat absorption also appears to be reduced in the critically ill.

Patients with acute severe pancreatitis comprise a particular diagnostic group in the intensive care unit with specific problems related to absorption, particularly of fat, due to reduced pancreatic exocrine activity. These patients frequently experience diarrhoea/steatorrhoea. The delivery of adequate enzyme concentrations into the duodenal lumen can reduce nutrient malabsorption as can the delivery of an elemental feed formulation.

Protein absorption has rarely been measured in critical illness. Reduced amino acid absorption has been reported in rats following haemorrhagic shock (Sodeyama et al., 1992), in patients with pancreatitis (Evenepoel et al., 2000), and in critically ill patients following trauma (Carlin et al., 1999). In the latter study both the plasma and breath L-[1- ¹³C] phenylalanine enrichment concentration was approximately 10% of normal at 24h slowly rising to 50% of normal at 7 days.

In summary, nutrient absorption is almost certainly impaired in critical illness, possibly mediated by inflammatory cytokines, but it is unclear, particularly in the case of glucose, whether this is related to reduced GE or to small intestinal factors. These could include local motor, perfusion, mucosal or enzymatic abnormalities. Available data support the hypothesis that glucose absorption is reduced independent of GE, but this needs confirmation as efforts to improve gastric motility or bypass the stomach to deliver nutrient to the small intestine may be less effective if absorption is independently reduced. A study describing the relationship between GE and glucose absorption in critically ill patients is described in chapter 12.

4.5 Summary

The abnormalities underlying problems with nutrition in the critically ill are, poorly defined. The rate of GE is variable, but delayed in a proportion of patients. However, due to limitations in previous studies, the true prevalence and associated factors are unclear. The motility disturbances underlying problems with nutritional delivery are also poorly understood. Antral motility is reduced and duodenal activity, although quantitatively normal, is qualitatively different from that in health, with persistence of phase III activity during feeding, the cause and significance of which is unclear. Pyloric motor activity and the coordination of propagated waves have not been examined. The relationship between GE and motility patterns has also not been adequately assessed. Furthermore, the aetiology of motility abnormalities has not been delineated. In particular, the effects of small intestinal nutrient feedback on the rate of gastric emptying have not been measured. Nutrient absorption appears to be reduced, but this has also not been examined in detail, and the relationship between GE and absorption is unclear. In this thesis the author attempts to address many of these deficiencies in our understanding of the pathogenesis of feed intolerance. In chapter 10 the prevalence and risk factors for feed

intolerance in an Australian ICU population is examined and the clinical causes for cessation of nutrient delivery described. In chapter 10 the prevalence and risk factors of slow GE is examined using scintigraphy to measure GE. In chapter 11, the motility disturbances underlying delayed GE including the role of enterogastric feedback are examined in a group of mechanically ventilated patients using perfusion manometry and breath test techniques. In chapter 12, abnormalities in glucose absorption, and the relationship between GE and glucose absorption in the critically ill are presented.

Chapter 5

Aetiology of gastrointestinal dysfunction in critical illness

5.1 Introduction

The aetiology of abnormal upper gastrointestinal motor activity in critical illness remains unclear, but is likely to be multifactorial. Potential causes include drugs, such as narcotics or catecholamines, electrolyte abnormalities, hyperglycaemia, recent surgery, shock, circulating cytokines, pre-existing medical conditions, and the admission diagnosis (Ritz et al., 2000). In any particular patient there are likely to be a number of factors that influence the success of enteral nutrition. Furthermore, there may be specific patient sub-groups that exhibit particular patterns of abnormal gastrointestinal motor function, but these have yet to be identified.

The aim of this chapter is to summarise current knowledge about the likely causes and risk factors for feed intolerance and delayed gastric emptying in the critically ill. The studies described in chapters 10 and 11 were designed to contribute to this body of knowledge. Furthermore, the information provided in this chapter was taken into account when planning the studies involving critically ill subjects, in an effort to minimise confounding factors. Finally, this chapter helps to put the overall findings of this thesis into perspective.

5.2 Potential impact of admission diagnosis on GE

The prevalence of delayed GE in a mixed critically ill population is as yet unclear, although limited studies to date suggest that it occurs in approximately 60% of critically ill patients (Tarling et al., 1997)(see chapter 4). It is also not known whether admission diagnosis affects the risk of delayed emptying and feed intolerance. Critically ill patients with traumatic brain injury and burns have previously been considered to be at increased risk, but high quality epidemiological studies examining the prevalence in particular subgroups have not been undertaken.

5.2.1 Traumatic Brain Injury

5.2.1.1 Feed intolerance in traumatic brain injury

Patients admitted to the intensive care unit after traumatic brain injury are considered to have increased risk of feed intolerance although the evidence for this is not conclusive. In a study, where feed intolerance was defined as a gastric residual volume (GRVs) >100 ml, only 30% of head injured patients tolerated nasogastric feeding in the first week after injury (Norton et al., 1988). However this volume is low (see chapter 6.3.4) and is likely to give a falsely high estimation of the prevalence of slow gastric emptying. In a further study, head injured patients received only 60% of calorie requirements delivered by enteral feeding in the first week after injury (Young et al., 1987). This is similar to the success rate reported in other critically ill subgroups (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). As these studies are descriptive in nature, the influence of traumatic brain injury as an individual risk factor on feed intolerance is uncertain.

Feed intolerance in traumatic brain injury may be due to raised intracranial pressure (Bochicchio et al., 2006; Norton et al., 1988). Bochicchio et al reported that none of 57 patients with refractory intracranial hypertension, receiving thiopentone infusions, tolerated enteral

feeding. Furthermore, they did not respond to prokinetics or post pyloric nutrient delivery (Bochicchio et al., 2006). It is unclear whether this was due to raised intracranial pressure, or the thiopentone infusion or a combination of the two. The effect of thiopentone on gastric emptying is unknown. These studies provide a possible cause for feed intolerance in patients with traumatic brain injury.

As patients with traumatic brain injury often have a prolonged stay in ICU and hospital, limited nutritional delivery can result in malnutrition and may potentially affect outcome. For example, a 10 kg loss of weight over 2-3 weeks was reported in a group of patients with traumatic brain injury (Weekes and Elia, 1996) and only 25% of the weight loss was fat, suggesting that the majority of loss was muscle bulk. Thus inadequate nutritional delivery may have significant clinical sequelae in this group.

5.2.1.2 Gastric emptying in traumatic brain injury

Patients admitted following traumatic brain injury are also at risk of delayed gastric emptying (see chapter 4). However, a wide range of prevalence has been reported (12-80%) (Kao et al., 1998; Ott et al., 1991; Power et al., 1989; Weekes and Elia, 1996). The degree of slowing of gastric emptying appears to correlate with the severity of injury. These studies all have significant limitations (see chapter 4) and the true prevalence of gastroparesis in this condition remains uncertain.

Consistent with the data above regarding the effect of intracranial pressure on feed intolerance, animal studies suggest that raised intracranial pressure markedly reduces gastric and duodenal motility possibly via vagal mechanisms (Garrick et al., 1988). Raised intracranial pressure is common following traumatic brain injury and this may account for the slow rate of gastric emptying in this group.

5.2.2 Burns

5.2.2.1 Feed intolerance in burns

Although burns patients are widely believed to be at high risk of feed intolerance, the risk may be less than previously supposed. For example, a study examining enteral feeding in 106 patients with burns demonstrated that 87% were successfully fed and 100% of nutritional goals were met by day 3. Feed tolerance was reduced in patients with severe burns (> 60% burnt surface area), but they still received about 75% of nutritional goals by day 4 (McDonald et al., 1991). Two further studies suggest that, with aggressive feeding protocols, 80% of patients with severe burns can be fed successfully naso-gastrically, and this is associated with improved outcomes (Hansbrough and Hansbrough, 1993; Raff et al., 1997). Of these three studies, only that reported by Raff *et al* specifically included mechanically ventilated patients. However, the results reported by that group were no different. Furthermore, in patients where nasogastric feeding fails, 80% can be successfully fed with postpyloric feeding (Sefton et al., 2002). Together these studies suggest that the enteral route is suitable for feeding patients with burns.

The nutritional requirements of burns patients are augmented due to an increased metabolic rate (Long et al., 1979). Successful enteral feeding is therefore considered a high priority. Achieving early successful feeding is thought to reduce subsequent hypermetabolism and improve clinical outcomes (Chiarelli et al., 1990; Mochizuki et al., 1984; Wasiak et al., 2007). Furthermore, early enteral feeding may reduce the incidence of stress ulcer bleeding (Choctaw

et al., 1980), a serious complication of severe burn injury. Accordingly, efforts to optimise nutrient delivery are of particular importance in these patients.

5.2.2.2 Gastric emptying in burns

While animal studies have demonstrated reduced gastric emptying and gastrointestinal motility after burns (Alican et al., 1995; Chen et al., 1982), this has not been shown in humans. Using the paracetamol absorption technique, gastric emptying of water was not found to be delayed in a group of non-critically ill patients with moderate second-degree burns (Hu et al., 1993). To date, gastric emptying has not been measured in critically ill patients with burns.

5.2.3 Sepsis

Although sepsis is common in critically ill patients, the prevalence of feed intolerance and delayed gastric emptying in this condition is unknown. Animal studies suggest that sepsis is associated with a number of abnormalities in gastrointestinal motor function including delayed gastric emptying (Hurwitz et al., 1975). In addition, absent fasting migrating myoelectric complexes (Cullen et al., 1996), and reduced small intestinal electrical activity, both during fasting and with feeding (Cullen et al., 1996) have been reported.

5.2.3.1 Endotoxin

Many of the clinical sequelae of sepsis are due to the presence of endotoxin (also known as lipopolysaccharide), a constituent of the cell wall of gram negative bacteria. Animal studies have shown that endotoxin inhibits gastric emptying (Cullen et al., 1999b; van Miert and van Duin, 1980), and increases intestinal transit rate (Cullen et al., 1999a), despite reduced gastric and small intestinal myoelectric activity (Cullen et al., 1996).

5.2.3.2 Inflammatory mediators

Endotoxin causes the release of a series of inflammatory cytokines, including tumour necrosis factor α (TNF α) and interleukin-1 (IL-1), which have been shown to affect gastrointestinal motility (Glatzle et al., 2004; Lodato et al., 1999). In animal models, cytokines inhibit gastric motility (Glatzle et al., 2004), impair intestinal smooth muscle function (Lodato et al., 1999), and impair fat absorption – the latter is apparently independent of any effect on gut motility (Almendro et al., 2005). The effects of cytokines on motility may be mediated, at least in part, by CCK. IL-1 increases CCK levels, and inhibition of CCK reduces the inhibitory effect of IL-1 on gastric emptying in rats (Daun and McCarthy, 1993). It is not known whether effective resuscitation and treatment, with a consequent decrease in cytokine production (Ranieri et al., 1999), will reverse the disturbances in gastrointestinal motility.

5.2.3.3 Nitric oxide

Nitric oxide (NO) is an important inhibitory neurotransmitter in the gastrointestinal tract (see section 3.3.3.1). NO levels are increased during sepsis (Wong et al., 1996) and could be responsible for the impaired gastrointestinal smooth muscle activity seen in this condition (Cullen et al., 1996; De Winter, 2003). Cytokines activate macrophages in the gastrointestinal wall, which up-regulates their expression of inducible NO synthase (iNOS) (De Winter, 2003) leading to smooth muscle relaxation (De Winter, 2003). Animal studies suggest that NO is not responsible for the slow gastric emptying observed in association with sepsis (Wirthlin et al.,

1996). Small intestinal transit has not been measured in septic humans, however in endotoxaemic animals, increased NO activity appears to mediate the increased small intestinal transit (Cullen et al., 1999a). NO production can potentially be manipulated therapeutically. For example, the administration of NO synthase inhibitors results in delayed small intestinal transit (despite an increase in motility) (Fraser et al., 2005). In addition to effects on the gastrointestinal tract, NO has major effects on vascular endothelium and may be the cause of the marked vasodilation and hypotension which is a feature of septic shock (Gonzalez et al., 1992). However, therapeutic NO inhibition probably has limited application in the critically ill as NO inhibition has been reported to increase myocardial adverse events and death in patients with severe sepsis (Lopez et al., 2004).

5.2.3.4 α -adrenergic agents

The inhibition of gut motility by endotoxin can be blocked by α 2 receptor antagonists, suggesting that adrenergic pathways may mediate this effect. In endotoxaemic mice, yohimbine, an α 2 receptor antagonist, improved delayed gastric emptying and gastrointestinal transit, possibly by down-regulating endotoxin-induced increased expression of iNOS (Hamano et al., 2007). This suggests that α 2 receptor antagonists have a potential therapeutic role.

5.2.3.5. Summary of the effect of sepsis and inflammatory mediators on gastrointestinal motility

Severe sepsis is likely to be associated with delayed gastric emptying and abnormal gastrointestinal motility. This may be due to the presence of lipopolysaccharide, the release of cytokines such as TNF and interleukins, and increased NO and adrenergic activity. Further investigation is required to confirm the importance of these findings in humans.

5.2.4 Spinal Cord Injury

High level, spinal cord injuries are another common reason for admission to the intensive care unit. The prevalence of delayed gastric emptying and gastrointestinal disturbance has not been examined in the acute phase following injury. However the interruption in extrinsic neurological control, particularly in high level lesions, is likely to affect motor function. Delayed gastric emptying in the chronic phase after spinal cord injury has been reported in 50-80% of patients (Fealey et al., 1984; Kao et al., 1999; Rajendran et al., 1992; Segal et al., 1995; Zhang et al., 1994). While age and injury duration were not significant factors influencing gastric emptying, gender and level of injury did have an effect. The effect of level of injury can be understood when considering the extrinsic neurological control of gastric emptying. Vagal innervation will not be affected by spinal cord injury as it arises from the brain stem. However, sympathetic control is from the spinal cord levels T5 to T 12. Cord injury above these levels will result in uninhibited sympathetic outflow, which will act to slow emptying. The effect of cord injury on gastrointestinal motility in the acute phase is likely to be similar to that reported in chronic patients, but warrants formal evaluation.

5.2.5 Other conditions

The relationship between feed intolerance and slow gastric emptying and other diagnoses (such as pancreatitis, postoperative patients, multi-trauma excluding head trauma) and illness severity is unknown.

5.3 Pre-existing conditions

Many patients admitted to the ICU have co-morbidities that can affect gastrointestinal function. The influence of pre-existing conditions, known to alter gastric emptying, on gastrointestinal motility after admission to the ICU are, however, unknown. For example, diabetes mellitus is a common chronic condition that affects a significant proportion of patients admitted to ICU for other reasons and is commonly associated with abnormal gastrointestinal motility.

5.3.1 Diabetes Mellitus

Delayed gastric emptying of solids occurs in 30-50% of type 1 and type 2 patients with longstanding diabetes mellitus in the community (Horowitz et al., 1989; Horowitz et al., 1991; Horowitz et al., 1996; Mearin and Malagelada, 1995; Samsom et al., 2003). The pathogenesis of abnormal upper gastrointestinal function in diabetes mellitus is incompletely understood but is likely to be multi-factorial (Camilleri, 2007; Samsom et al., 1997). Disordered accommodation and contraction of the fundus, antrum and duodenum have been demonstrated in these patients and are thought to be primarily due to autonomic dysfunction and hyperglycaemia (Horowitz and Fraser, 1994; Horowitz et al., 1996; Rayner et al., 2001; Samsom et al., 1998). However, while these abnormalities result in delayed gastric emptying of *solid* meals, gastric emptying of *liquid* feeds may be delayed, normal, or even rapid in both type 1 and type 2 diabetes (Bertin et al., 2001; Frank et al., 1995; Jones et al., 1996; Lipp et al., 1997; Phillips et al., 1991, 1992; Schwartz et al., 1996; Weytjens et al., 1998). Rapid gastric emptying has also been reported in euglycaemic type 2 diabetics without autonomic neuropathy (Bertin et al., 2001). Furthermore, delayed transit of solids, but accelerated emptying of liquids can occur in the same individual (Cavallo-Perin et al., 1991; Chang et al., 1996). The above data indicate that even patients with delayed gastric emptying of solids prior to hospital admission could have normal or even rapid emptying of liquid meals when fed in the intensive care unit. This is an area that requires further study.

5.4 Autonomic dysfunction

As well as occurring in diabetes mellitus, autonomic dysfunction frequently accompanies critical illness, particularly certain conditions such as Guillain Barre Syndrome (Hahn, 1996) and tetanus (Freshwater-Turner et al., 2007). However, both the incidence and impact on gastrointestinal function have not been evaluated. Bolton et al reported the prevalence of autonomic dysfunction in ICU patients with various neurological disorders, using electrocardiographic R wave interval variability as an index of parasympathetic function, and the sympathetic skin response for sympathetic assessment. Eight of the 29 patients with sepsis-related neuropathy or encephalopathy had abnormal R-R variability. Furthermore the sympathetic skin response was absent in all but 2, suggesting that there is a high incidence of autonomic dysfunction in these patients which is probably under-recognised (Bolton et al., 2007). It is possible that autonomic dysfunction contributes to the delayed gastric emptying seen in critical illness but this has not been formally evaluated and is outside the scope of this thesis.

5.5 Hyperglycaemia

The relationship between acute hyperglycaemia and gastric motility and emptying is well characterised (Andrews et al., 1998; Fraser et al., 1990; Hebbard et al., 1996; Jones et al., 1999; MacGregor et al., 1976; Oster-Jorgensen et al., 1990; Rayner et al., 2001; Schvarcz et al., 1995;

Schvarcz et al., 1997). Severe hyperglycaemia (≥ 15 mmol/l) markedly slows gastric emptying by relaxing the proximal stomach, reducing antral motility and the coordination of antroduodenal contractions, and stimulating isolated pyloric pressure waves (Fraser et al., 1991; Fraser et al., 1990; Hebbard et al., 1996; MacGregor et al., 1976; Oster-Jorgensen et al., 1990). Even changes in blood glucose concentrations within the normal postprandial range (4-8mmol/l) have a significant impact on gastric emptying in both normal subjects and patients with insulin dependent diabetes (Andrews et al., 1998; Jones et al., 1999; Schvarcz et al., 1997). Conversely, insulin induced hypoglycaemia increases gastric motility and accelerates gastric emptying (Russo et al., 2005; Schvarcz et al., 1995). The underlying mechanisms mediating the effects of blood glucose concentration on gut motor function are unclear but abnormalities in neural, humoral and cellular pathways have been described (Horowitz et al., 1996). Hyperglycaemia is uniformly present in critical illness (Boord et al., 2001), mainly as a consequence of the excessive release of 'stress' hormones such as catecholamines, glucocorticoids, growth hormone, and glucagon; and inflammatory cytokines such as tumour necrosis factor, interleukin-1, and interleukin-6 (Boord et al., 2001; McCowen et al., 2001; O'Neill et al., 1991). It would thus seem probable that hyperglycaemia contributes to delayed gastric emptying in critical illness, but there are as yet no studies formally examining this. This is particularly relevant given that there is evidence that intensive insulin therapy, designed to achieve target blood glucose concentrations of 4.4 to 6.1 mmol/L, during the management of critical illness, reduced both in-hospital morbidity and mortality (Kransley, 2004; Malmberg et al., 1995; van den Berghe et al., 2001). If there is a relationship between hyperglycaemia and disturbed gastric motility in critical illness, the routine use of intensive insulin therapy would be expected to reduce the incidence of delayed gastric emptying and feed intolerance. This is yet to be evaluated.

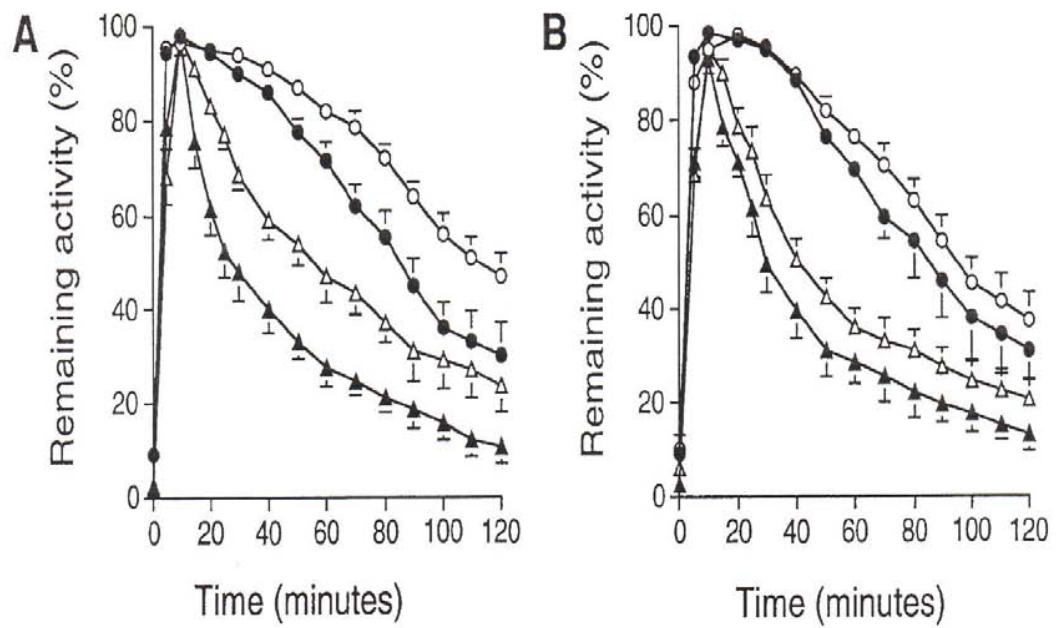


Figure 5.1 Gastric emptying of the solid (circles) and liquid (triangles) component of the meal and blood glucose concentrations of 4 (●) and 8 (○) mmol/l. Gastric emptying is slower at a BGL of 8 mmol/l. Mean and SEM. A - normal subjects and B- patients with insulin dependent diabetes mellitus. Reproduced with permission (Schvarcz et al., 1997).

Hyperglycaemia also affects motility in other regions of the gastrointestinal tract. Marked hyperglycaemia decreases small intestinal motility (Bjornsson et al., 1994), reduces the cycle length of interdigestive motor activity in the fasted state (Oster-Jorgensen et al., 1992), and slows small-intestinal transit (de Boer et al., 1993; Russo et al., 1996). Elevation of the blood glucose concentration to the upper end of the physiological range (10 mmol/l) decreases duodenal compliance while increasing the stimulation of duodenal waves by duodenal balloon distension (Lingenfelter et al., 1999); a less compliant duodenum may contribute to the slowing of gastric emptying during hyperglycaemia (Rayner et al., 2001).

Not only does blood glucose concentration influence GE, but the rate of GE also affects blood glucose concentrations. The contribution of disordered GE to poor glycaemic control is unclear, but is likely to be significant (Gonlachavit et al., 2003; Horowitz et al., 2002). This may also be important in critical illness. The relationship between blood glucose and gastric emptying in critical illness is explored in the study reported in chapter 12.

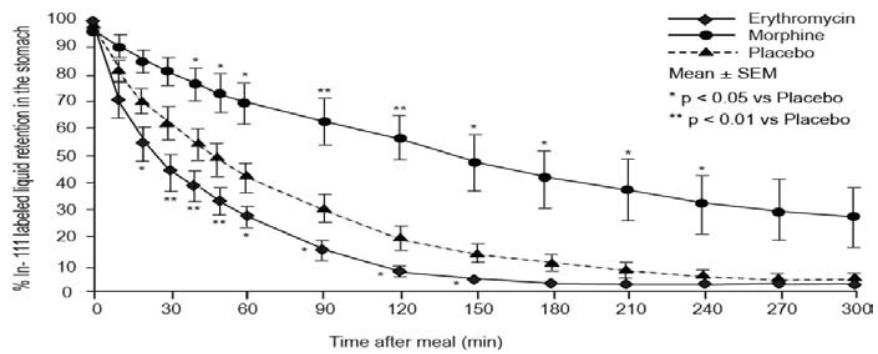
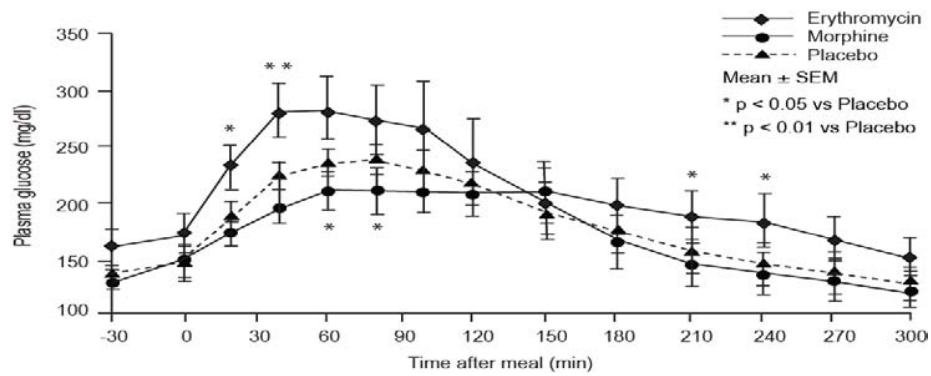


Figure 5.2 The relationship between GE and blood glucose concentrations. When GE is accelerated by erythromycin there is a greater increment and higher peak blood glucose concentration. Conversely when GE is delayed by morphine the increment in blood glucose concentrations is delayed and smaller. Reproduced with permission (Gonlachanvit et al., 2003).

5.6 Fasting/malnutrition

Prior patterns of nutrient intake can influence subsequent gastric emptying and gastroduodenal motility (Cunningham KM & Daly J, 1991, Cunningham KM & Horowitz M, 1991, Horowitz M, 1996, Rigaud 1988). In particular, nutrient deprivation for as little as 4 days slows gastric emptying (Corvilain B, 1995, Beckoff K, 2001). In about 50% of patients with anorexia nervosa, gastric emptying is delayed (Rigaud 1988, Dubois 1979, Holt 1981) and appears to normalize with recommencement of adequate intake, before weight gain occurs (Rigaud 1988). In many ICU patients there is a period of time prior to admission when nutrition has been suboptimal. Also nutritional needs may not be addressed immediately following admission due to the priorities of resuscitation. The mechanisms which underlie the alterations in gastric emptying, occurring in response to variations in gastrointestinal nutrient exposure, almost certainly arise from the small intestine (Rigaud 1988, Robinson 1988). It is not known whether adaptive changes in gastric emptying occur as a result of changes in small intestinal receptor affinity and/or the number of receptors exposed to nutrient. However, it is possible that a period of nutrient deprivation results in upregulation of small intestinal feedback. This would result in an exaggerated enterogastric response causing a marked reduction in GE with subsequent introduction of nutrients. This may occur in the critically ill. The enterogastric feedback response in critical illness was investigated by the author and is reported in chapter 11. Also, because of the potential effects of nutrient deprivation on GE, efforts were made to quantify the nutritional history of patients included in the studies reported in this thesis, prior to the studies being performed.

It is possible a period of starvation may also affect gut mucosal function which may adversely affect absorption. In animal studies, prolonged starvation is associated with mucosal atrophy and reduced enzymatic activity (Dou et al., 2001). Mucosal atrophy manifests itself in reduced villous height and mucosal thickness, changes in crypt depth, reduced mucosal weight and decreased protein content. Animal studies have demonstrated a functional down-regulation of the mucosa within 12-18 hours of intestinal starvation and an increased rate of bacterial translocation after 24 hours (Bark et al., 1995; Levine et al., 1974). The absorption of glucose in a group of critically ill patients is reported in chapter 12.

In summary, there is the potential for gastrointestinal sequelae to result from a period of reduced, or absent nutritional intake in critically ill patients, and this may contribute to the subsequent success of feeding or absorption.

5.7 Drugs

Many drugs administered in the ICU have the potential to affect feed tolerance, gastric emptying, gastrointestinal motility and gut function. Drugs frequently implicated include opioids and catecholamines. Both are commonly used, and have been shown to have a marked effect on gastrointestinal motility in animal studies and in healthy humans. It is also likely that other agents will affect motility.

5.7.1 Opioids

Sedatives and analgesics are required in the management of critically ill patients to minimise discomfort and maximise tolerance of ICU procedures. Opioids are frequently used to provide both analgesia and sedation. These drugs are widely recognised to have adverse effects on the gastrointestinal tract, by their action on peripheral μ receptors (Murphy et al., 1997;

Stanghellini et al., 1984). Even at low doses opioids slow gastric emptying, (Yuan et al., 1998), by causing fundal relaxation (Hammas et al., 2001), and reducing antral contractions (Schurizek et al., 1989). They may also increase duodenal phase 3 frequency (Bosscha et al., 1998; Thorn et al., 1996). As discussed (chapter 4) diminished antral activity and increased duodenal phase 3 frequency are both features of critical illness (Bosscha et al., 1998; Dive et al., 1994b; Moore et al., 2001; Toumadre et al., 2001). Opioids are thus known to cause some of the patterns of gastrointestinal dysmotility that have been reported in critical illness.

Heyland *et al* reported an association between the use of opioids and slow GE in a mixed group of 72 critically ill patients (Heyland et al., 1996b). However, as this was a descriptive study, causation cannot be assumed. In contrast, in another descriptive study, involving 27 critically ill patients, no relationship was observed between GE and the use of opioids (Tarling et al., 1997). Similarly, the choice of sedative agent did not appear to affect GE in a study in which 21 critically ill patients with traumatic brain injury were randomised to receive either morphine or propofol (McArthur et al., 1995). The reason for the discrepancy between the results of these studies is unclear. It is possible that the latter 2 studies were underpowered to show a difference, or that morphine and propofol have similar inhibitory effects on GE. However, it is also possible that the effect of opioids on GE is overshadowed by other, more potent factors in critically ill patients. Thus the contribution of the administration of opioids to subsequent slow GE and feed intolerance in critical illness has not yet been fully clarified.

Fentanyl is another opioid frequently used in the ICU. There are no studies comparing the relative effects of fentanyl and morphine on gastric emptying. However, equipotent analgesic doses of morphine delay GE more than *alfentanyl* (Bennett et al., 1994), and *alfentanyl* causes more delay in GE than fentanyl (Milligan et al., 1988). Thus fentanyl may be a better choice of opioid in patients with feed intolerance.

The similarity in gastrointestinal motor patterns observed in the critically ill to that known to be induced by opioids suggests that the use of opioids may contribute to the delays in gastric emptying and feed intolerance. However, this cannot be stated with certainty without comparative studies. Also, it is likely that there are multiple causes for delayed GE in critical illness and the relative importance of opioid administration remains uncertain. Establishing the contribution of opioids to feed intolerance, would, if the effects prove to be substantial, suggest the use of alternative agents, and/or the administration of locally active antagonists, to improve nutrient delivery. This issue is, however, outside the scope of this thesis.

5.7.2 Other analgesics

Paracetamol is frequently used in critically ill patients as a weak analgesic in order to reduce opioid requirements. While it has previously been thought to have almost no intestinal adverse effects at recommended doses (Kehlet and Dahl, 2003), paracetamol (0.01-100 μ M) has recently been reported to have an inhibitory effect on guinea pig peristalsis, while acetylsalicylic acid and metamizole (a non-steroidal anti-inflammatory drug) did not (Herbert et al., 2005). Paracetamol is used frequently as an analgesic and antipyretic. Its use could thus contribute to feed intolerance in the ICU

5.7.3 Benzodiazepines

Midazolam is often administered as an infusion in combination with morphine to provide sedation, anxiolysis and amnesia during ICU admission. Midazolam may also contribute to

abnormal gastrointestinal motility. In mice, midazolam slows gastric emptying, and prolongs gastrointestinal transit (Inada et al., 2004b). The effect of midazolam on human gastric motility and emptying is unknown. In healthy humans, small doses of midazolam were reported to increase the duration and amplitude of duodenal phase III pressure waves without affecting phase III frequency (Castedal et al., 2000a). The clinical implications of this are unclear, but are likely to be minimal. There is no information relating to the effect of midazolam infusion on gastrointestinal motility or feed intolerance in critically ill patients.

5.7.4 Propofol

Propofol is a sedative that has been introduced relatively recently into ICU practice. The main advantage of this agent is its short half life, so that patients wake rapidly when the infusion is switched off. However, as propofol has no analgesic activity, it is of limited benefit when analgesia is required. Low doses of propofol have no effect on gastric emptying in healthy humans (Chassard et al., 2002; Hammas et al., 1998; Hammas et al., 2001). However, there may be a dose-related effect, as propofol slows gastric emptying and increases small intestinal transit time at anaesthetic doses in mice (Inada et al., 2004b). Slower intestinal transit has also been reported in humans (Hammas et al., 1998). This may reflect a prolongation of phase 1 of the MMC (Schnoor et al., 2005). In humans, propofol prevents morphine-induced fundal relaxation, but has no effect on morphine-induced delay in GE (Hammas et al., 2001). In a retrospective cohort study, propofol was associated with feed intolerance in critically ill patients with traumatic brain injury (Rhoney et al., 2002). However, it remains unclear whether propofol causes feed intolerance or delayed GE in this group.

5.7.5 α 2-adrenoceptor agonists

The α 2-adrenoceptor agonists, clonidine and dexmedetomidine, are supplementary analgesic and sedative agents in intensive care practice. By causing a reduction in acetylcholine release (James et al., 2004), they have been shown to inhibit gastric, small bowel and colonic motility in animal and human studies (Asai et al., 1997a; Asai et al., 1997c; Herbert et al., 2002; James et al., 2004; Qian et al., 2001). Animal studies suggest that; (i) dexmedetomidine slows GE to a lesser extent than clonidine (Asai et al., 1997a); (ii) both agents have a comparable effect on gastrointestinal transit (Inada et al., 2004a); (iii) the effect on GE is less than that of morphine (Asai et al., 1997b); (iv) the effect of dexmedetomidine on transit is additive to the effects of morphine (Asai et al., 1998).

The effects on small intestinal transit may have important clinical sequelae in critically ill patients. Clonidine has been implicated as a cause of pseudo-obstruction (Stieger et al., 1997) and as a possible cause of small bowel necrosis (Frey et al., 2001). Gastric emptying during dexmedetomidine infusion has been reported to be similar to that observed during the infusion of propofol. In this study, the GRVs in the group receiving propofol were higher, but this difference was not clinically significant, and no patient in either group was feed intolerant (Memis et al., 2006). In summary, these studies suggest that α 2 agonists may have adverse effects on gastrointestinal motility and gastric emptying but this requires further study. These agents were not studied for this thesis.

5.7.6 Catecholamines

High levels of circulating catecholamines, either endogenous or exogenous, are common in critically ill patients. Sympathetic stimulation slows gastric emptying and gastrointestinal

motility by a beta₂ adrenergic effect (Clark et al., 1980; Gati et al., 1975). In an in vitro study, using guinea pig ileum, adrenaline had the greatest potency for reducing peristaltic activity, followed by noradrenaline, dopamine, and dobutamine (Fruhwald et al., 2000). Other than adrenaline, all the drugs at low doses had a stimulatory effect (Fruhwald et al., 2000). In addition, there are specific dopamine₂ receptors in the gastrointestinal tract (Lanfranchi, 1978; Van Nueten and Schuurkes, 1984). Dopamine has been shown to reduce antral contractions, increase phase III frequency (Dive et al., 2000) and slow gastric emptying (Van Nueten and Schuurkes, 1984) and oro-caecal transit (Levein et al., 1999). Furthermore the administration of dopamine was an independent risk factor for reduced GE in a study involving 27 mechanically ventilated, critically ill patients (Tarling et al., 1997). In addition to slowing GE and reducing the success of feeding, high dose catecholamines may also inhibit the prokinetic effect of erythromycin (Barnert J, 1998). In summary, while the use of catecholamines may be unavoidable in the critically ill hypotensive patient, it is likely that these agents contribute significantly to delayed GE and feed intolerance.

5.7.7 Other drugs used in the management of critically ill patients

A number of other drugs may be used in ICU that are known to slow gastric emptying. These include anticholinergics, levodopa (Robertson et al., 1990), omeprazole (Rasmussen et al., 1991) and ranitidine (Corinaldesi et al., 1984). The effect of ranitidine is disputed, however, as in a subsequent study, there was no difference between gastric emptying of 500ml nasogastric feed measured by ultrasound in critically ill patients given ranitidine when compared to cimetidine (Pelfrene et al., 1996). Similarly the neuromuscular blocking agent (cisatracurium) did not affect gastric emptying or feed tolerance (Tamion et al., 2003). These agents are less frequently used than those described above, so their impact on ICU practice is likely to be limited.

5.8 Fluid management

Fluid and electrolyte management may affect gastrointestinal motility and the success of feeding. Administration of large quantities of intravenous fluid is sometimes necessary in the initial resuscitation of the critically ill patient. This can result in splanchnic oedema, which could potentially reduce gastrointestinal motility (Mecray, 1937). Delayed gastric emptying times associated with low serum albumin concentrations have been normalised in dogs by salt and water restriction (Mecray, 1937). In humans, the effect of fluid management on gastrointestinal function has only been studied in perioperative patients; however, it is likely that similar effects would occur in the critically ill population. One study performed in patients having colonic resection for cancer showed that gastric emptying was faster on the 4th postoperative day in the group where intravenous fluids were restricted compared to those where liberal amounts of fluid were given – (median solid and liquid phase scintigraphic t_{1/2}; 175 vs. 72.5 min, difference 56 [95% CI 12-132], P=0.028; and 110 vs. 73.5 min, 52 [9-95], P=0.017, respectively). Median passage of flatus was delayed by 1 day; median passage of stool by 2.5 days; with a 3 day longer postoperative hospital stay in the standard group compared to the restricted group (Lobo et al., 2002). This study has been criticised because of a lack of blinding of the investigators. Furthermore, gastric emptying was not measured in all subjects - and was assumed to be delayed in 3 subjects in the liberal fluid group where GE measurements were not performed because of vomiting or large nasogastric aspirate volumes (Heyland and Paterson, 2002). However, similar results were reported in a subsequent study which also demonstrated a shorter time to the passage of flatus and faeces, and a shorter

hospital stay in patients who had restricted fluid administration following elective abdominal surgery (Nisanevich et al., 2005).

These data, accordingly suggest that fluid restriction in the ICU may improve gastric emptying and feed intolerance. However, this premise is refuted by Wakeling et al who used oesophageal doppler measurements of cardiac output to guide intraoperative fluid management in a group of patients having elective abdominal surgery. This resulted in a greater volume of intraoperative colloid administration, a shorter hospital stay, more rapid recovery to full oral intake, and shorter time to passage of stool (Wakeling et al., 2005). This study was also limited by lack of blinding of the investigators and the fact that the outcome measures, apart from the passage of stool, were subjective.

In summary, the effect of fluid management on gastrointestinal motility and feed administration is unclear and may warrant further investigation.

5.9 Electrolyte disturbances

A direct effect of electrolyte abnormalities on intestinal motility has been demonstrated only for potassium and magnesium. Hypokalaemia and hypermagnesaemia have both been implicated as possible causes of postoperative ileus (Behm and Stollman, 2003; Golzarian et al., 1994).

5.10 Humoral effects

The possible contribution of gastrointestinal peptides to abnormalities in gastrointestinal function in critical illness is discussed in chapter 4. However, significant alterations in the hypothalamic-pituitary axis also occur in critical illness although, it is unclear if these are the cause or result of physiological aberrations. Some of the resulting changes in hormonal concentrations may affect gastrointestinal function. The response of the anterior pituitary to critical illness is biphasic, consisting initially of activated function followed by reduced secretion in the chronic phases (Van den Berghe, 2002). Hormones that may affect gastrointestinal function include corticotrophin releasing factor (CRF), and thyrotropin releasing hormone.

5.10.1 Corticotrophin releasing factor

As corticotrophin releasing factor (CRF) is a key mediator of the central stress response, levels are elevated in critical illness (Beishuizen and Thijs, 2003). This results in elevated corticotrophin concentrations and, thereby, elevated cortisol levels which mediates many of the physiological responses to stress. CRF itself can slow gastric emptying (Tache, Maeda-Hagiwara et al. 1987), by a central mechanism (Garrick et al., 1987) that is blocked by vagotomy (Tache et al., 1990; Tsukamoto et al., 2006). Interestingly, CRF receptor 1-deficient mice do not develop postoperative gastric ileus (Luckey et al., 2003). The importance of CRF in abnormalities in gastrointestinal motility in critical illness is uncertain however it warrants further investigation. It also offers therapeutic possibilities in terms of CRF inhibition to improve feeding success.

5.10.2 Thyrotropin releasing hormone

Prolonged critical illness is characterized by reduced pulsatile thyroid stimulating hormone secretion, causing reduced thyroid hormone release and profound changes in thyroid hormone

metabolism, resulting in low circulating T(3) and elevated rT(3) levels (Debaveye et al., 2005). It is unclear how thyrotropin releasing hormone (TRH) levels are affected in critical illness. However TRH increases gastric emptying (Maeda-Hagiwara and Tache, 1987). It has been suggested that TRH could be administered to the critically ill to prevent protein catabolism (Van den Berghe, 2002) and if this were to occur there may be additional benefits on gastrointestinal motility.

5.11 Mechanical ventilation

Tournadre *et al* (2001) suggested that mechanical ventilation may affect gastrointestinal motility. This hypothesis was based on the observation that during mechanical ventilation, immediately after vascular surgery, the migration of burst activity was abnormal. These investigators reported that when the patients were weaned to spontaneous breathing, the burst migration patterns returned to more typical phase III pattern of activity (Tournadre et al., 2001). As this occurred later in the patients' illness, however, it may have been related to an improvement in overall status rather than an effect of mechanical ventilation per se. Furthermore, as patients are 'weaned' from the ventilator, sedative and analgesic drugs (which may be affecting gastrointestinal motility) are also reduced. An effect of mechanical ventilation on gastrointestinal motility is yet to be demonstrated.

5.12 Splanchnic blood flow

Splanchnic hypo-perfusion in critically ill patients can cause impaired oxygen delivery to enteric cells. Splanchnic hypo-perfusion is mediated via vasoconstriction and preferential distribution away from the splanchnic circulation. Postoperative splanchnic hypo-perfusion is associated with decreased gastrointestinal motility, but it is unclear whether decreased blood flow causes the decreased motility, or both are responses to the same insult (Behrendt 2004). It is possible that hypoperfusion contributes to the abnormalities in gastrointestinal motility seen in critical illness and this warrants further investigation.

5.13 Summary

In summary, the causes and underlying mechanisms responsible for gastrointestinal dysmotility in the critically ill are poorly defined. Many factors are implicated, including the underlying diagnosis, drugs and electrolyte disturbances. The relative importance of these is as yet unclear. It is likely that in individual patients, different factors will have additive effects. Comprehensive, well designed studies examining the prevalence of delayed gastric emptying in ICU patients and the importance of the possible risk factors are needed. A study focusing on the prevalence and risk factors for delayed gastric emptying in an ICU population is presented in chapter 10.

There are multiple pathways which could be implicated in the mediation of the abnormalities in gastrointestinal motility observed in critical illness. Inflammatory cytokines are frequently elevated in critical illness irrespective of the underlying diagnosis and these have an impact on the release of neurotransmitters, such as CCK and NO, and also activate adrenergic pathways. Other potential pathways include; (i) modification of the small intestinal feedback response which may be induced by prior nutrient deprivation; (ii) opioid receptor activation related to sedative administration; (iii) vagal inhibition, for example in association with raised intracranial pressure; (iv) sympathetic stimulation (catecholamine administration, high spinal cord injury, CRF release in response to stress). The small intestinal feedback response was investigated in a

group of critically ill patients and the results are reported in chapter 11. The relationship between blood glucose and gastric emptying is reported in chapter 12.

Chapter 6

Evaluation of gastric and small intestinal motor and absorptive function in critical illness

6.1 Introduction

Comprehensive evaluation of gastric and small intestinal motility and absorption requires the measurement of multiple parameters. These include intraluminal volume, flow, pressure, wall motion, electrical activity and absorption. No single technique can measure all of these concurrently. Consequently, a complete assessment of gastrointestinal function can only be obtained by the simultaneous use of different techniques.

In this chapter, the advantages and limitations of different techniques used to measure gastrointestinal function are discussed, with a particular focus on those suitable for use in the unique environment of the intensive care unit.

Techniques for measurement of gastrointestinal function	Parameters measured
Measurement of gastric residual volume	Volume emptied from stomach over time; (does not take into account secretion)
Scintigraphy	Gastric volume emptied &/or transit; (does not take into account secretion)
Ultrasound	Wall motion, intragastric volume and change in volume over time
Absorption kinetics of orally administered drugs (paracetamol)	Rate of GE and absorption
Magnetic resonance imaging	Wall motion, intragastric volumes
Fluoroscopy	Wall motion, intragastric volumes
Breath test- recovery of ingested labelled markers	Rate of GE and absorption (does not take into account secretion)
Double indicator technique	GE including the effect of secretion
Electrical impedance tomography	GE including the effect of secretion
Manometry	Intraluminal pressures (tonic & phasic)
Strain gauge	Intraluminal pressures (tonic & phasic)
Substrate absorption – 3-O-methyl-glucose, D-xylose, labelled triolein, labelled leucine	Absorption rate and total absorption
Lactulose/ rhamnose absorption	Mucosal Permeability
(51) Cr EDTA absorption	Mucosal Permeability

Table 6.1 Techniques for measurement of gastrointestinal function. GE = gastric emptying.

6.2 Measurement in the Intensive Care Unit

The Intensive Care Unit presents some unique advantages and difficulties when measuring physiological derangements. Patients are usually sedated and attached to many lines, tubes and monitoring devices. Perhaps paradoxically, this may facilitate measurement, as these allow ready access to body fluids such as blood, urine, faeces and saliva, as well as expired gases. Furthermore, the potential for discomfort caused by these measurements is reduced as patients are commonly sedated as part of their routine ICU management.

Performing studies in critically ill patients, especially those who are mechanically ventilated poses a number of challenges. There is limited space around the patient due to the presence of essential but bulky equipment, such as a ventilator and dialysis machine. Clinical staff may object to the presence of additional equipment if it limits access to the patient, particularly if this has the potential to compromise appropriate care in an emergency. Studies may also need to be terminated prematurely due to unexpected clinical requirements. Of particular concern is that measurement techniques may not perform in the same way in the critically ill patient as they do in a more controlled research setting. This may reflect technical difficulties exclusive to the intensive care environment, or physiological derangements in the patient caused by their clinical condition, or treatment. For example, electrical fields generated by clinical equipment may interfere with recordings such as TMPD (see below). In addition, because liver function is frequently impaired in critical illness, techniques which require predictable hepatic metabolism, such as breath tests (see section 6.3.3), or those which may be affected by drug metabolism (including paracetamol absorption- see section 6.3.6), may be less reproducible in this group. Ideally, all measurement techniques should be validated in critically ill patients before widespread use.

6.3 Measurement of gastric emptying (GE)

Slow GE appears to be a major factor limiting the success of nutrient administration to the critically ill. Measurement of GE was thus pivotal to the studies described in this thesis. Formal measurement of GE is rarely performed in the critically ill other than for research purposes. There are a number of techniques available, but all have potential limitations and particular difficulties for use in this population

6.3.1 Introduction

Comparison of different methods of measurement of GE is limited by the practical inability to perform some measurements concurrently. Also different techniques measure different parameters which can make direct comparisons difficult. Changes in gastric volume over time can be quantified by techniques such as scintigraphy, fluoroscopy, ultrasound and MRI. Techniques such as labelled carbon breath tests, or paracetamol absorption, require small intestinal absorption, as well as GE of the substrate. In the case of breath tests, metabolism of the substrate must also occur before excretion into expired air.

Assessment of GE also requires careful definition of the variable to be measured. Whilst solid meals are generally considered to be a more reliable indicator of abnormal gastric emptying than liquids, these are not applicable to the critically ill patients where liquid formulae are used for feeding. Accordingly, GE of nutrient liquid was measured in the studies described in this thesis (chapters 9,10,11,12,13 and 14). GE is also dependant on the composition of the nutrient

(i.e. proportion of carbohydrate, lipid or protein). The presence of a nasogastric tube, and other devices in the gut lumen can also affect measurements (chapter 4).

6.3.2 Scintigraphy

Radionuclide methods, considered the 'gold standard' for measurement of GE, involve labelling a substrate with a radioactive marker, which is placed in the stomach. This 'meal' can be solid, or liquid, and the liquid can be nutrient or non-nutrient. The disappearance of radioisotope attached to a meal component from the field of view is measured over time with a gamma camera, a parallel collimator and recorded to a computer program. This technique measures total abdominal radioactivity. A region-of-interest can be defined to include all, or part, of the stomach. Care is required to exclude structures outside the area of interest. This can be difficult when there is overlying bowel and this is a potential source of inaccuracy (Chatterton, 2004).

6.3.2.1 Radionuclide marker

The choice of radioisotope is crucial to the success of the measurements. Ideally it should be non-toxic, not absorbed onto the gastric mucosa, and homogeneously distributed through the component of the 'meal' being evaluated. Markers are available to measure emptying of specific meal components, such as solid, liquid or fat etc. but these need to be tightly bound to that component. Solid and liquid emptying can be measured concurrently using different markers attached to each phase and dual headed gamma cameras. Liquids and solids empty at different rates and if, for example, a liquid marker is absorbed into the solid phase, the rate of liquid emptying will be underestimated (Chatterton, 2004).

6.3.2.2 Data analysis

Although direct observation of the images provides useful subjective information, meaningful comparisons require standardised parameters. In practice, the results are frequently expressed as a half emptying time or the proportion of the total dose remaining after a period of time. The latter is particularly relevant when GE is markedly delayed or fluctuating as may occur in the ICU population. When emptying of solids is measured, a lag phase is observed, corresponding to the time taken for breakdown of particles to 1mm in size prior to transpyloric emptying (Collins et al., 1983). In addition to total GE, distribution of the meal within the stomach can be assessed (Horowitz and Dent, 1991). Comparison of results between different centres must be performed with care as meal properties and acquisition profiles may differ, and affect measurements. Normal ranges may therefore vary. In 2000, Tougas et al attempted to develop a standardised scintigraphic method of measurements for GE. They performed scintigraphic measurements of GE using a standardised technique in 123 individuals in 11 different centres. They were then able to develop a normal range for solid GE (Tougas et al., 2000). This is of limited relevance to the GE of nutrient liquids in the ICU.

6.3.2.3 Errors and limitations of the technique

Accurate evaluation of GE using scintigraphy requires a number of 'correction factors' to account for technical issues associated with the method. With commonly used isotopes such as technetium, which has a short half life, there is a significant decay in the tracer radioactivity over the time of the study. Correction for decay is therefore routine. Where a single scintillation camera is used, movement towards, or away from the detector with the passage of the meal from the proximal to the distal stomach, results in a change in attenuation of the readings. This problem may be overcome by using cameras placed anteriorly and posteriorly (Christian et al., 1980), but this is not possible in a supine, mechanically ventilated, intensive care patient.

Another solution to this problem is to take images from the left anterior oblique projection as this views the entire stomach in the same plane (Ford et al., 1992; Maurer et al., 1991; Yung, 1993). This method is most convenient in the ventilated patient. Although artefact due to patient movement can influence the results, immobility is usually maintained in ICU with sedation, and clinical staff can be instructed to avoid patient movement during a study.

Scintigraphy measures the *relative* GE of the amount of tracer remaining in the stomach over time compared to that originally instilled into the stomach or ingested (per cent of total dose). The *absolute* emptying cannot be measured with this technique because the volume of gastric secretions both present initially and produced during the study cannot be quantified. Although the rate of GE may potentially be misinterpreted due to the effects of drugs on gastric secretion, this effect is likely to be minor (Chatterton, 2004).

Exposure to ionising radiation constitutes an ethical concern when these studies are performed for research, rather than clinical, purposes. The radiation dose for scintigraphic GE studies is dependent on the radioisotope used, the dose administered and the gastrointestinal transit time. A typical dose of 20MBq of ^{99m}technetium labelled sulphur colloid is approximately 0.5mSv. This is of the same order of magnitude of radiation exposure as that from a contrast study (Chatterton, 2004).

Scintigraphic measurement of GE is a physiological, reliable, non-invasive and reproducible technique. It is considered to be the most accurate method and is widely used in both clinical and research studies to determine the prevalence of slow GE in certain populations (see chapter 10), to investigate the effect of drugs on GE and also to validate other potential methods of measurement of GE (see chapter 9). However it is rarely used in critically ill patients because it usually requires movement of the patient to a nuclear medicine department. Although use of a mobile camera overcomes this obstacle, patient movement and staff access are limited for the period of the study (figure 6.1).



Figure 6.1 Example of a scintigraphic study performed in a mechanically ventilated patient using a mobile gamma camera in ICU. Note the limited space and lack of access to the patient. In the studies reported in this thesis the study was performed over 4hours.

6.3.3 Breath tests

Although scintigraphy is considered the most accurate method of measurement of GE it has limitations for routine use in the ICU (see above). A simpler, more convenient technique would allow more frequent measurement of GE for clinical and research purposes. The breath test technique is a relatively recent development which allows measurement of the GE of solids, nutrient liquids and non-nutrient liquids using carbon isotopes incorporated into a substrate (Ghoos et al., 1993). Unlike scintigraphy, MRI and ultrasonography, which are all direct measurements of GE, the breath test reflects the emptying of the octanoic acid from the stomach, small intestinal absorption, hepatic metabolism and pulmonary excretion of labelled CO₂ (Ghoos et al., 1993). In healthy humans, the speed of delivery of octanoic acid into the duodenum is the rate-limiting step in this process. Following the ingestion of a substrate containing ¹³C or ¹⁴C-labelled octanoic acid, expired air samples are collected over time. Whereas ¹⁴C is a radioisotope of carbon, ¹³C is a stable isotope and is, therefore, preferred as it can be used repeatedly, as well as in situations where radiation exposure is contraindicated such as in children and pregnant women. The two substrates can be used with similar results (Ghoos et al., 1993). The concentration of labelled CO₂ in the expired gas is measured intermittently over a period of time, usually 4 hours (Ghoos et al., 1993). ¹³C is measured using mass spectrometry, while ¹⁴C is measured using a radio-isotope counter. The ¹³CO₂ concentration (percent of total dose per hour) is plotted over time and the resultant curves used to calculate a GE coefficient (GEC), a global index for the GE rate. This accounts for both the rate of appearance and disappearance of the label in breath (Ghoos et al., 1993). In addition, the gastric half emptying time (BTt₅₀) is usually calculated. Total CO₂ production is assumed to be 300 mmol/m² body surface area per hour. The latter is calculated using height and weight (Ghoos et al., 1993).

The octanoic acid breath test has been validated against scintigraphy in healthy subjects for both solid and non-nutrient liquid emptying (Bluck et al., 2002; Braden et al., 1995; Bromer et al., 2002; Chey et al., 2001; Delbende et al., 2000; Ghoos et al., 1993; Maes et al., 1994; Minderhoud et al., 2004; Pfaffenbach et al., 1995) and in a number of disease states including; diabetes, dyspepsia, respiratory disease and gastroparesis (Braden et al., 1995; Braden et al., 2004; Bromer et al., 2002; Gatti et al., 2000; Pfaffenbach et al., 1995; Zahn et al., 2003; Ziegler et al., 1996) (Delbende et al., 2000). In all these studies there was a strong correlation between the results of the breath tests and scintigraphy (r values 0.66-0.97). Low inter- and intra-individual variability of the breath tests results has been reported (Barbosa et al., 2005; Choi et al., 1997). In addition when compared to scintigraphy, both the specificity (73-94%) and sensitivity (67-100%) of the breath test was acceptable. (Braden et al., 2004; Bromer et al., 2002; Delbende et al., 2000; Zahn et al., 2003; Ziegler et al., 1996). However, few studies included subjects with marked gastroparesis, so the performance of the test at very slow rates of GE is not known (see below). The reduced sensitivity of breath test measurement may pose a limitation to its widespread use for the clinical diagnosis of delayed GE in individual patients. However, its reproducibility makes it ideal for pharmacological studies.

NOTE:

This figure is included on page 102 of the print copy of the thesis held in the University of Adelaide Library.

Figure 6.2 Relationship between half emptying times derived from the breath test and scintigraphic techniques in 88 subjects (34 healthy and 54 non-critically ill patients with reflux or dyspeptic symptoms) This demonstrates a close relationship between the two techniques of measurement, although at slower rates of GE there may be greater disparity. Reproduced with permission (Delbende et al., 2000).

Potential limitations of the technique at very slow rates of gastric emptying may be important when studying ICU patients. Delbende et al compared breath test measurement to scintigraphy in relatively large groups of non critically ill patients (Delbende et al., 2000). In 5 patients where the scintigraphic $t_{1/2}$ was approximately twice normal, the disparity between the 2 techniques appeared to be greater at slower rates of emptying (see figure 6.2). However, the small numbers preclude meaningful interpretation, and further evaluation of the technique at very slow rates of GE is warranted.

Although breath tests have been compared to scintigraphy for the measurement of the GE of milk in infants with reflux (Barbosa et al., 2005), this technique has not been formally validated for measurement of liquid nutrient emptying. Liquid nutrient emptying is of most relevance when considering the administration of nutrition to the critically ill. The ^{13}C acetic acid breath test has been compared to the double indicator technique to measure liquid nutrient emptying in healthy subjects (Mossi et al., 1994). Varying the composition of the liquid nutrient had similar effects on the 2 different techniques of GE measurement. However, this was not a quantitative validation of the technique. The ^{13}C acetic acid breath test has also been compared to MRI for the measurement of GE of a liquid nutrient and there was an excellent correlation between exhaled cumulative doses and MRI sequential volumes ($r=-0.9$). However, in this study there was no correlation between calculated variables, such as half emptying time. This may reflect differences in the parameters measured by the two techniques as the half emptying time using the breath test requires intestinal absorption and hepatic metabolism prior to excretion in exhaled air (Haans, 2005).

Prior to the author's work there were no published studies using breath tests for the measurement of GE in the critically ill. In these patients it is possible that factors other than GE could have an impact on the rate of excretion of marker into expiratory gases. Duodenal absorption and hepatic metabolism may be affected by critical illness, however, this is unlikely to have a major effect on the accuracy of the test. Chiolero et al (2003) compared ^{13}C acetate absorption following jejunal infusion to that following intravenous administration in a mixed group of critically ill patients and reported no differences (Chiolero et al., 2003). This suggests that small bowel absorption of that particular substrate is not limited in the critically ill. Nevertheless, the technique needs to be validated in the critically ill population before it can be used for research or clinical purposes. Breath test techniques are a potentially practical method to measure GE in the mechanically ventilated patient due to the easy access to expired gases. However, the presence of lung disease, or the use of differing modes of ventilatory support could potentially affect measurements. Breath tests were chosen as a method of measurement of GE for the studies reported in this thesis because of their convenience and practicality in the intensive care setting. Furthermore the accuracy in other patient groups appeared to be acceptable but as the accuracy of the test was unknown in this patient group, a study comparing breath test measurement of GE of liquid nutrient to scintigraphic measurement in healthy subjects and critically ill patients was performed and is reported (see chapter 9).

6.3.4 Gastric residual volume

Regular measurement of gastric residual volume (GRV) during the infusion of enteral nutrition is frequently used as a convenient clinical marker of GE, success of feeding and the risk of aspiration. However, several factors may limit the utility of GRV in clinical practice. The relationship between GRV and GE is unclear. As the measurement of GRV is dependent on tube position, tube type, the volume of syringe used (Zaloga, 2005) and the operator performing the test (Metheny, 1993), doubts have been raised about the validity of the measured values.

There is also a lack of consensus on an acceptable value for GRV during enteral feeding (Zaloga, 2005). Furthermore, the risk of aspiration may depend on factors other than, or in addition to, gastric volumes.

Although GRVs are generally considered to indicate GE, it is likely that volumes aspirated are also affected by the rate of feed administration, gastric secretion and duodeno-gastric reflux. Consistent with this, studies where feed intolerance was defined as a GRV >50ml did not demonstrate a relationship between feed intolerance and GE (measured by a paracetamol absorption technique) (Goldhill et al., 1997; Tarling et al., 1997). This may be because 50ml is too low a volume, thus overestimating the occurrence of slow GE. In patients with head injury, a threshold GRV of < 100ml, was associated with rapid, or normal, GE measured scintigraphically (Ott et al., 1991). A further small study reported GE (paracetamol absorption) to be normal in 25% of critically ill patients in whom the GRV was >150ml. These patients could continue to be fed successfully without prokinetic therapy (Cohen et al., 2000). MacClaren *et al* also reported a weak relationship between GRV and Cmax using the paracetamol absorption technique ($r = -0.50$; $P = 0.049$) (MacLaren et al., 2001) in a mixed group of mechanically ventilated patients.

In summary, the relationship between GRV and GE appears weak at best. A threshold GRV of > 150 ml may be required to reliably predict delayed GE. High GRVs are, however, thought to be a marker for the risk of regurgitation and aspiration and acceptance of higher GRVs during feeding could raise safety concerns. These concerns are not supported by a study by McClave *et al* in which the rate of micro-aspiration in nasogastrically fed, critically ill patients was reported to be very high, but independent of GRV (McClave et al., 2005). This suggests that adopting a higher GRV for the day-to day management of feeding may be safe.

Currently, most intensive care units have protocols for nasogastric feeding that change the delivery rate or route of nutrient administration when a GRV is between 150-400mls. A computer-simulated model that takes into account gastric secretion and the inhibition of GE by enterogastric feedback, suggests that GRV should plateau between 225 and 900 mL during enteral feeding at a rate of 0-125ml/h (Burd et al., 2001; Lin and Van Citters, 1997), a volume similar to normal postprandial gastric volumes. Soulsby et al examined this proposition in vivo in healthy subjects using electrical impedance and scintigraphy and demonstrated that feeding at 120 ml/h resulted in steady state volumes of 50-125ml (Soulsby et al., 2006). It is unclear how these data apply to the critically ill as enterogastric reflexes may not be normal. More information on the relationship between GRV and GE is required, but the data to date suggest that GRVs greater than those currently in widespread use would be a more accurate indication of delayed GE and allow more successful feeding.

In the intensive care unit at the Royal Adelaide Hospital, GRVs of >250ml are an indication to reduce the rate of administration of feed and consider administration of prokinetics. A study evaluating the relationship between GRV and scintigraphic measurement of GE in the critically ill is reported in chapter 9.

6.3.5 Ultrasound

Conventional real-time ultrasound can be used to study antral contractility, GE, transpyloric flow, gastric configuration, intragastric distribution of meals, gastric accommodation and strain measurement of the gastric wall (Gilja, 2007). Individual peristaltic contractions can be visualized. The antrum can be imaged by two- and three-dimensional ultrasonography, and

changing volumes are used as a measure of GE. The movements of gastroduodenal contents and velocity curves of transpyloric flow can be concurrently visualized by duplex ultrasound, which is a combination of Doppler measurement and B-mode image (Hausken et al., 1992; King et al., 1984). Three dimensional ultrasound has refined the technique significantly and improved its clinical applicability. This allows the evaluation of transpyloric flow and duodenogastric reflux using a three dimensional guided digital colour doppler imaging model (Hausken et al., 2001). This method minimizes geometric assumptions and angular ambiguity improving standardization of both data acquisition and analysis. 3D imaging also make ultrasonography less operator dependant and facilitates easier interpretation of ultrasonographic images (Gilja et al., 2007). Ultrasonography has technical limitations in the critically ill due to increased tissue fluid. This technique has not yet been used to measure GE in this group. However, the non-invasive nature and relative simplicity of this technique make it an attractive option, which may be worthy of further investigation, but this is outside the scope of this thesis.

6.3.6 Paracetamol absorption

Paracetamol absorption has commonly been used to measure GE in critically ill patients. A known dose of paracetamol is ingested and after emptying from the stomach is absorbed into the blood stream in the small intestine. Blood (and in ambulant subjects, salivary) samples (Maddern et al., 1985) are taken over the subsequent 4 hours and the peak paracetamol level, time to peak and area under the curve can be calculated. As delivery of paracetamol to the duodenum is the rate limiting step in the process, this provides an assessment of GE. This method is similar to the breath test technique in that it correlates moderately well with scintigraphy but the sensitivity for identification of delayed GE is reduced (Maddern et al., 1985; Willems et al., 2001). Although the technique has been compared to scintigraphy in some patient groups its accuracy at very slow rates of GE is unclear (Willems et al., 2001). Unfortunately, comparison of data between studies performed at different sites is limited by the lack of standardisation in the performance of these measurements. There are thus variations in the dose of paracetamol used, the form (tablets or solution), and the type of meal with which it is administered. There is also a lack of consistency in the calculated parameters used to report the results. These include the concentration at a specific time point, maximal concentration, time to reach maximal concentration, area under curve, and the proportion of area under curve at certain time points.

Because of the ease of administration, the paracetamol absorption technique has been used in the critically ill (Cohen et al., 2000; Goldhill et al., 1995; Jooste et al., 1999; Lucey et al., 2003; Marino et al., 2003; Power et al., 1989; Tamion et al., 2003; Tarling et al., 1997). However, in addition to the lack of standardisation, the technique has a number of further limitations which may restrict its application in this patient group. Despite its frequent use, paracetamol absorption has never been formally validated in critically ill patients. Thus, its accuracy and reproducibility are unknown. Frost et al suggested that plasma levels could be affected by variable hepatic function (Frost et al., 1997), which is a common feature of critical illness. Reduced metabolism of paracetamol in severely ill patients may result in the false impression of an apparent increase in GE. There is also a contraindication to the administration of paracetamol in patients with liver dysfunction. Calculation of GE requires multiple plasma samples and frequent blood taking is thought to contribute to the anaemia which is almost inevitable in long stay intensive care patients. For these reasons the labelled breath test technique, rather than paracetamol absorption, was used in the studies described in this thesis.

6.3.7 Dye dilution technique

Measurement of GE using the dye dilution technique has potential application in critically ill subjects. The technique involves nasogastric intubation of the stomach, the instillation of marker, and the removal of gastric samples to analyse the concentration of marker (George, 1968). A major detraction of this technique in healthy subjects is the insertion of a nasogastric tube, but this is part of routine care of the critically ill. The underlying principle is that the volume of fluid in a container can be ascertained by determining the increase in concentration of a dye (commonly phenol red) produced by the addition of a small volume of a known concentration of the same dye (George, 1968).

$$\text{Volume}_{\text{stomach}} = \text{Volume}_{\text{added dye}} \cdot \frac{\text{Conc.}_{\text{dye}} - \text{Conc.}_{\text{after}}}{\text{Conc.}_{\text{after}} - \text{Conc.}_{\text{before}}}$$

A modification involving a double indicator technique obviates the necessity of emptying the stomach to determine the volume of its contents. Changes in gastric volume can be followed by repeating the following cycle: remove aliquot of gastric contents, add a known amount of concentrated dye, mix gastric contents, and remove second aliquot. A modification of the calculations has been described to obviate inherent errors in the technique (Hurwitz, 1981). Dye dilution methodologies have rarely been used in critical illness and were not used for the studies reported in this thesis. However a dye dilution technique was used in a study measuring GE in a group of head injured patients (Weekes and Elia, 1996). A further modification of this technique uses a refractometer to determine changes in the concentrations of feed residue in gastric aspirates (Brix value) after the instillation of known volumes of feed or water (Chang et al., 2005; Chang et al., 2004a, b; Chang et al., 2007). The technique has never been validated in the critically ill and it does not offer any advantage in terms of convenience, or simplicity over breath test techniques. It does however afford a means of measuring GE that also accounts for gastric secretions.

6.3.8 Fluoroscopy

Fluoroscopy was one of the original techniques used for the measurement of GE. It is a technique where the emptying of a radio-opaque contrast medium, such as barium from the stomach is recorded by video fluoroscopy. This allows a second by second analysis of wall motion and transpyloric flow (Tougas et al., 1992). The technique can be combined with other methods such as manometry to provide a comprehensive evaluation of gastric mechanics. Fluoroscopy, however, has a number of disadvantages which limits its usefulness. Firstly, it does not provide a quantitative analysis of GE. The results are qualitative and comparative studies are, therefore, virtually impossible. There is also significant exposure to ionising radiation, even with modern imaging techniques, which is prohibitive when considering the length of time studies would be required in the patients in the ICU with delayed GE. This also is restrictive when considering comparative studies in healthy controls. Furthermore, barium is a non physiological substance which may cause mucosal irritation and alter gastric motility. Performance of videofluoroscopy is also difficult in the critically ill. Transfer of patients out of the ICU is considered dangerous and videofluoroscopy may also not be possible with the standard beds required for intensive care management. Accordingly, this technique has not been used for measurement of GE in the ICU although some centres use it for placement of postpyloric feeding tubes.

6.3.9 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) uses sophisticated detection devices and high powered computing techniques. It measures the response of protons in hydrogen molecules to changes in a magnetic field. Therefore, the technique does not involve exposure to ionising radiation. It has been used to quantify both the amount of gastric ingesta emptied and the component of emptying due to gastric secretion (Schwizer et al., 1992). In addition MRI permits direct visualisation of gastric wall motion and morphological abnormalities. However, the technique is unlikely to be useful in the critically ill due to the risks of transferring mechanically ventilated patients to the MRI unit. The risks of performing an MRI are further increased by the incompatibility of many supportive and monitoring devices with the MRI environment.

6.3.10 Electric Impedance Tomography & Applied Potential Tomography

Electric impedance tomography (EIT) is a non-invasive technique for measurement of GE. Current is applied to electrodes placed around the abdomen and changes in impedance in the stomach recorded during the emptying of a meal of fixed resistivity. Results are usually expressed as a GE half time. EIT provides an accurate measurement of volume changes in vitro, and in vivo. There is a good correlation between GE measured by EIT and dye dilution and also scintigraphy (Avill et al., 1987; Mangnall et al., 1991; Wright, 1995). The technique requires gastric acid suppression (Avill et al., 1987). Not only is the system non-invasive, but it is also small and portable offering the potential for bedside measurements. It may, therefore, be suitable for use in critically ill patients, but to date has only been studied in healthy subjects.

A recent study in 10 healthy humans evaluated the performance of EIT against that of scintigraphy during continuous infusion of enteral feed (Soulsby et al., 2006). Although some qualitative similarities were seen between the techniques, overall concordance was poor. This result is unsurprising as scintigraphy measures emptying excluding gastric juices, while EIT measures emptying of the entire gastric content. Further comparison with dye dilution method (which also measures total gastric emptying) would be useful.

Applied potential tomography is another non-invasive method of measurement of GE. The technique involves the measurement of change in electrical resistance through a cross section of the upper abdomen that includes the stomach. Applied potential tomography appears to be more reproducible and has greater concordance with scintigraphic measurements than EIT (Mangnall et al., 1988). Due to the non-invasive nature of these techniques they may be worthy of further consideration in the measurement of GE in the critically ill but that is outside the scope of this thesis.

6.4 Measurement of gastrointestinal pressures

6.4.1 Introduction

The measurement of changes in intraluminal pressures allows an indirect evaluation of contraction of the smooth muscle in the wall of the gastrointestinal tract. Contractile activity does not necessarily result in flow of intraluminal contents. There are numerous techniques for pressure measurement, however ‘manometry’ is the term used to describe a method using a perfused catheter for the evaluation of intraluminal gastrointestinal pressures.

6.4.2 Manometry

Gastrointestinal intraluminal pressures are most frequently recorded using a water-perfused manometric system (Heddle et al., 1988a; Houghton et al., 1988b). This can be portable to allow studies outside a dedicated laboratory, including in the intensive care unit. The technique requires a multilumen tube with transducers attached to the proximal end of each lumen to convert the pressure signal to an electrical impulse. The information is digitised and recorded directly into a computer for later analysis. Lumina are perfused continuously with a low flow rate of water to maintain patency, and reduce compliance within the manometric channels (Heddle et al., 1988a; Houghton et al., 1988b). The lumina open at different points along the tube to allow pressure recording through the antropyloroduodenal region. Although side-hole manometry provides an accurate picture of pressure waves occluding the lumen, and allows direction of spread to be determined, this technique does not detect all contractions. Thus studies that have combined manometry with wall motion detection using fluoroscopy (White et al., 1981) or an antral 'probe' technique (Fone et al., 1990a) have shown that non lumen occluding antral contractions are common and do not always result in a pressure wave of sufficient amplitude to be detected by manometry.

Although side-hole manometry can be used to monitor antral and duodenal pressures, it is unsuited to recording pyloric pressures due to the short length and the mobility of the pyloric sphincter (Heddle et al., 1988c). Even precise positioning of a single side hole across the pylorus and monitoring its position with transmucosal potential difference recording does not provide a reliable record of pyloric motility. Side holes are very focal pressure sensors, recording only the pressure over the diameter of the hole. To overcome this problem the sleeve sensor was devised in the 1970s by Professor Dent (Dent, 1976), initially for use across the gastro-oesophageal junction. The sleeve sensor can accurately record pressures along its length regardless of where the sphincter is positioned (Linehan et al., 1985). This sensor can be used to measure pressures from the narrow (3-6mm) high pressure zone at the pylorus (Fone et al., 1990a; Fone et al., 1989; Fone et al., 1990b; Fraser et al., 1991; Heddle et al., 1989; Tougas et al., 1992).

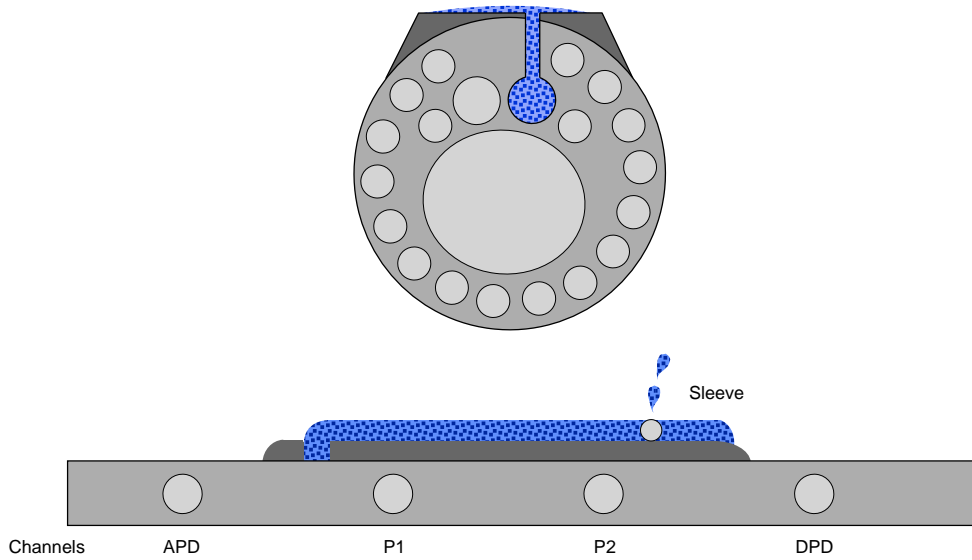


Figure 6.3 Cross sectional and longitudinal views of a sleeve sensor showing multiple lumina and positions of sideholes. APD = antral potential difference channel – used to measure potential difference. P1 = 1st pyloric port, P2 = 2nd pyloric port, DPD = duodenal potential difference channel. The sleeve also has a port to allow flow of water through the sleeve to ensure patency and allow measurement of pressure.

The multilumen catheters required for antropyloroduodenal manometry can be tailor made for the specific studies. The catheters used for the studies reported in this thesis were manufactured by Dentsleeve (Adelaide – South Australia). They were made of silicone, with side-holes positioned at intervals, usually 1.5 or 2 cm with a chain of side holes along the sleeve sensor to provide a comprehensive analysis of pressures in the distal stomach, pylorus and proximal duodenum. The assemblies vary in length, number of lumina, distance between side-holes, and presence or absence of gastric and/or duodenal infusion ports. Additional optional modifications to assist placement include; distal weights, distal balloons, and the capacity to place a wire or stiffening device within the central lumen, according to the requirements of a particular study.

Positioning of the manometric catheter is usually by transnasal or oral intubation. Correct positioning can be difficult particularly in mechanically ventilated patients. Following passage through the nose, healthy subjects usually swallow the tube and gastric peristaltic activity, particularly phase 2 and 3 activity, result in migration of the tube across the pylorus. The position of the catheter can be monitored using transmucosal potential difference (TMPD) (see below) measurement, or fluoroscopy. TMPD is preferred, as it does not require exposure to radiation and can be continued throughout the study to ensure the tube remains in the correct position. Critically ill subjects have reduced gastric motility (see chapter 4) and tubes do not readily move across the pylorus spontaneously. In this group endoscopic placement is usually required. This may involve endoscopic placement of a guide wire, and subsequent insertion of the manometric catheter over the wire, or endoscopic placement of the tube itself. This procedure can be technically challenging and requires an experienced operator. In intensive care, patients on artificial ventilation are sedated to ensure comfort, and additional requirements for sedation during endoscopy are minimal.

6.4.2.1 Transmucosal potential difference

The measurement of transmucosal potential difference (TMPD) can be used to monitor the position of the manometric catheter across the pylorus. This is based on the variation in the potential difference in the mucosa of the stomach and duodenum (Andersson and Grossman, 1965). The manometric side holes at either end of the sleeve sensor are perfused with saline, and connected to a bridge, to allow electrical conduction. Bridges are filled with 1 M KCl in 3% agar. The other end of the bridge is connected to a calomel half cell. To complete the electrical circuit a subcutaneous common reference electrode is used, filled with isotonic saline and connected via a KCl agar bridge to a reference calomel cell. Two potentiometers are then used to measure the voltages from the channels at either end of the sleeve sensor. Duodenal TMPD should be equal to or more positive than -15mV whereas gastric TMPD is equal to or more negative than -20 mV. The difference between the two should be at least 15 mV (Hedde et al., 1988a).

Although gastric pH is frequently artificially elevated in the critically ill due to acid suppression for stress ulcer prophylaxis this appears to make gastric potential difference more negative (-42 to -62 mV) despite a rise in gastric pH from 2 to 7 (Ivey and Mackercher, 1978). Thus acid suppression should not prevent TMPD from facilitating accurate identification of the gastroduodenal junction in critical illness although this has not been confirmed.

6.4.3 Solid state transducers

Strain gauges measure changes in gastrointestinal wall tension and in animal studies can be chronically implanted in the wall of the gut (Garrick et al., 1988; Siegle and Ehrlein, 1989b; Toyota, 1998). They are sensing elements which can convert the deformation of a metallic part by a change in wall pressure to a change in electrical activity. In humans, micro strain gauge transducers can be placed on a catheter which can be inserted into the gastrointestinal tract to allow measurement of pressures at various sites (Rees et al., 1979). Results are comparable to those generated by perfused manometry (Gill et al., 1990). Strain gauges have rarely been used to measure gastrointestinal motility in patients (Neild et al., 2000) and there are no reports of the use of this technique in the critically ill.

Perfused manometry is a well established technique and is suitable for use in patients in intensive care despite the technical difficulties in tube placement. This technique was used to measure gastrointestinal motility in the studies described in this thesis (chapter 11).

6.5 Measurement of absorption

6.5.1 Introduction

The measurement of absorption is fundamental to the assessment of gastrointestinal function as it is the final result of digestion. A number of approaches have been developed to quantify absorption. Substrates that are absorbed by the gut, but not metabolised and are, therefore, excreted unchanged, can be measured in blood, saliva and/or urine to indicate rate or extent of absorption. Urinary levels will give a measure of total absorption while blood concentrations measured over time are used to evaluate absorption rate. Alternatively labelled substrates that are metabolised can be manufactured and concentrations of labelled carbon can be measured in expired air. The rate and extent of absorption is influenced by a number of factors including the rate of delivery of substrate to the small intestine (i.e. GE), small intestinal motility (Beaugerie et al., 1996; Hebbard et al., 1995; Yuasa et al., 1994), as well as small intestinal absorption. Paradoxically while slow GE may reduce the *rate* of absorption, *total* absorption may potentially be increased (Beaugerie et al., 1996; Sun et al., 1996). GE has been shown to be the main determinant of a reduced rate of absorption in a group of patients after cardiac surgery (Berger et al., 2000) and a mixed group of critically ill patients (Chiolero et al., 2003). Access to expired gases, blood, saliva, urine and faeces has no practical limitations in the critically ill and measurement of absorption is likely to be technically simpler than that of other gastrointestinal parameters. The individual nutrient components (carbohydrate, lipid, protein) can be measured separately, however, glucose absorption is of particular interest because of the adverse influence of hyperglycaemia on mortality in the critically ill (van den Berghe et al., 2001).

6.5.2 Glucose absorption

6.5.2.1 3-O-Methyl-Glucose (3-OMG)

Two sugars are commonly used to measure glucose absorption. 3-OMG is completely absorbed and not metabolized, while D-xylose is incompletely absorbed and partially metabolised. 3-OMG uses the same active, carrier mediated, transport mechanism in the gut as glucose, and is renally cleared; plasma concentrations of 3-OMG may, therefore, be used as an index of the rate of glucose absorption (Fordtran et al., 1962), while urinary concentrations may be used to

indicate the extent of absorption. 3-OMG is probably less useful for the measurement of total absorption, as there is considerable capacity in the small intestine for its absorption, whereas because D-xylose is incompletely absorbed malabsorption is likely to have a quantitative effect on total absorption (Soergel and Fordtran, 1962). Total glucose absorption is reduced in critically ill subjects (Hadfield et al., 1995; Johnston et al., 1996). Hadfield et al reported that only about 10% of 200mg of 3-OMG was recovered from the urine of critically ill patients compared with 50% in healthy subjects (see figure 2.2) (Hadfield et al., 1995). It is not clear how reduced glomerular filtration rate, which is common in critical illness, may affect the urinary excretion of 3-OMG and hence urine concentrations. The rate of 3-OMG absorption, using plasma levels has never been measured in critical illness. Because of concerns about the effect of renal dysfunction, glucose absorption following the gastric administration of glucose was measured using plasma levels of 3-OMG in the study described in chapter 12.

6.5.2.2 D-xylose absorption

D-xylose is a pentose of vegetable origin that is passively, but incompletely, absorbed by a carrier mediated process in the small intestine. In normal subjects receiving 25 g of D-xylose, about 70% is absorbed, 30% metabolized in the liver, and 30–40% excreted in the urine (Craig and Atkinson, 1988; Craig and Ehrenpreis, 1999). Factors that can influence D-xylose absorption include intestinal bacterial flora composition and renal dysfunction (particularly when measuring urinary excretion of D-xylose) (Craig and Atkinson, 1988; Craig and Ehrenpreis, 1999). In critically ill patients D-xylose absorption has been reported to be reduced by up to 75% (Chiolo et al., 2003; Hadfield et al., 1995; Singh et al., 1994). 3-OMG was used in the studies described in this thesis, rather than D-xylose, as 3-OMG absorption and metabolism was thought to be more reliable in the critically ill population.

6.5.3 Lipid absorption

6.5.3.1 Triolein breath tests

Chemical analysis of fat in a three-day stool collection has been the standard method for quantification of fat malabsorption. More recently breath test techniques have been developed, using triolein labelled with either the radioactive (^{14}C) or stable isotope (^{13}C) of carbon which can be measured in expired air (Newcomer et al., 1979; Ritz et al., 2004). This technique appears to be an accurate, convenient method for the measurement of fat absorption although the quantitative value and sensitivity of the test has been questioned (Benini et al., 1984; Duncan et al., 1992). Fat absorption, using the triolein breath test, has been measured in patients after abdominal aortic aneurysm repair and found to be 50% of normal on day 1 and 20% of normal on day 3 (Fraser et al., 2006). It is likely that fat absorption will be reduced in other patient groups in the intensive care unit, but this has not been investigated. The measurement of fat absorption was outside the scope of this thesis.

6.5.4 Protein absorption

6.5.4.1 Leucine breath tests

As reduced absorption of carbohydrate and lipid has been demonstrated in critically ill patients, it is likely that protein absorption is also affected. Protein absorption is, however, measured less frequently than the other macronutrients. Stable and radioactive labelled amino acid analogues have been manufactured. A radio labelled amino acid analogue (aminoisobutyric acid) has been

used to demonstrate reduced amino acid absorption in rats following haemorrhagic shock (Sodeyama et al., 1992) and L-[1-¹³C] phenylalanine has been used to measure amino acid absorption in critically ill patients following trauma (Carlin et al., 1999). A more recent approach involves the use of egg protein containing labelled leucine which can be obtained by feeding laying hens a 0.2% leucine-deficient food supplemented with 0.2% L-leucine-¹³C (Evenepoel et al., 1997). This has been used to demonstrate reduced protein absorption in patients with pancreatitis (Evenepoel et al., 2000). These tests have not been formally validated, and as there is no 'gold standard' measurement of protein absorption, this would be difficult. Protein absorption was not measured in the studies described in this thesis.

6.6 Small intestinal mucosal permeability.

Small intestinal mucosal permeability may be increased in critical illness, particularly when patients are not enterally fed (Gianotti et al., 1994; Hadfield et al., 1995; Sax et al., 1996). Increased mucosal permeability facilitates bacterial translocation in animal models and this is thought to fuel sepsis in critical illness although, bacterial translocation has never been demonstrated in humans. Measurement of small intestinal permeability can be performed by instilling sugars, commonly rhamnose and lactulose, or ⁵¹Cr-EDTA, into the gut lumen and measuring levels in blood or urine. Rhamnose measures transcellular and lactulose measures paracellular transport. More recent studies suggest that the new water-soluble, low- and iso-osmolar, roentgen contrast media (iodixanol and iotrolan) may be as effective as ⁵¹Cr-EDTA in detecting injury to the intestinal mucosal barrier (Andersen and Laerum, 1995). This technique also offers the advantage of allowing observation of the bowel wall with the aid of fluoroscopy. Assessment of small intestinal permeability was however, outside the scope of this thesis.

6.7 Summary

The intensive care unit provides a challenging, and sometimes hostile, environment for the specialised measurement of physiological parameters for research purposes. The studies in this thesis applied complex, sophisticated techniques for the measurement of gastrointestinal function in the critically ill. Scintigraphic measurement of GE is considered the most accurate method, and the technique against which other methods to quantify GE should be validated. Gastric residual volume measurements, although not validated, are used clinically to assess feed tolerance. Breath test measurement of GE is convenient and simpler than scintigraphy, but has not been validated in the ICU population. The aim of the study described in chapter 9 was to investigate the accuracy of breath test measurement of GE and measurement of gastric residual volumes, in the critically ill, by comparing these two techniques to scintigraphy. Measurement of antral, pyloric and duodenal pressures is optimally performed with intraluminal perfused manometry using a side hole array and sleeve sensor in parallel. This technique was used in chapter 11 to demonstrate antropyloroduodenal motility in critical illness and the response to intraduodenal infusion of nutrient. Measurement of plasma 3-OMG is a sound method to measure glucose absorption and this technique was used to explore the relationship between GE and glucose absorption in the critically ill. This study is described in chapter 12.

Chapter 7

Strategies for improving the enteral delivery of nutrition in critical illness

7.1 Introduction

Although there are many deficiencies in our current understanding of the mechanisms underlying difficulties with feeding the critically ill, the most important factor appears to be delayed gastric emptying (GE). Hence, to date, most therapeutic interventions have been aimed at accelerating GE, or bypassing the stomach altogether and infusing nutrient directly into the small intestine. Total parenteral nutrition is now only used as a last resort when enteral feeding proves technically impossible, or persistently fails (see chapter 2). Several studies reported in this thesis examine aspects of management of feed intolerance in critically ill patients (chapters 13,14,15). This chapter summarises our current knowledge of the treatment of feed intolerance to put the author's experimental results into context. Simple, but as yet unproven procedures, commonly used as preventative strategies, including nutritional protocols, avoidance of known precipitants and posture are addressed first. Prokinetic agents which modify gastric and/or duodenal motility and thereby accelerate emptying are available, but have not yet been fully evaluated in the intensive care setting. Newer agents may offer a better risk-benefit ratio. Other techniques for the administration of nutrition include the placement of feeding catheters into the small intestine and our current knowledge regarding this is also summarised. Therapeutic manoeuvres may improve nutrient delivery to the gut, but effects on absorption have not yet been established.

7.2 Non-pharmacological measures

7.2.1 Nutritional protocols

The introduction of protocols to guide the administration of nutrition in clinical practice appears to improve outcomes (Barr et al., 2004; Martin et al., 2004). For example, in one centre, the introduction of an enteral feeding protocol increased the use of enteral feeding and shortened the duration of mechanical ventilation (Barr et al., 2004). In 2004, the Canadian Critical Trials Group published a study where they randomised 14 centres to introduce either an evidence based nutritional protocol or to continue standard care. They demonstrated that patients in the intervention hospitals (n = 248) received more days of enteral nutrition (6.7 v. 5.4 per 10 patient-days; P = 0.042), had a shorter mean stay in hospital (25 v. 35 days; P = 0.003) and showed a trend toward reduced mortality compared to the control institutions (27% v. 37%; P = 0.058) (Martin et al., 2004). The mechanisms underlying these findings are unclear. The latter study has been replicated by the Australian Critical Trials Group but the results are yet to be published. The success of the feeding protocol at the Royal Adelaide Hospital had not been assessed prior to the study reported in chapter 9.

7.2.2 Avoidance of drugs known to slow gastrointestinal motility

Drugs used frequently in the management of critically ill patients, such as opiates and catecholamines, are known to slow GE and adversely affect gastrointestinal motility (see chapter 5). Other drugs such as anticholinergics are used less frequently but are also likely to have a marked effect. Reducing the use of such drugs to the minimum required may potentially

improve gastrointestinal function. The effect of reducing opiate usage on feeding success and GE has, however, not been studied.

7.2.3 Correction of blood glucose and biochemical abnormalities

Hyperglycaemia, and biochemical disturbances such as hypokalaemia and hypermagnesaemia may all be implicated in reduced gastrointestinal motility (see chapter 5). However the importance of these abnormalities in the ICU setting is not yet known. It would appear prudent to maintain these parameters in normal ranges to optimise GE and feed tolerance.

7.2.4 Posture

In health, the effect of posture (whether the subject is sitting or supine) on the GE of liquid nutrient is unclear as there are conflicting data from existing studies (chapter 3). However, the overall impact is likely to be minimal (Burn-Murdoch et al., 1980; Jones et al., 2006). The effect of posture on GE has not been studied in the critically ill. However, a semi recumbent posture is encouraged because this has been demonstrated to decrease the risk of aspiration and ventilator associated pneumonia (Torres et al., 1992). It is therefore likely that gravity does affect the incidence of gastro-oesophageal reflux.

7.2.5 Early institution of feeding

As outlined in detail in chapter 5, GE can be delayed after a period of starvation. This has been demonstrated in patients with anorexia nervosa, (Holt et al., 1981; Robinson et al., 1988) and in normal and obese subjects. Furthermore, fasting for as little as 4 days can reduce GE (Corvilain et al., 1995). Fasting is common in critical illness, particularly during the early stages of ICU admission, and this might be detrimental to later nasogastric feeding. However, although early initiation of feeding may improve subsequent feeding success, this approach has not been investigated.

7.3 Pharmacologic agents

There are a number of agents which stimulate gastric motility by a variety of means and may be used to promote GE and feed tolerance in the critically ill. As yet the safest, most effective agents have not been identified. It is also uncertain whether these drugs should be used routinely in all critically ill patients, or only in those who fail feeding. There are some data to suggest that prokinetics accelerate GE only in subjects where GE is delayed (Brown and Khanderia, 1990; Edwards et al., 1987). Agents may be given by the enteral or parenteral route. Where absorption is unreliable, the parenteral route may be more appropriate, however, some agents are not available in this form. Tolerance to the effect of agents may also limit the period of effectiveness. Current knowledge regarding prokinetic agents with the potential for use in critically ill is summarised below.

Drug	Available in parenteral formulation	Dosage	Mechanism of action	Action in critically ill
Metoclopramide	Yes	10 -20mg IV 4-6hrly	5-HT ₃ receptor antagonist, dopamine (D2) antagonist, 5-HT ₄ agonist, indirect cholinergic.	Enteral administration ineffective. IV accelerates GE in a mixed group but not in pts with early TBI. No effect on GRV.
Erythromycin	Yes	1-3mg/kg	Motilin agonist	Increases antral activity and accelerates GE
Dompriidone	No	10-20mg 6 hrly	Dopamine (D2) antagonist	No data
Cisapride	No	10mg 6 hrly	5-HT ₄ receptor agonist, & other multiple actions	Increases GE. No longer available due to cardiac adverse effects.
Tegaserod	No	6mg 12 hrly	5-HT ₄ receptor partial agonist	No data. No longer available due to adverse effects on small intestinal mucosa
Naloxone	Yes - but should be given enterally for this indication	8mg nasogastric 6 hrly	Opiate antagonist	Reduces GRV and the incidence of VAP
Alvimopan	No	6mg 12 hrly	Opiate antagonist	No data
Dexlorglumide	No	200mg 8 hrly	CCK receptor antagonist	No data
Neostigmine	Yes	2mg IV or 0.4-0.8mg/h infusion	Cholinergic	Underpowered study - trend to improvement in GE & reduced GRVs
Cephalosporins	Yes	No data	No data	No data
Itopride	No	100-200mg 8 hrly	Dopamine (D2) antagonist, Cholinergic	No data

Table 7.1 Prokinetic agents that could be considered for use in the intensive care unit. GE = gastric emptying; TBI = traumatic brain injury; GRV = gastric residual volume. VAP = ventilator-associated pneumonia.

7.3.1 *Metoclopramide*

7.3.1.1 Drug characteristics

Metoclopramide is a commonly used antiemetic and prokinetic which acts predominantly as a dopamine (D2) receptor antagonist with both central and peripheral effects (see table 7.2). Administration causes release of acetylcholine from enteric neurones (Sanger and King, 1988), which antagonises the inhibitory effect of dopamine on gastrointestinal motility (Valenzuela and Dooley, 1984). The drug can be given by the enteral or parenteral route. In non-critically ill patients with gastroparesis, metoclopramide accelerates GE by triggering an intense burst of gastric contractions which resemble phase III activity (Horowitz et al., 1987; Malagelada et al., 1980). In healthy subjects it can hasten small intestinal transit (Prokop et al., 1988). The long term benefits on GE are uncertain as tachyphylaxis has been reported in patients with diabetic gastroparesis (Brown and Khanderia, 1990). In non-critically ill patients adverse effects occur in up to 20% of subjects and these include drowsiness, agitation, symptoms associated with increased prolactin levels and extra pyramidal effects. Metoclopramide may be contraindicated in head injured patients, as it has been reported to raise ICP (Deehan and Dobb, 2002).

7.3.1.2 Studies in the critically ill – enteral formulation

There are limited data on metoclopramide use in critical illness. A small, multiple cross over study comparing the effects of a metoclopramide, cisapride and erythromycin on GE in feed intolerant critically ill patients showed no change in either gastric residual volume (GRV), or GE (assessed using the paracetamol absorption technique) following 10mg enteral metoclopramide (MacLaren et al., 2000) (table 7.2). However, only 10 patients were enrolled in this study and the design of the trial, including the multiple measurements of GE performed 12 hours apart, meant that residual effects of the prokinetic agents during subsequent studies cannot be excluded. The performance of studies so close together also raises the possibility of incomplete clearance of paracetamol prior to the subsequent study, particularly in a group of subjects who may have limited hepatic clearance, which would further compromise interpretation of the results. It is not stated whether the paracetamol levels returned to baseline between studies. A further study by the same group reported an improvement in GE following the administration of metoclopramide. However, this study was not placebo controlled and as GE measurements were taken before and after the administration of 7 enteral doses of 10 mg metoclopramide given every 8 h, an order effect cannot be excluded (MacLaren et al., 2001).

If metoclopramide accelerates GE in the critically ill, it may reduce the prevalence of ventilator associated pneumonia. However, this also does not appear to be the case. Yavagal et al randomised 305 patients to receive 10mg metoclopramide enterally 8 hourly, or placebo, for the duration of their ICU admission. Metoclopramide did not prevent the occurrence of ventilator associated pneumonia although the onset was delayed from 4.5 to 6 days (Yavagal et al., 2000).

7.3.1.2 Studies in the critically ill – intravenous formulation

An early, small, descriptive study suggested that intravenous metoclopramide accelerated GE in patients when it was delayed late after traumatic brain injury (Jackson and Davidoff, 1989). A subsequent small randomised controlled trial confirmed this finding in a mixed group of critically ill patients (Jooste et al., 1999). However, no reduction was observed in gastric residual volumes (table 7.2). That study also showed that patients who received placebo on day

2 had faster GE than patients who received it on day 1, consistent with an 'order effect', either due to a residual action of the metoclopramide, or an improvement in GE with time.

In a more recent study, 10 mg metoclopramide given intravenously 8 hourly for 48 hours to 21 patients soon after head injury did not accelerate GE (table 7.2). In this study patients were not selected for feed intolerance. Thus as GE was normal in over half of the patients prior to the administration of metoclopramide, a potential benefit of the drug in patients with delayed GE may have been missed (figure 7.1) (Marino et al., 2003). Furthermore, in this study GE was slower on day 2 than on day 1 after ICU admission possibly reflecting a worsening in the patients' condition. In contrast the improvement in GE over time reported by Jooste et al (above) was observed in patients studied between 3 and 26 days after admission, at which time physiological disturbances may have been returning to normal. A further limitation of the study by Marino et al is the use of an historical control group from another centre.

Metoclopramide has also been reported to facilitate the correct placement of postpyloric feeding tubes (Heiselman et al., 1995; Kittinger et al., 1987; Whatley et al., 1984) however, not all groups have found it effective (Paz et al., 1996).

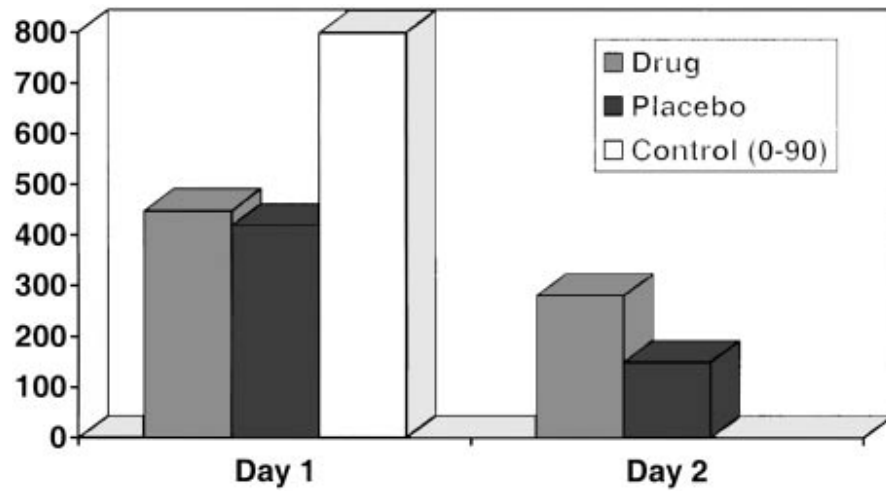


Figure 7.1 Gastric emptying (paracetamol absorption - AUC₁₂₀) on day 1 (baseline) and day 2 (following 48h of IV metoclopramide give 8hrly or placebo). The figure demonstrates that GE was reduced on day 2 despite metoclopramide. Control data were taken from a previously studied group of healthy humans at another centre (Power et al., 1989). Reproduced with permission (Marino et al., 2003).

7.2.3.3 Summary

The role of metoclopramide in the treatment of delayed GE and feed intolerance in the critically ill is uncertain. Overall these data suggest that the enteral administration of metoclopramide is ineffective as a prokinetic in the critically ill (although the studies to date are inconclusive), while intravenous metoclopramide may increase GE in some patients. However, there is no evidence to support the routine use of metoclopramide in ICU patients receiving enteral nutrition as it does not improve the success of feeding or reduce the prevalence of ventilator-associated pneumonia. It is unclear whether it has any benefits in patients who are feed intolerant and if so whether these effects are sustained.

Authors	No. & type of patients	Outcome measures	GE	Factors affecting GE
(Jooste et al., 1999)	10 mixed ICU pts Crossover trial 10 mg IV Metoclopramide vs. placebo	GE using paracetamol absorption	AUC ₂₀ 994±624 mg.min/l - saline vs. 1367 ± 516 mg.min/l - metoclopramide; P=0.04	Metoclopramide accelerates GE but had no effect on GRV
(MacLaren et al., 2000)	10 mixed pts failing feeds, multiple crossover study, 10mg enteral metoclopramide	GE using paracetamol absorption & GRV	GRV 127±115ml placebo, 125±164ml metoclopramide, NS. AUC 2559±209 placebo vs. 2244±210, metoclopramide	No effect of metoclopramide
(MacLaren et al., 2001)	7 mixed ICU pts; measurements before and after 7 x 10mg 6hrly doses enteral metoclopramide	GE using paracetamol absorption	AUC ₂₄₀ 1,421 +/- 780 mg/L x min; metoclopramide vs. 839 +/- 546 mg/L x min; baseline; P = 0.043	GE improved with time and metoclopramide. (Not randomised or placebo controlled)
(Marino et al., 2003)	20 TBI Pts immediately after ICU admission 10mg IV metoclopramide 8hrly for 48h vs. placebo	GE using paracetamol absorption	AUC ₁₂₀ 149± 161 mg min ⁻¹ l ⁻¹ , saline, AUC ₂₄₀ 281± 222mg min ⁻¹ l ⁻¹ , metoclopramide, NS	No effect of metoclopramide. GE worse on day 2

Table 7.2 Studies in critically ill patients examining the effect of metoclopramide on gastric emptying and/or feed tolerance. GE = gastric emptying; TBI = traumatic brain injury; GRV = gastric residual volume, AUC = area under curve, IV = intravenous, ICU=intensive care unit.

7.3.2 Erythromycin

7.3.2.1 Drug characteristics

Macrolide antibiotics, such as erythromycin, are competitive agonists of motilin. Motilin receptors are found in abundance in the smooth muscle in the gastric antrum and proximal duodenum and, when stimulated, induce contractions (see chapter 3). At lower concentrations erythromycin also has a cholinergic chronotropic effect mediated by neuronal motilin receptors (Parkman et al., 1995). Erythromycin increases the coordination of antroduodenal motility, by stimulating antral activity and abolishing isolated pyloric pressure waves (Fraser et al., 1992b), motor effects which would be expected to accelerate GE.

7.3.2.2 Dose related effects of erythromycin

The dosage of erythromycin required to increase GE is less than that required for its antibacterial action. The effect of erythromycin on gastric motor activity is dose dependent (Otterson and Sarna, 1990). Very low doses of erythromycin (40mg) have different effects on motility when compared with moderate doses (200mg or 350mg) (Coulie et al., 1998). In healthy volunteers and patients with diabetic gastroparesis, 40mg erythromycin infused intravenously induced premature antral phase III activity, which migrated to the small intestine (Coulie et al., 1998; Kawamura et al., 1993). These motor patterns are likely to accelerate GE in a very efficient way. In contrast, 200-350mg erythromycin induced prolonged periods of strong antral contractions (Coulie et al., 1998), which did not migrate and were not followed by motor quiescence (Tack et al., 1992). Antibiotic doses (500mg-1g) of erythromycin caused strong antral contractions which were associated with upper abdominal pain and nausea, and were not mediated by motilin (Sarna et al., 1991).

7.3.2.3 Role of erythromycin as a prokinetic

The prokinetic effects of erythromycin have been extensively investigated, particularly in patients with diabetic gastroparesis (Janssens et al., 1990). It accelerates GE in diabetics refractory to other prokinetics (Annese et al., 1997; de Graaf-Strukowska et al., 1995; Okano et al., 1996), patients after gastric and nongastric surgery (Altomare et al., 1997; Mozwecz et al., 1990), anorexia nervosa (Stacher et al., 1993), and progressive systemic sclerosis (Fiorucci et al., 1994). Chronic usage is associated with some attenuation of effect (Janssens et al., 1990; Richards et al., 1993). It has also been administered preoperatively, to provide an empty stomach prior to anaesthesia (Kopp et al., 1997).

7.3.2.4 Role of erythromycin in the critically ill

In contrast, the investigation of erythromycin in the critically ill has been limited. Erythromycin increases antral motility and accelerates GE in unselected critically ill patients (Dive et al., 1995). In this study it was administered in a dose of 200 mg, however the optimal dosage for accelerating GE in the critical care setting is uncertain. The suggestion by Frost et al that up to 500 mg QID of intravenous erythromycin may be used (Frost and Bihari, 1997) is likely to be incorrect as doses of this magnitude have been reported to disrupt electrical control activity in the stomach and small intestine leading to nausea and vomiting (Otterson and Sarna, 1990). For acute treatment and administration, most investigators have used 200mg erythromycin intravenously over 20 to 30 minutes, but recent reports in healthy volunteers (Kluger M, 1999) and critically ill patients (Barnert J, 1998) suggest that 50 mg erythromycin may be as effective as 200 mg to improve GE. With the smaller dose, a reduction in side effects was achieved (Kluger M, 1999). To avoid adverse effects but retain adequate acceleration of GE, studies on the effects of lower doses

of erythromycin in the critically ill population are needed. The use of erythromycin to facilitate transpyloric placement of feeding tubes for small intestinal nutrient delivery has been reported (Di Lorenzo et al., 1990; Gharpure et al., 2001; Griffith et al., 2003; Kalliafas et al., 1996; Komenaka et al., 2000).

Hyperglycaemia and a requirement for catecholamines are both common in critical illness. Both are known to slow GE (chapter 5), and may obscure the effects of erythromycin on gastrointestinal motility. Barnert *et al* (1998) reported a diminished effect of erythromycin on GE and gastroduodenal motility in the presence of high dose catecholamines (Barnert J, 1998). Similarly the erythromycin-induced acceleration of GE of hypertonic liquids in diabetic patients was reduced by hyperglycaemia (Petrakis et al., 1999b). There are thus features of critical illness that may reduce the prokinetic effect of erythromycin.

7.3.2.5 Potential adverse effects of erythromycin in critical illness

Enthusiasm for the use of erythromycin is tempered by fears of cardiac toxicity and bacterial resistance (Hawkyard and Koerner, 2007; Ray et al., 2004). Erythromycin has been reported to prolong the Q-T interval and this may be a direct effect on motilin receptors (Rubart et al., 1993). Potentially fatal ventricular arrhythmias can occur, particularly in combination with other drugs with the same effect. For this reason erythromycin and cisapride should not be used together, and administration with fluconazole is also contraindicated. Cardiac toxicity can be minimised by using the lowest effective dose. The potential for development of antibiotic resistance in the microbiology of the intensive care unit remains a theoretical concern and investigation of motilin agonists without antibiotic effect is warranted. Attenuation of the prokinetic effect over time may also limit the clinical usefulness of erythromycin (Janssens et al., 1990). The mechanisms underlying this are unclear, but may relate to the down regulation, desensitization and endocytosis of motilin receptors (Lamian et al., 2006; Thielemans, 2005). Although erythromycin accelerates GE, it can slow intestinal transit (Edelbroek et al., 1993; Landry et al., 1995). However, this may not be of major importance as a prolongation of transit is likely to increase absorption (Edelbroek et al., 1993).

7.3.2.6 Summary

In summary, erythromycin is a promising agent for the treatment of gastroparesis and feed intolerance in the critically ill. It accelerates GE by increasing antral motor activity in unselected critically ill patients, but its effect on feed intolerance is unclear. The optimal dose and dosage intervals are also unknown, as is the relative effect of erythromycin compared to other prokinetics.

7.3.3 Cisapride

Cisapride is a substituted benzamide with multiple actions on the enteric nervous system. Primarily it is a serotonin type 4 receptor agonist, which selectively enhances cholinergic motor activity throughout the gastrointestinal tract. It thus increases oesophageal motility, and lowers oesophageal sphincter tone, and, by increasing the frequency of antropyloroduodenal pressure waves (Fraser et al., 1993b), it accelerates GE and oro-caecal transit (Bergmann et al., 1992). In critically ill patients, a single enteral dose of 20 mg of cisapride accelerated GE (Heyland et al., 1996a), and, when given at a dose of 10mg enterally every 6 hours over a 7 day period, it improved GE and feed tolerance (Spapen et al., 1995). Recently the availability of cisapride has been restricted because of Q-T interval prolongation, torsades des pointes and ventricular arrhythmias. The lack of a parenteral formulation also limited its use in this setting.

7.3.4 Domperidone

Domperidone is a peripherally acting dopamine₂-receptor antagonist which increases oesophageal, gastric and small intestinal motility (Barone, 1999). It also has antiemetic activity as a result of blockade of dopamine receptors in the chemoreceptor trigger zone. An oral dose of 10mg caused similar symptomatic improvement to metoclopramide and cisapride in patients with diabetic gastroparesis (Barone, 1999). Domperidone has also been reported to reduce symptoms in patients with dyspepsia or gastro-oesophageal reflux. Furthermore, it prevents nausea and vomiting associated with chemotherapy and antiparkinsonian drugs (Barone, 1999). Because very little domperidone crosses the blood-brain barrier, central nervous system adverse effects are rare. This provides a theoretical advantage for domperidone over metoclopramide. However, similar to metoclopramide, domperidone causes the release of prolactin, and chronic use is associated with hyperprolactinaemia. The clinical importance of elevated prolactin concentrations in the critically ill is uncertain. Domperidone reduces gastrointestinal symptoms after acute myocardial infarction (Lencz, 1991) but otherwise has not been studied in the intensive care setting. The intravenous formulation has not been marketed in Australia because of case reports of ventricular arrhythmias and sudden death. The lack of an intravenous formulation and the potential for cardiac side effects has limited the drug's appeal to the intensivist.

7.3.5 Tegaserod

Tegaserod is a selective, serotonin type 4, receptor partial agonist, which was developed for the treatment of irritable bowel syndrome (Galligan and Vanner, 2005). Studies examining the effect of tegaserod on GE in healthy humans produced inconsistent results (Degen et al., 2001; Talley et al., 2006). However, clinical improvement was reported in uncontrolled studies, involving small numbers of critically ill patients with persistent feed intolerance (Banh et al., 2005; Stephens et al., 2007). Recent reports of ischaemic colitis during post marketing surveillance have led to a restriction of the availability of tegaserod (Brinker et al., 2004; DiBaise, 2005; Shetzline et al., 2005; Woollorton, 2004). The implications of these adverse events for use of this drug in critical illness are unclear but are likely to limit its application.

7.3.6 Opiate antagonists

As opiate administration may be an important cause of reduced gastrointestinal motility and unsuccessful feeding in the critically ill, opiate antagonists, such as naloxone, are a logical option for treatment. Eight mg naloxone administered 6 hourly via a nasogastric tube, (to avoid antagonism of the analgesic and sedating properties of opiates), reduced GRV and the incidence of ventilator-associated pneumonia in 84 mechanically ventilated patients receiving fentanyl infusions (Meissner et al., 2003). As these patients were not selected for feed intolerance the importance of this finding for patients not tolerating nasogastric feeding is unclear. Further investigation of its efficacy in patients who are feed intolerant is needed.

Alvimopan is an enterally administered opioid receptor antagonist that is minimally absorbed and has a high affinity for μ receptors. It does not cross the blood-brain barrier (Meissner et al., 2003). When administered to postoperative patients at a dose of 6mg, 12 hourly, it shortened both the time to recovery of bowel function (passage of flatus and bowel action) and time to discharge from hospital (Taguchi et al., 2001). Alvimopan is yet to be investigated in the critically ill population but opiate antagonists are promising agents for the treatment of feed intolerance.

7.3.7 CCK Receptor Antagonists

Elevated CCK levels inhibit GE and motility in health (Debas et al., 1975) but the role of CCK in the delayed GE observed in critical illness is unclear. CCK antagonists accelerate liquid emptying (Schwizer et al., 1997). Dexloiglumide is a selective, and highly potent, CCK1 receptor antagonist which accelerates GE in animals (Varga, 2002) and humans (Cremonini et al., 2005). It therefore, has the potential to be an effective treatment for delayed GE and feed intolerance in the critically ill. It has been used safely, but with variable success at a dose of 200mg given 8 hourly in patients with irritable bowel syndrome (Cremonini et al., 2005) and functional dyspepsia (Varga, 2002).

More detailed investigation of the impact of CCK on feed intolerance in critical illness is required before a CCK antagonist can be considered as a treatment option.

7.3.8 Parasympathetic agents

Increasing cholinergic activity increases gastrointestinal motility (see chapter 3). Acetyl cholinesterase inhibitors such as neostigmine have been used to treat postoperative ileus although their use is not widespread. Neostigmine was compared to placebo in a cross-over trial examining GE measured by paracetamol and gastric residual volumes in a mixed group of critically ill patients. Unfortunately the study was underpowered (n=11) to demonstrate a result, although there was a trend for more rapid GE and reduced GRVs after neostigmine administration (Lucey et al., 2003). Cholinergic activity may be combined with sympatholysis such as may be achieved with epidural analgesia to increase the effect on gut motility (Holte and Kehlet, 2000). Potential adverse effects of cholinergic agents include bradycardia and increased gastrointestinal and respiratory secretions (Ponec et al., 1999). Further studies are required before neostigmine can be recommended for use as a prokinetic in the critically ill.

7.3.9 Itopride

Itopride is a prokinetic agent with dopamine blocking and cholinergic properties. In studies in healthy humans it did not accelerate GE (Choung et al., 2007) and only modestly accelerated GE in patients with longstanding diabetes (Stevens et al., 2008). The results of studies in patients with functional dyspepsia are inconsistent (Holtmann et al., 2006; Talley et al., 2007). It is thus unlikely that itopride will be effective in the critically ill.

7.3.10 Cephalosporins

The cephalosporin class of antibiotics have been reported to have prokinetic activity in a mouse model (Kuo et al., 1998). The agent with the greatest prokinetic effect and largest therapeutic window appeared to be cefazolin (Kuo et al., 1998). Intraperitoneal injection of cefazolin (2, 20, 200, and 1000 mg/kg) in mice had a greater effect on GE than either erythromycin or metoclopramide (Kuo et al., 1998). Cefazolin has also been reported to stimulate gastric and small bowel motility in healthy humans, and patients with gastroparesis (Lampton, 1995), in a manner similar to that seen with erythromycin; although the effect was less pronounced than that of erythromycin. If cefazolin were shown to have prokinetic effects in the critically ill, the lack of cardiac toxicity and adverse gastrointestinal effects would give it some advantage over erythromycin. The mechanism of action is unknown. The prokinetic effect of cefazolin has not been studied in enterally fed patients in intensive care.

7.4 Postpyloric feeding

Failure of nasogastric nutrition can also be treated by bypassing the stomach and delivering the nutrient directly into the small intestine. While GE is delayed due to antral hypomotility (see chapter 4), small intestinal motility is believed to be quantitatively normal (Dive et al., 1994b). Therefore delivery of nutrient into the duodenum or small intestine is likely to be more successful than delivery into the stomach (Boulton-Jones et al., 2004). However, to date a positive impact on nutritional delivery or clinical outcomes when post pyloric feeding is instituted early has not been demonstrated (Ho et al., 2006; Marik and Zaloga, 2003). For example, a systematic review by Ho et al including 637 patients from 11 randomised controlled clinical trials compared gastric to postpyloric feeding. None of the outcome measures (mortality, length of ICU stay, incidence of nosocomial pneumonia) were affected by the route of feeding. In addition, in patients who fail nasogastric feeding, post pyloric tubes and intravenous erythromycin are equally effective (Boivin and Levy, 2001). Thus current evidence suggests that post pyloric feeding should be reserved for patients who fail nasogastric feeding and do not respond to prokinetics. Furthermore, small intestinal motility and absorption have not been systematically studied in the critically ill population so it is unclear whether postpyloric delivery of nutrient will result in normal absorption. However, there is a widespread belief that small intestinal delivery of nutrition is superior to nasogastric and further studies are currently in progress to establish its efficacy and limitations.

An important limiting factor in the initiation of postpyloric delivery of nutrition is the placement of a feeding tube distal to the pylorus. A number of methods have been described, most of which are technically difficult, time consuming, invasive, and require specialised equipment. Common techniques involve endoscopy or fluoroscopy. Endoscopy requires technical support from an experienced gastroenterologist. Simpler techniques include patient positioning and the administration of erythromycin, but are less reliable (Komenaka et al., 2000). A simpler, more convenient method of post pyloric tube placement would facilitate feeding in this group. Preliminary studies using a novel technique in a series of mechanically ventilated patients are described in chapter 15

7.5 Summary

A number of potential strategies are available to improve the delivery of enteral nutrition to critically ill patients. However, to date there are insufficient data to determine which methods are the safest and/or most effective. Outside intensive care prokinetics are evaluated for their effect on upper gastrointestinal symptoms. In contrast, in critically ill subjects, the outcomes of primary interest are feed tolerance or GE. Ultimately however, studies should be large enough to determine the effect of interventions on morbidity, such as infective complications, and mortality. This is important because an improvement in nutrient delivery may be outweighed by adverse effects, which can significantly affect outcome.

At present feed intolerance is commonly treated initially with prokinetics and then, if this fails, with small intestinal delivery of nutrition. The relative place of these treatments and the ideal drugs, including dosage and dosage intervals, are as yet unknown. Erythromycin is a promising agent that is available for parenteral administration and has been demonstrated to increase GE in a critically ill population. Its clinical utility needs confirmation and optimal dosage, dosage interval and duration of treatment need to be ascertained. Studies examining the administration of erythromycin to critically ill patients are reported in chapter 13. Cefazolin also warrants further investigation in this patient group as it may offer a safer alternative to erythromycin (chapter 14). If a non-invasive, convenient method of

postpyloric tube insertion were available this could avoid the need for drug administration. A novel technique for insertion of tubes into the small intestine is reported in chapter 15.

Chapter 8

Subjects and methods used in the studies reported in this thesis

8.1 Introduction

The studies described in this thesis investigated gastrointestinal dysfunction in critically ill patients in the intensive care unit at the Royal Adelaide Hospital. Studies were also performed in healthy (control) cohorts for comparison. Gastric emptying, feed tolerance, antropyloroduodenal motility, glucose absorption and blood glucose concentrations were measured. Techniques used included, quantification of gastric residual volume, measurement of gastric emptying by both scintigraphy, and breath test techniques, manometry, assessment of glucose absorption using 3-OMG and blood glucose measurement. These methods have all been previously described and are well validated (see chapter 6). Patient demographic data were also documented and analysed. This chapter provides a description of the methods used in the studies reported in this thesis. Additional variations in protocols, methods or techniques specific to individual studies will be discussed in the relevant chapters.

8.2 Subjects

8.2.1 Healthy volunteers

Healthy adult volunteers were recruited by advertisement and from lists maintained in the Department of Medicine (University of Adelaide) of individuals prepared to volunteer for research studies. Subjects were questioned regarding their past medical history and medications. (Any drug has the potential to affect gastric emptying and/or gastrointestinal motility.) Any subjects with a medical condition or the use of any medication including over-the-counter medications such as antihistamines were not enrolled in studies. Pregnancy, or possible pregnancy, was an exclusion criterion in all studies. Where this was particularly critical (e.g. scintigraphic studies) a pregnancy test was performed on the day of study before the study activities were commenced. As age may affect GE, older subjects were specifically sought to better match the critically ill population. Subjects with previous exposure to nasogastric intubation were preferred, and, in the study examining gastric emptying, were specifically sought, as anxiety can slow gastric emptying. Informed consent was obtained from all subjects prior to their enrolment in the study.

8.2.2 Critically ill patients

Mechanically ventilated, critically ill patients were recruited from the intensive care unit at the Royal Adelaide Hospital. This is a mixed, medical and surgical, intensive care unit with 24 ventilated beds with approximately 1500 admissions per year. The patients are high acuity with a mean admission APACHE II score of 18. The unit admits all critically ill patients apart from paediatric and postoperative cardiothoracic patients. A broad cross section of ICU patients was deliberately sought for the studies reported in this thesis. In some studies a convenience sample was used. In others, patients with large gastric residual volumes (>250ml), indicative of failure of enteral nutrition, were recruited. In all cases the patients were unable to provide their own consent and informed consent was obtained from the next of kin. Studies were performed in accordance with NH&MRC guidelines on the involvement of critically ill subjects in research.

8.3 Measurement of gastric emptying

8.3.1 Gastric residual volumes

Regular measurement of gastric residual volume (GRV) during the infusion of enteral nutrition is a convenient clinical tool to determine success of feeding and indicate gastric emptying, and the risk of aspiration (see chapter 6). It is used in the day to day management of enteral feeding. In the intensive care unit at the Royal Adelaide Hospital GRVs are routinely measured every 6 hours and, if the volume is greater than 250 ml, the rate of administration of nutrient is reduced, the volume aspirated is discarded, and the use of prokinetics or post pyloric delivery of nutrition is considered (see protocol figure 10.2.1). These volumes were documented for the purpose of the studies described in this thesis (see chapter 6).

As discussed in chapter 6, GRVs are dependent on a number of factors, including the rate of feed administration. An additional, and possibly more precise, measure of GE is to determine the volume of nutrient emptied from the stomach. This can be calculated by noting the total volume of nutrient administered over a period of time and subtracting gastric residual volumes that are removed and discarded (study described in chapter 13).

8.3.2 Scintigraphy

Scintigraphy was used to measure gastric emptying in healthy subjects and ICU patients (chapters 9 & 10). All tests commenced at approximately 0800 hours after an overnight fast in healthy subjects and after a 4 hour fast in the critically ill. In healthy subjects a nasogastric tube was passed, in patients a nasogastric tube was usually already in position as part of routine ICU management. After verifying the correct position of the nasogastric tube (12-Fr Flexiflo [Ross Laboratories, Columbus, OH] or 14-Fr Levin tube [Pharma-Plast, Lyngø, Denmark]) by air insufflation and measurement of the gastric fluid pH, all gastric contents were aspirated and discarded. Following aspiration of the nasogastric tube, 100 ml of Ensure (standard liquid feed – 1kcal/ml) labelled with 20 Mbq ^{99m}Tc- rhenium sulphide colloid (RAH radiopharmacy, Adelaide, South Australia), (radiation dose 0.5mSv) was infused through the nasogastric tube into the stomach over 5 minutes.

In patients, the scintigraphic measurement of GE was performed in the ICU using a mobile gamma camera (GE Starcam 300 AM -GE with 3 minute dynamic frame acquisition). Healthy subjects were studied in the Department of Nuclear Medicine, PET & Bone Densitometry, Royal Adelaide Hospital, using a single headed, stationary, gamma camera (GE millennium MPR UK) with data acquisition in 3 minute frames. Reframed data were corrected for patient movement and radionuclide decay and scatter. All subjects were studied for 4 hours supine, in the 20° left anterior oblique position (Yung, 1993). A region of interest that represented the stomach was identified. The isotopic counts within the region of interest were measured and used to derive gastric emptying curves (expressed as % of the maximum content of the total stomach). The intragastric content at 60,120,180, and 240 minutes was determined (Jones, 1996; Jones et al., 1996). Where possible a scintigraphic half emptying time was also calculated, (Collins et al., 1983).

8.3.3 Breath tests

Gastric emptying was also measured using a labelled carbon breath test technique (see chapter 6).

8.3.3.1 ^{14}C breath test technique

The ^{14}C breath test technique for measurement of GE was compared to the scintigraphy in a group of mechanically ventilated patients using the following technique (chapter 9). After verifying the correct position of the nasogastric tube (12-Fr Flexiflo [Ross Laboratories, Columbus, OH] or 14-Fr Levin tube [Pharma-Plast, Lyngø, Denmark]) by air insufflation and measurement of the gastric fluid pH, all gastric contents were aspirated and discarded.

Test Meal:

A test meal which consisted of 100ml Ensure (Abbott laboratories BV, Zwolle, Holland) doped with 20 Mbq $^{99\text{m}}\text{Tc}$ - rhenium sulphide colloid (RAH radiopharmacy, Adelaide, South Australia) and 75 KBq octanoic acid, [$1\text{-}^{14}\text{C}$] sodium salt (MP Biomedicals Australasia, Sydney NSW) was then infused into the stomach via the nasogastric tube. The total caloric content of the meal was 100 kcal.

Breath Sampling:

Expiratory breath samples were collected immediately prior to nutrient infusion and then every 10 minutes for the first hour, and every 15 minutes thereafter for a further 3 hours. In the patients, breath samples were collected from the expiratory limb of the ventilator tubing. The healthy subjects were asked to expire into sample tubes. A proprietary non-toxic metallic hydroxide, CO_2 trapping solution (RAH Nuclear Medicine, Adelaide, South Australia) was used to collect 0.5 mMol CO_2 . A colour change in the solution indicated the appropriate amount of CO_2 . Samples were solubilised with 10ml Starscint liquid scintillation counting solution (Packard instruments, Meriden, CT) and counted in a Packard 2100TR Tri-Carb liquid scintillation counter (Packard instruments, Meriden, CT) to a 1% CV. Resultant counts per minute were corrected to disintegrations per minute using an open window, full spectrum, curve stripping algorithm (Packard Direct DPM) with colour and chemical quench correction programs.

Calculations:

CO_2 production was assumed to be 300 mmol/ M^2 body surface area, assessed using the height /weight formula of Haycock et al (Haycock et al., 1978). The results were expressed as percentage of $^{14}\text{CO}_2$ recovery / hour and as cumulative values over the sampling period. Mathematical curve fitting using non-linear regression (GraphPad Prism 4, San Diego, CA), as previously described by Ghossein et al (Ghossein et al., 1993), allowed calculation of three main parameters of gastric emptying; half emptying time (BT_{50}), lag time, and gastric emptying coefficient (GEC).

8.3.3.2 ^{13}C breath test technique

The ^{14}C breath test has been demonstrated to be interchangeable with the ^{13}C breath test (Maes et al., 1994). The use of the stable isotope ^{13}C avoids exposure of the patients to radiation, and this isotope was used in subsequent cross over studies to assess the effect of cefazolin as a prokinetic (chapter 14), and to compare the effect of 2 different doses of erythromycin (chapter 13.3). The ^{13}C breath test technique was performed in the studies described in this thesis (chapters 11, 13, 14) as follows.

After verifying the correct position of the nasogastric tube as described above, all gastric contents were aspirated and discarded.

Test Meal:

One hundred microliters ^{13}C -octanoic acid (Cambridge Isotope Laboratories, Andover, MA) were added to 100 mL Ensure (Abbott Australasia, Kurnell, Australia). The labelled Ensure was shaken for 1 min to distribute the marker in the meal before it was infused into the stomach over 5 mins.

Breath Sampling:

Expiratory breath samples were collected immediately prior to the test meal, every 10 minutes for the first hour after nutrient infusion, and every 15 minutes thereafter for a further 3 hours. To collect exhaled air from mechanically ventilated patients, a side arm (straight T adapter, Datex-Engstrom, Helsinki, Finland) was connected to the ventilation tube and a Vacutainer holder (blood needle holder, Reko, Lisarow, Australia) containing a needle (VenoJect, Terumo, Tokyo, Japan) was attached. Preliminary studies and tracings on the time-flow curves of the ventilator showed that equilibration of CO_2 concentration between the ventilation tube and evacuated 10-mL tubes (Exetainer, Buckinghamshire, England) took a fraction of a second. To avoid obtaining other than end-expiratory air, samples were timed to the end-expiratory phase by observation of the patient and the time-flow curve on the ventilation monitor (Figure 8.2). In volunteers, end-expiratory samples were collected by asking them to blow through a straw into similar tubes. The concentration of CO_2 and the percentage of $^{13}\text{CO}_2$ was measured in each sample with an isotope ratio mass spectrometer (ABCA model 20/20, Europa Scientific, Crewe, UK). Samples containing <1% CO_2 were regarded as being non-end-expiratory and were excluded from further analysis.

Calculations:

The $^{13}\text{CO}_2$ breath concentration over time was plotted and the resultant curves used to calculate a gastric emptying coefficient (GEC) (Ghoos et al., 1993). After the breath test, enteral feeding was resumed, as indicated clinically.

A normal range for gastric emptying using the ^{13}C breath test technique had previously been established at the candidates institution (Ritz et al., 2001) in 22 healthy subjects studied supine, using 100ml of Ensure labelled with ^{13}C octanoic acid infused through a nasogastric tube. The interquartile range of the GEC was 3.2-3.8 and that of the gastric half emptying time was 120-145 mins. These values were used in the study described in chapter 13 to identify patients with delayed GE.

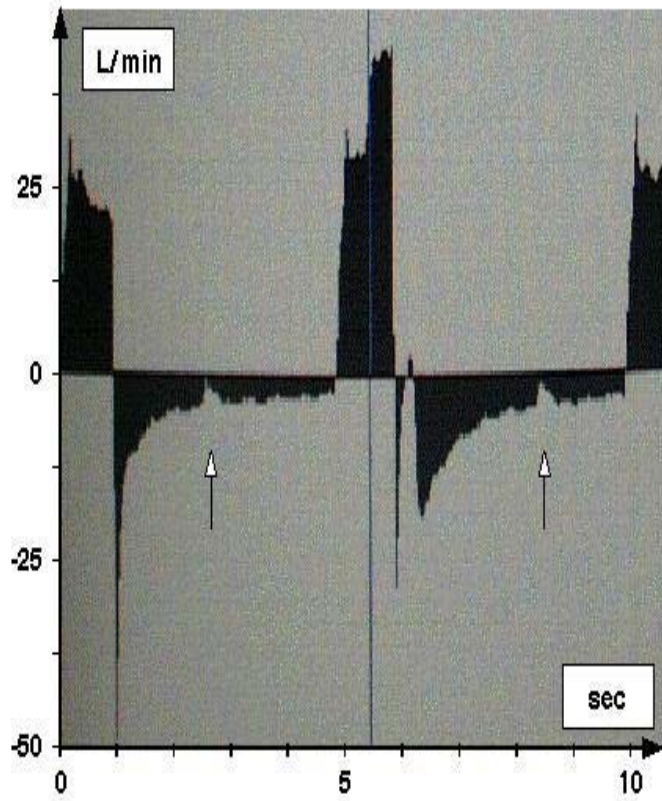


Figure 8.1 Effect of opening vacutainer to expiratory limb of ventilator on expiratory flow measured through the ventilator.

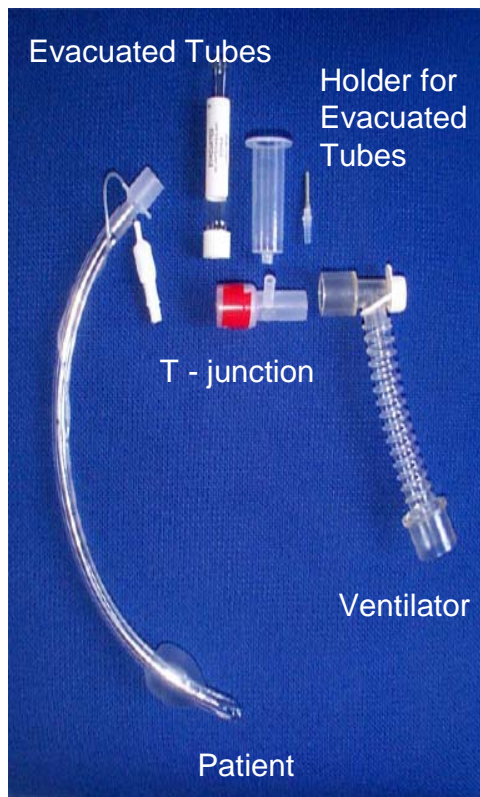


Figure 8.2 Technique for sampling expired air in mechanically ventilated patients. To collect exhaled air from mechanically ventilated patients, a side arm (straight T adapter, Datex-Engstrom, Helsinki, Finland) was connected to the ventilation tube and a Vacutainer holder (blood needle holder, Reko, Lisarow, Australia) containing a needle (VenoJect, Terumo, Tokyo, Japan) was attached.

8.4 Measurements of antro-pyloro-duodenal motility

8.4.1 Manometry

Intraluminal pressures in the distal stomach, pylorus and proximal duodenum were recorded using a water-perfused portable manometric assembly (chapter 11) (Heddle et al., 1988a; Houghton et al., 1988b). A purpose built 100cm, weighted, silicone, multilumen tube of 3.5 mm outer diameter, incorporating a sleeve sensor and an infusion port located 2.75 cm from the tip, was used (Dentsleeve - Adelaide, South Australia). The assembly (depicted in figure 8.4) incorporated 15 pressure-recording channels (side-holes spaced 1.5 cm apart). Following transnasal intubation, the assembly was manoeuvred so that the sleeve sensor was positioned across the pylorus using an endoscopic technique in patients and by phase II or III activity in healthy subjects. Measurement of the antro-duodenal transmucosal potential difference (TMPD) gradient was used to monitor the position of the sleeve sensor across the pylorus (Dent, 1976; Heddle et al., 1988a; Houghton et al., 1988b), so that five side-holes were located in the antrum and six in the duodenum (see below 8.4.2). The infusion port, located at the catheter tip, enabled the delivery of enteral feed into the duodenum, 9cm distal to the pylorus. Each lumen was connected to a pressure transducer (Abbott Critical Care, Illinois) and perfused with gas-free distilled water (or saline for the TMPD channels) by an infusion pump at a rate of 0.08 (side holes) or 0.15 (sleeve sensor) mL min⁻¹. The outputs from pressure transducers were recorded online at 10Hz with a Power Macintosh computer (7100/80, Apple, Cupertino, CA), using custom-written software developed in-house (HAD, Associate Professor G. Hebbard, Victoria, Australia) and Labview as a base program, and logged directly to disk for subsequent analysis. Manometric data were recorded using the software (Biopac System Inc, Santa Barbara, Ca, USA) for storage and analysis.

Manometric Assembly

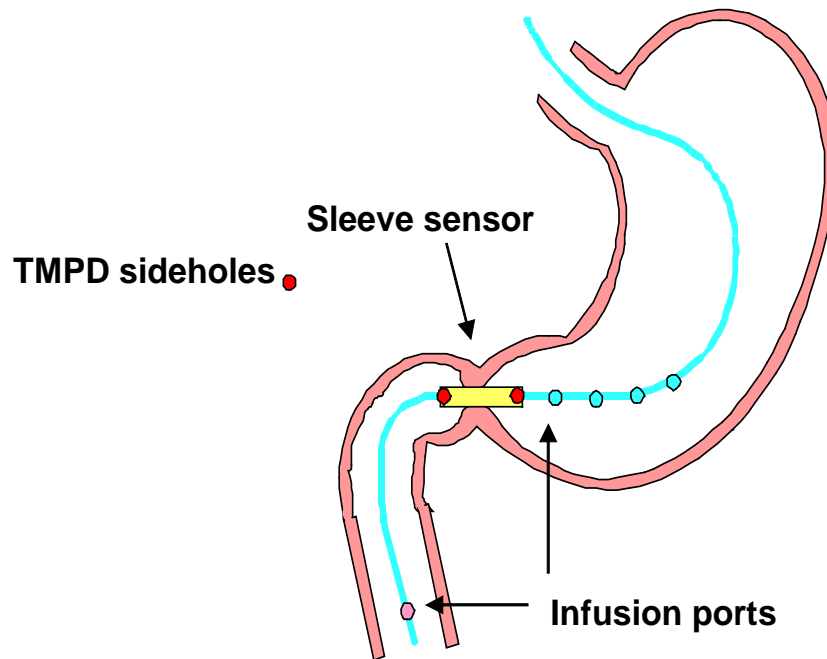


Figure 8.3 Manometric assembly used for study described in chapter 11.

8.4.2 Measurement of transmucosal potential difference

The maintenance of the position of the manometric assembly across the pylorus is essential to the performance of the studies which examined pyloric as well as antral and duodenal motor activity. This was achieved by measuring the transmucosal potential difference (TMPD) in the stomach and duodenum. The technique is described in detail in chapter 6. Two channels at either end of the sleeve sensor in the manometric assembly were perfused with saline. The potential difference was measured with a potentiometer and electrical contiguity was maintained by attaching a reference electrode to a subcutaneous line also primed with saline. While the technique has been validated in healthy subjects and is reliable in the laboratory setting, there were some initial difficulties with electrical interference in the ICU which were overcome by using a grounding line.

TMPD values were recorded continuously throughout each experiment and the manometric catheter was manipulated as necessary to maintain the position of the sleeve sensor across the pylorus. The TMPD data were recorded with the manometric data so that the position of the tube could be ascertained at all times during the analysis. Isolated pyloric pressure waves could only be identified when the correct position of the tube could be confirmed by TMPD. The criteria used to define the correct placement of the sleeve were that the antral TMPD was more negative than -20mV, and the duodenal TMPD was more positive than -15mV and that the difference between the two was at least 15 mV (Fone et al., 1989; Fone et al., 1990b; Heddle et al., 1988a; Heddle et al., 1988b; Heddle et al., 1988c; Houghton et al., 1988a; Houghton et al., 1988b).

8.4.3 Analysis of antro-pyloro-duodenal pressures

Manometric recordings were analysed manually. Pressure waves were only included in the analysis when the assembly was positioned correctly according to TMPD criteria (see above section 8.4.2) (Heddle et al., 1988a). The frequency of phasic pressure waves in the second channels in both the antrum (i.e. 6 cm proximal to the pylorus) and the duodenum (i.e. 3 cm distal to the pylorus) were determined. In the antrum a pressure wave was defined as a pressure rise ≥ 10 mmHg, lasting between 1 and 20 s and, in the duodenum, as a pressure rise ≥ 6 mm Hg, lasting between 0.8 and 7 s (Andrews et al., 2001). Isolated pyloric pressure waves (IPPWs) were defined as pressure waves, of at least 10 mmHg amplitude, recorded only in the sleeve channel (Heddle et al., 1988a). Changes in pyloric tone (basal pyloric pressure) were calculated as the difference in baseline pressure in the sleeve sensor from the duodenum, (Defilippi and Gomez, 1985), calculated for the whole of the study period, and analysed in 20 minute time blocks. Artefacts due to straining and coughing were excluded. Wave frequencies were determined for the whole of the study periods and analysed in 30 minute time intervals.

Antro-duodenal motility recordings were also analysed to determine the frequency, origin and characteristics of propagated pressure sequences. When analysing propagated wave sequences, pressure waves in adjacent channels were regarded as temporally related if they had onsets within ± 5 s (in the antrum) or ± 3 s (in the duodenum) of each other. A pressure wave sequence (propagated wave) was defined as 2 or more temporally-related pressure waves (Andrews et al., 2001). Pressure wave sequences were divided into those limited to the antrum, those limited to the duodenum and those waves propagating from antrum to duodenum. Both the direction (antegrade, retrograde or mixed) and the length (based on side-hole spacings) of propagation of the sequences were assessed. Whether or not the sequence occurred during phase 3 activity was also noted. During burst, or phase 3 activity, waves were defined as propagating towards the channel with a subsequent wave closest in time.

Antral “burst” or phase III activity was defined as rhythmic pressure wave activity occurring at maximum frequency (three pressure waves min^{-1}) for at least 1 min in a temporal relationship with duodenal phase III activity (Bosscha et al., 1998; Toumadre et al., 2001). Duodenal phases of the MMC were defined as follows: phase I, quiescence, no more than two pressure waves per 10 min for at least 5 min and preceded by phase III; phase II, irregular activity with pressure waves at a rate of more than two per 10 min; phase III/burst, regular pressure wave activity at a maximum frequency of 10-12 pressure waves min^{-1} for at least 2 min. followed by motor quiescence (phase I) (Bosscha et al., 1998). Episodes of “atypical” burst activity (*i.e.* high frequency pressure waves not fulfilling all the above criteria for phase 3) were also documented. MMC periodicity, the time to first MMC or burst activity after gastric bolus, and percentage of time in phases were calculated.

8.5 Glucose absorption

8.5.1 Measurement of blood glucose concentrations

Blood glucose levels were measured using a bedside Glucometer (MediSense Precision, Abbott Laboratories, MediSense Products, Bedford, MA USA) technique, using arterial (patients) or venous (healthy subjects) samples at baseline and at predetermined intervals (5,15,30,45,60,90,120,150,180,210 and 240 minutes). Blood glucose concentrations were analysed to determine baseline, peak, difference between peak and baseline, and time to peak concentrations. The relationship between blood glucose and GE was examined.

8.5.2 3-O-methyl glucose absorption

Glucose absorption was measured using 3-O-methyl glucose (3-OMG) absorption. Two grams of 3-OMG were mixed in 100 ml Ensure (Abbott Australasia, Kurnell, Australia) and infused into the stomach. Absorption of 3-OMG was measured by taking arterial (patients) or venous (healthy subjects) blood samples at baseline and at 5,15,30,45,60,90,120,150,180,210 and 240 minutes for measurement of 3-OMG. Samples were sent to the Department of Gastroenterology at the Women's and Children's Hospital in Adelaide where they were analysed for 3-OMG concentrations using a High Performance Exchange Chromatography technique. The results were then analysed to assess peak concentration, time to peak concentration and area under the curve. Individual concentrations at certain time points were also compared.

8.6 Statistical analysis

Data are shown as mean values and standard deviation or standard error of the mean (SEM); or median and range, as appropriate. Statistical analysis was performed using PRISM (GraphPad Prism Version 4.02 for Windows -GraphPad Software, San Diego, CA, USA), SAS version 9.1 (SAS Institute, Cary, NC, USA), SPSS version 14.0 or Minitab 13 for windows. Non parametric data were analysed using a chi-squared test (e.g. feed tolerance - chapter 10). The distribution of parametric data was determined using D'Agostino Pearson omnibus test. Differences between normally distributed data were analysed using student t test, paired (chapter 14 - saline vs. cefazolin) or unpaired (chapter 10, 11 - feeding study; manometry) as appropriate. Data not normally distributed were analysed using the Mann Whitney U test (unpaired data – e.g. chapters 11, 13) and the Wilcoxon rank tests (paired data – e.g. day 1 vs. day 2 - chapter 13.3). In studies where a numbers of measures were performed over time, a repeated analysis of variance (ANOVA) was used to analyse the data (e.g. chapter 10). Analysis of wave frequency was by mixed model ANOVA to allow for missing data. Correlations were performed using the Spearman, or Pearson correlation coefficients (e.g. the relationship between GEC and IPPWs, antral waves and pyloric tone – chapter 11). Linear regression was performed to compare breath tests and scintigraphic data

(chapter 10). Normal ranges were defined as the range of values in the healthy cohort. A P value of ≤ 0.05 was considered significant in all analyses.

Studies

Chapter 9

The measurement of gastric emptying in critical illness

Gastric emptying (GE) is rarely measured in routine intensive care practice. However it has been assessed for research purposes using a number of techniques, principally to quantify the prevalence of delayed emptying as a cause of feed intolerance (Kao et al., 1998; Ott et al., 1991; Tarling et al., 1997) or to quantify the response to prokinetic agents (Dive et al., 1995; Goldhill et al., 1997; Heyland et al., 1996a; Heyland et al., 1996b; Jooste et al., 1999; MacLaren et al., 2000; MacLaren et al., 2001; Marino et al., 2003; Spapen et al., 1995; Tamion et al., 2003). Most of these studies have used the paracetamol absorption technique (Cohen et al., 2000; Dive et al., 1995; Goldhill et al., 1997; Heyland et al., 1996a; Jooste et al., 1999; Lucey et al., 2003; MacLaren et al., 2000; MacLaren et al., 2001; Marino et al., 2003; Tamion et al., 2003; Tarling et al., 1997). Other techniques that have been used include scintigraphy (Kao et al., 1998; Ott et al., 1991; Spapen et al., 1995), and ultrasound (Pelfrene et al., 1996). None of these techniques has been validated in this patient group i.e. reproducibility and accuracy have not been determined.

As discussed in chapter 6 (section 6.3.2), scintigraphy is considered to be the most accurate method for the measurement of GE but is technically difficult to perform in critically ill patients. In most centres scintigraphic measurement of GE involves moving the patient to a Nuclear Medicine Department. Interhospital transport of mechanically ventilated patients is, however, both difficult and potentially dangerous. A mobile gamma camera was used in the studies reported in this thesis which allowed measurements of GE to be performed in the Intensive Care Unit (see figure 6.1). Prior to work by our group, breath test techniques had not been used to measure GE in the critically ill, despite their obvious potential advantages (chapter 6.3.3). They are simple, convenient, do not require blood sampling, and there is easy access to expired gases in the ventilated patient. There are, however, a number of reasons why breath tests may be inaccurate in the critically ill. They have not been validated in patients with severe gastroparesis and also abnormal hepatic and respiratory physiology may affect the results.

The study reported in this chapter was designed to address the role of labelled carbon breath test techniques in the measurement of GE in critically ill patients.

9.1 The evaluation of labelled carbon breath tests as a measure of gastric emptying in critically ill patients

9.1.1 Introduction

The recent development of breath test methods (chapter 6.3.3) has allowed non-invasive GE measurements in a variety of patient groups. These could potentially provide a practical method of quantifying GE in the ICU, but have not been validated in this setting.

Gastric residual volumes (GRVs) are aspirated from the stomach via a nasogastric tube as part of routine management of the nasogastric administration of nutrition. GRVs (chapter 6.3.4) are a convenient, albeit imprecise, indication of GE in the critically ill (McClave et al., 1992; Tarling et al., 1997) as gastric aspiration is frequently incomplete due to tube position or blockage and is, therefore, likely to underestimate the severity of delays in GE.

The primary aim of this study was to evaluate the relationships between GE of liquid nutrient measured by scintigraphy and labelled carbon breath tests in mechanically ventilated patients in an ICU setting. A secondary aim was to compare gastric residual volume measurements to the other indices of GE. The prevalence of delayed GE was also determined and this is described more fully in chapter 10.

9.1.2 Materials and methods

Subjects.

Twenty seven mechanically ventilated patients who were receiving, or eligible to receive, nasogastric feeding were enrolled in the study. This is the same patient cohort as those in the studies described in chapters 10 and 12.

Patients were excluded if:

1. There was a contraindication to nasogastric tube placement
2. There was a history of surgery on the oesophagus, stomach or duodenum within the previous 3 months.
4. They were pregnant or lactating

Prokinetic drugs were withheld for the period of the study. The patients remained on the sedative regimen they were receiving as part of their ICU care.

Gastric emptying was also measured in 14 healthy subjects and the results from these measurements were used to generate a normal range of GE using this technique.

Protocol

Following aspiration of the nasogastric tube, 100 ml of Ensure (standard liquid feed – 1kcal/ml) labelled with 20MBq ^{99m}Tc sulphur colloid and 74 kBq ^{14}C octanoic acid was infused into the stomach over 5 minutes. The study was performed over the subsequent 4 hours in accordance with the methods set out in chapter 8. Gastric emptying was measured using scintigraphy and the octanoic acid breath test technique. Before and after the study, the GRV was determined at 6 hourly intervals as per the usual ICU feeding protocol. The total volumes aspirated for the 24 hours preceding the study were documented. After the study period, nasogastric feeding and routine aspiration of the nasogastric tube were recommenced in the patients as indicated clinically.

Data analysis

The positive and negative predictive values of the breath test and GRV parameters were determined. The positive predictive value (PPV) is the proportion of patients with positive test results who are correctly diagnosed according to a ‘gold standard’. This is an important measure of a diagnostic method as it reflects the probability that a positive test indicates the underlying condition being tested for. Its value does, however, depend on the prevalence of the disease, which may vary. Similarly, the negative predictive value is the proportion of patients with negative test results who are correctly diagnosed.

9.1.3 Results

The demographics of the study subjects are shown in table 9.1. Complete data were obtained in the healthy cohort. Two patients did not complete the study because of regurgitation or vomiting. Technical difficulties resulted in loss of scintigraphic data in a

further patient. In an additional patient breath test data could not be fully analysed, because emptying was so slow that the curves could not be subjected to the standard mathematical modelling. GE data were available for analysis in 25 patients in whom 3 were incomplete. The scintigraphic $t_{1/2}$ could not be calculated in 5 patients because 50% emptying had not occurred at the end of the 4 hour period. Full details regarding the prevalence of delayed GE are given in chapter 10, however the prevalence using various parameters is shown in table 9.2. When compared to the healthy subjects approximately 50% of the critically ill patients had delayed GE, and in about 20% the GE was markedly slow.

9.1.3.1 Relationship between scintigraphy and breath tests (Table 9.3).

In patients there was a strong positive correlation between breath test t50 (BTt50) and gastric retention at all time points. There was a strong negative correlation between GEC and gastric retention. In healthy subjects there was a correlation between BTt50 and gastric retention at 60 & 120 minutes and there was a negative correlation between GEC and gastric retention at 120 & 180 mins. The positive and negative predictive values of the breath test compared to scintigraphy are shown (table 9.4).

9.1.3.2 Relationship between scintigraphy and gastric residual volume (table 9.5).

There was a strong correlation between gastric residual volumes and scintigraphy (Table 9.5). The positive and negative predictive values of the GRV measurement compared to scintigraphy are shown (table 9.4). A number of patients with delayed GE according to scintigraphy were not identified by large GRVs.

	Healthy Subjects n=14	ICU Patients n=25
Age - median (range)	62y (19-84)	66 (49-72)
Gender	8M	17 M
BMI	26 (20-30)	26 (20-40)
APACHE II score on day of study		14 (7-30)
Diagnostic groups		6 trauma, 6 ICH, 6 sepsis, 4 resp failure, 2 vascular, 1 postop ENT, 1 burns
Hospital Survival		80%
No. patients with pre-existing Diabetes Mellitus	0	6
Continuous Renal Replacement Therapy		3
No. of patients receiving insulin		10
Baseline blood glucose concentration (mmol/L) mean (SEM).	5.5 (0.16)	8.26 (0.47)*
No. patients receiving prokinetics prior to study		9
No. patients receiving catecholamines		3
No. patients receiving propofol		4

*Table 9.1 The demographics of the study subjects. *P<0.001. Postop = postoperative, resp = respiratory failure. ICH = intracranial haemorrhage.*

Parameter	Prevalence
BT t50	22% (5/23)
GEC	29% (7/24)
Scintigraphic t _{1/2}	46% (11/24)
Percentage retention at 60 min	33% (8/24)
Percentage retention at 120 min	54% (13/24)
Percentage retention at 180 min	50% (12/24)
Percentage retention at 240 min (>10%)	50% (12/24)
GRV >150 ml in 24 h	41% (9/22)
GRV > 250 ml in 24 h	23% (5/22)

Table 9.2 Prevalence of delayed GE using various parameters.

	Patients		Healthy	
	R value	P value	R value	P value
BTt50 & % Retention at 60 min	0.66	<0.001	0.78	<0.001
BTt50 & % Retention at 120 min	0.74	<0.001	0.76	0.0016
BTt50 vs. % Retention at 180 min	0.75	<0.001		NS
BTt50 vs. % Retention at 240 min	0.76	<0.001		NS
BTt50 vs. scintigraphic t _{1/2}	NA		0.74	<0.001
GEC & % Retention at 60 min	-0.68	<0.001	-0.48	0.08
GEC & % Retention at 120 min	-0.74	<0.001	-0.73	0.003
GEC vs. % Retention at 180 min	-0.76	<0.001	-0.58	0.03
GEC vs. % Retention at 240 min	-0.76	<0.001		NS
GEC vs. scintigraphic t _{1/2}	NA		-0.53	0.035

Table 9.3 The relationship between scintigraphy and breath tests in patients and healthy subjects.

Values compared	Positive predictive value	Negative predictive value
GEC vs. Retention at 180 min	0.86 (0.42-0.99)	0.71 (0.44-0.98)
BT _{t50} vs. Retention at 180 min	1 (0.46-1)	0.72 (0.46-0.89)
GEC vs. Scintigraphic t _{1/2}	0.86 (0.42-0.99)	0.76 (0.49-0.92)
BT _{t50} vs. Scintigraphic t _{1/2}	1 (0.46-1)	0.78 (0.52-0.93)
GEC vs. Retention at 240 min	1 (0.52-1)	0.72 (0.46-0.89)
BT _{t50} vs. Retention at 240 min	1 (0.46-1)	0.72 (0.46-0.89)
GRV (>150ml) vs. Retention at 180 min (>13%)	0.78 (0.4-0.96)	0.85 (0.54-0.97)
GRV (>250ml) vs. Retention at 180 min (>13%)	1 (0.46-1)	0.76 (0.50-0.92)

Table 9.4 Positive and negative predictive values and confidence intervals of breath test and GRV measurements compared to scintigraphic parameters.

	Patients	
	R value	P value
GRV & BT _{t50} min	0.72	<0.001
GRV & GEC	-0.46	0.003
GRV & Retention at 60 mins (%)	0.5	<0.001
GRV & Retention at 120 mins (%)	0.66	<0.001
GRV & Retention at 180 mins (%)	0.73	<0.001
GRV & Retention at 240 mins (%)	0.77	<0.001

Table 9.5 The relationship between scintigraphy (retention at 1, 2, 3 & 4h), breath tests (BT_{t50} & GEC) and gastric residual volume (GRV).

9.1.4 Discussion

This is the first study to validate a technique for the accurate measurement of GE in the critically ill. A strong correlation between GE measurement using C¹⁴ breath tests and scintigraphy was demonstrated, suggesting that the breath test technique can be used to measure GE in this patient group. This study is also the first to demonstrate the accuracy of the breath test technique in measuring the GE of a liquid nutrient. In addition, a relationship between GRV and the scintigraphic measurement of GE was demonstrated. The results suggest that an aspirate volume of >250ml in 24h can reasonably reliably predict delayed GE.

Breath test measurement of GE, first described by Maes and Ghooos in 1993 (Ghooos et al., 1993), has been validated against scintigraphy in healthy subjects for both solid and non-nutrient liquid emptying (Bluck et al., 2002; Braden et al., 1995; Bromer et al., 2002; Chey et al., 2001; Ghooos et al., 1993; Maes et al., 1994; Minderhoud et al., 2004; Pfaffenbach et al., 1995). However, prior to the current study, the accuracy of breath test techniques had not been clearly demonstrated in subjects with marked gastroparesis (see chapter 6). Also the breath test technique had not been validated for measurement of liquid nutrient emptying, which is of most interest in the critically ill population.

The results of this study are consistent with previous studies comparing breath tests to scintigraphy. In a recent study where scintigraphy was compared to labelled carbon breath tests for the measurement of GE of solids in healthy subjects and patients with dyspepsia, reflux and diabetes, the correlation was good with an r value of 0.74 (comparing the half emptying times generated by the 2 techniques) (Delbende et al., 2000). This is comparable to the r values generated in this study in both patients (r=0.66-0.76) and healthy subjects (r=0.48-0.78) (table 9.3). The study by Delbende et al also documented low inter- and intra-individual variability of the breath tests results which has been noted previously (Barbosa et al., 2005; Choi et al., 1997). In the study by Delbende et al the breath test detected delayed gastric emptying with a specificity of 80% and sensitivity 67%. Similarly Ziegler et al found the breath test to have 86% specificity and 75% sensitivity in the accurate identification of abnormal GE, when comparing breath testing to scintigraphy in diabetic patients (Ziegler et al., 1996). Again, these results are comparable to the positive and negative predictive values of the breath tests demonstrated in this study (table 9.4). These values are acceptable but the breath test did not identify all subjects with delayed GE. In the current study 5 subjects, out of 12 with delayed GE as measured by scintigraphy, were not identified by the breath test technique. The performance of breath test measurement in the measurement of gastric emptying of liquid nutrient in critically ill patients (some of whom had very delayed gastric emptying) appears comparable to the measurement of solid emptying in other groups.

Although scintigraphic measurement is currently considered to be the most accurate technique for measurement of GE there are some limitations to its use. It is difficult to perform in the critically ill and three dimensional pictures cannot be generated due to the necessity for the patient to remain supine. To overcome this, in this study the patients and healthy subjects were studied in the left anterior oblique position (Ford et al., 1992; Maurer et al., 1991; Yung, 1993). In addition, identification of the stomach can be affected by radiation from overlying bowel, which may hamper interpretation. Furthermore, neither scintigraphic nor breath test techniques measure total GE, as neither take into account gastric secretion, the importance of which is unknown in the critically ill. It should also be recognised that the two techniques are measuring slightly different parameters. The breath test technique requires GE, duodenal absorption, liver metabolism and respiratory excretion to occur. GE is thought to be the rate limiting step in this

process, but it is possible that in certain critically ill patients marked derangements in the other steps may interfere with the accuracy of the measurements. However, the strong relationship between scintigraphy and breath tests demonstrated in this study suggests otherwise. It is also important to recognise that the scintigraphic $t_{1/2}$ and the breath test t_{50} are not measuring the same parameters and so are not comparable measurements even though they are both expressed in minutes (see chapter 8.3.3).

The breath test technique has several advantages over the commonly used paracetamol absorption technique. It has now been evaluated in the ICU setting and does not require blood sampling which can contribute to the anaemia of the critically ill. It also avoids staff exposure to blood. Paracetamol also cannot be administered to individuals with liver dysfunction, whereas the breath test can be performed in these patients.

Gastric emptying is rarely directly measured in the critically ill other than for research purposes whereas regular measurement of gastric residual volume (GRV) during the infusion of enteral nutrition is part of routine management. It is considered a convenient clinical tool and is used to indicate GE, success of feeding and the potential risk of aspiration. Despite widespread acceptance of GRV in feeding protocols, the utility and significance of this measurement is controversial, as it is dependent on a number of factors in addition to GE (see chapter 6). There are conflicting data on the relationship between GRV and GE in the literature, which have led to a lack of consensus on an acceptable value for GRV during enteral feeding. Studies where feed intolerance was defined as a GRV >50ml did not demonstrate a relationship between GRV and GE (Goldhill et al., 1997; Tarling et al., 1997). This may be because this small volume overestimates the occurrence of slow GE. In contrast, a relationship between delayed liquid GE measured by scintigraphy and feed intolerance defined as a GRV > 100ml has been reported (Ott et al., 1991). Cohen et al showed that 25% of patients with a GRV > 150 ml had normal GE (measured by paracetamol absorption) and could continue to be fed successfully without prokinetics (Cohen et al., 2000). It would seem logical that the use of a larger GRV as an indication of delayed emptying would result in less false positive diagnoses of delayed GE. This is supported by the data from this study (table 9.4), which suggests that if a GRV of 250ml is used to indicate delayed GE, the positive predictive value approaches 1. However some patients with delayed GE are not identified by this approach and it is unclear how this relates to feed intolerance.

There are several limitations of this study. While the correlations suggest that both the breath test technique and GRV measurement provide a reasonable approximation of the rate of GE, the accuracy of the measurements are more difficult to ascertain. The positive and negative predictive values suggest that both tests lack sensitivity i.e. will not identify all cases of delayed emptying. However these calculations are based on at least two assumptions. Firstly, the normal range of GE defined in this study is generated from a small group of only fourteen subjects. As interindividual GE is known to be variable, even in health, this may not be a true normal range. Tougas et al measured GE scintigraphically in 123 subjects to generate a normal range for the rate of GE of a solid meal (Tougas et al., 2000). Also it is unclear which is the best scintigraphic parameter to use as the “gold standard” (scintigraphic $t_{1/2}$, retention at 60, 120, 180 or 240 minutes). Several parameters are examined in table 9.3. The ‘limits of agreement’ method of comparing two techniques of measurement could not be used because the techniques measure different parameters.

In conclusion; these data demonstrate a strong correlation between the breath test technique and scintigraphy suggesting that breath tests can be used for the measurement of GE in the critically

ill for research purposes. The reduced sensitivity of breath test measurement (when compared to scintigraphy) may limit its widespread use for the clinical diagnosis of delayed GE in individual patients. However, its reproducibility and high specificity support a potential role for breath testing in critically ill patients for epidemiologic and pharmacological studies. The measurement of GRV also gives an indication of GE, although the value of GRV measurement in feeding protocols is yet to be determined.

Chapter 10

Feed intolerance and delayed gastric emptying in the critically ill

10.1 Introduction

As discussed in chapter 2, the enteral route of nutritional support is clearly preferred over the parenteral particularly as it is associated with lower infection rates (Kudsk et al., 1992; Moore et al., 1992), better wound healing (Schroeder et al., 1991), reduced mortality (Herndon et al., 1989) and lower cost (Frost and Bihari, 1997). In addition enteral nutrition preserves gut mucosal integrity (Hadfield et al., 1995) which may act as a barrier against the endogenous bacteria implicated in the pathogenesis of nosocomial pneumonia, sepsis and multiple organ failure (Carrico et al., 1986; Heyland and Mandell, 1992). However, enteral nutrition often fails to deliver the desired energy requirements for critically ill patients whilst parenteral nutrition reliably achieves nutritional goals (Herndon and Curreri, 1978; Robertson et al., 1984).

While feed intolerance has been quantified in other populations (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988) it has never been formally quantified in an Australasian ICU (see chapter 2.4.1). Furthermore, although GE has been examined in critically ill patients (Goldhill et al., 1995; Heyland et al., 1996b; Kao et al., 1998; Ott et al., 1991; Spapen et al., 1995; Tarling et al., 1997), these studies are few, and have limitations in terms of numbers of patients studied, the method of measurement of GE and the performance of the study (see chapter 4.2.1.1). Furthermore, some of these studies examined GE only in specific diagnostic subgroups (Goldhill et al., 1995; Kao et al., 1998; Ott et al., 1991). Thus the prevalence and determinants of delayed GE in a mixed ICU population are still unclear. This chapter presents the results of two studies aimed at quantifying feed intolerance and the prevalence and determinants of delayed gastric emptying in an Australasian critically ill population.

10.2 A prospective audit of enteral nutrition in the critically ill

10.2.1 Introduction

A number of studies have shown that enteral nutrition delivers less than optimal amounts of energy and protein when administered to critically ill patients (see chapter 2) (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). In these studies, the success rate of enteral nutrition varied from 26 to 86%. The most important reason limiting the success of enteral administration of nutrition appears to be upper gastrointestinal dysfunction (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). This is usually evident clinically by large gastric residual volumes, indicative of delayed gastric emptying.

The aim of this audit was to evaluate the adequacy of the feeding protocol in a mixed medical-surgical, Australian intensive care unit and identify factors which influence the successful delivery of nutrition to this group of critically ill patients.

10.2.2 Materials and Methods

Subjects

Forty consecutive patients requiring enteral nutrition, who were expected by the medical staff to stay in the ICU for more than 5 days, were prospectively enrolled in the study.

Protocol

Data were collected for a seven day period unless death or discharge from the intensive care unit occurred sooner. Prior to initiation of enteral feeding, the unit dietician determined the ideal daily energy requirements for each patient as the product of the basal energy expenditure calculated using the Harris- Benedict equation and an injury factor determined by the patient's admission diagnosis (see chapter 2) (Herndon and Curreri, 1978; Robertson et al., 1984). This value was then set as the patient's goal for each day of the study period. All patients received an iso-osmotic feed (Osmolite, Ross laboratories, Columbus, Ohio) via a nasogastric tube. Feed was administered according to the feeding protocol at the time (Figure 10.2.1) and was managed by the ICU medical and nursing staff. Successful enteral feeding was defined as achieving 90% of the ideal calorie requirement on 2 consecutive days (Heyland et al., 1995). The age, sex, diagnosis, admission APACHE II score, time to commencement of feeding, reasons for reducing or ceasing feeding, the use of sedative, paralyzing or prokinetic agents, and daily plasma albumin levels were also recorded.

For each patient the actual energy intake was compared with their ideal estimated requirements for each day of the study.

10.2.3 Results

The patients demographics were as follows; 10 female and 30 male; median (range) age of 52 (14-84) years, weight 79 (35-140) kg and admission APACHE II score 20 (8-43). Admission diagnoses to the Intensive Care Unit are summarised in table 1.

Feeding was commenced a median of 4 days (range; 0-15) following admission to ICU. Enteral nutrition was the sole source of nutrition in 38 patients. The remaining 2 patients received supplemental parenteral nutrition; one for one day and the other for 4 days during initiation of enteral feeding. Thirty-nine patients were fed via a nasogastric tube and one patient via a nasojejunal tube. Thirty patients (75%) were fed for the entire seven days. Thirty two patients received morphine and sixteen received neuromuscular blocking agents. The mean ideal energy requirement was 9566 ± 2586 kJ per day.

Values for day 1 were excluded due to the time delay between the decision to commence feeding and delivery of feed. Figure 10.2.2 shows the average daily energy intake. Patients received a mean of $51 \pm 38\%$ of their ideal energy requirements during the entire study period. The effect of the admission diagnosis on the success of feeding is shown in table 10.2.1. Using the criteria stated previously only 10 patients (25%) were fed successfully during the 7 day study period.

There were a variety of causes for the failure to deliver the prescribed feed (Table 10.2.2). The major reason was gastrointestinal intolerance, which accounted for approximately 50% of failed feeding. The administration of nutrition was ceased at some time over the 7 days due to gastrointestinal intolerance in 19 of the 40 patients (48%). There was no association between the volume of feed delivered and the use of neuromuscular blocking agents ($P=0.73$), the dose of morphine ($r=-0.096$, $P=0.11$), the dose of midazolam ($r=-0.065$, $P=0.28$), or either the plasma albumin concentration on day 7 ($r=-0.091$, $P=0.68$) or the change in plasma albumin concentration over the study period ($r=-0.001$, $P=0.9$). (The plasma albumin did not change significantly).

There were 13 deaths in the study group. There was no difference in energy intake between patients who survived (51% of goal) or died (48% of goal) ($P=0.124$).

Prokinetic agents (erythromycin, cisapride or metoclopramide) were used in 25 patients at some time during the 7 days. This group of patients had an average energy intake of only 31% of the estimated goals compared with 53% in those who did not receive a prokinetic agent ($P=0.01$). Overall, there was no significant improvement in the success of feeding following the use of prokinetic drugs, although where it was possible to assess the effects of these agents, 8/14 patients had increased delivery of feed after their administration.

Diagnosis	Number	Percentage nutritional goal achieved Mean (\pmSD)
Medical	19	49 (37)
Trauma (excludes head trauma)	7	37 (22)
Neurological (includes trauma)	6	43 (23)
Surgical	4	64 (23)
Burns	4	71 (25)

Table 10.2.1 Number of patients in each diagnostic group and percentage of nutritional goal achieved.

Reason	Number of patient days (n=257)
Gastrointestinal dysfunction: large GRVs, vomiting, distension, diarrhoea	57
Airway procedures: planned extubation, tracheostomy insertion, tube change	30
Procedures visits to radiology, hyperbaric oxygen therapy, theatre, radiotherapy	19
Other: Formula not available, unstable, problems with jejunostomy, involvement in an investigational study	12

Table 10.2.2 Causes for cessation of enteral nutrition in 40 critically ill patients

Nasogastric feeding protocol
Royal Adelaide Hospital – Intensive Care Unit
At time of audit (1999)

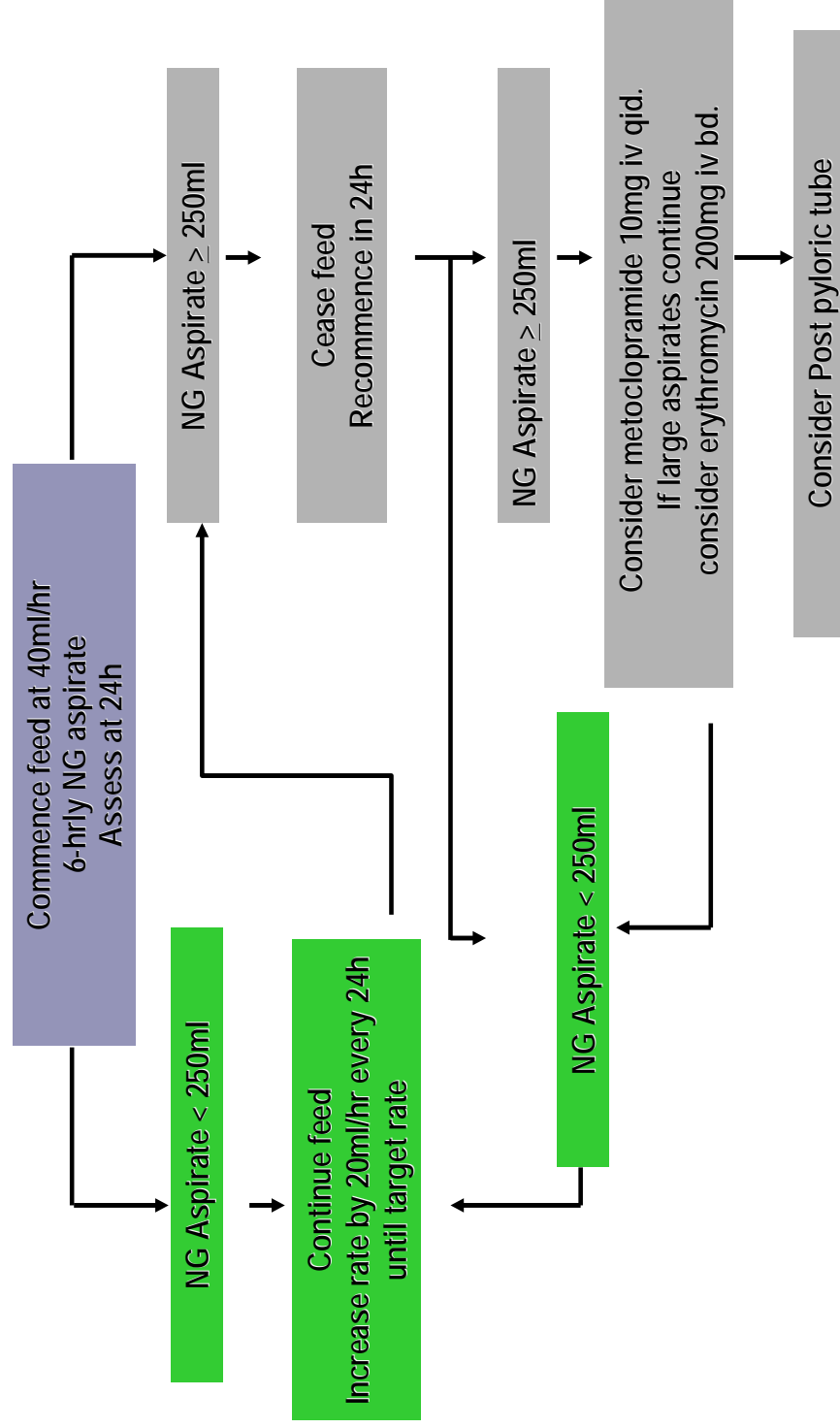


Figure 10.2.1

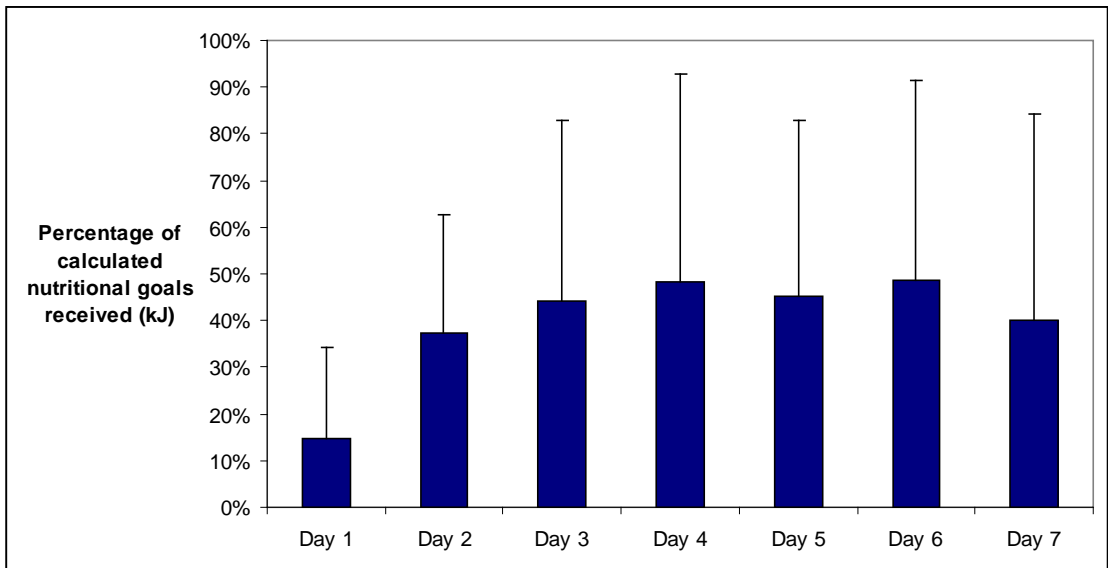


Figure 10.2.2 Percentage of nutritional goals achieved each day in 40 ICU patients (mean, standard deviation).

10.2.4 Discussion

In this study the nutritional goals of 40 unselected critically ill patients were not met by enteral feeding. Overall, patients received only 51% of their ideal energy requirements and only 25% of patients met the criteria for successful feeding at any time in the 7 day audit period. Just under half of the patients developed feed intolerance at some time. These data are consistent with a number of previous studies that have also reported low success rates (Heyland et al., 1995), and inadequate delivery of calories (Abernathy et al., 1989; Kemper et al., 1992; Rapp et al., 1983), with enteral nutrition. Thus while the provision of nutrients via the gut lumen has become the preferred means of feeding critically ill patients, it is clear that this frequently results in less than optimal feeding (Griffiths, 2000).

The two most frequent causes for the failure to meet target feeding goals were slow gastric emptying, as indicated by large gastric residual volumes, and fasting in preparation for airway procedures or prior to surgical or radiological procedures. The high incidence of gastrointestinal intolerance is in agreement with data from a number of other studies (Abernathy et al., 1989; Cataldi-Betcher et al., 1983; Heyland et al., 1995; Norton et al., 1988). Slow gastric emptying in the critically ill may result from a number of factors. In this study, Intensive Care Unit admission diagnosis apparently had limited influence on feeding success (table 10.2.1). However patients with intracranial pathology or neuro-trauma appeared to be fed less successfully than other groups. Patients with head injuries have been reported to have a high incidence of gastric dysmotility and delayed gastric emptying consistent with this observation (chapter 5).

A variety of approaches have been suggested to overcome slow gastric emptying. These include the use of prokinetics (Heyland et al., 1996a; Jooste et al., 1999) or naso-duodenal / jejunal feeding (Moore and Jones, 1986) (see chapter 5). The current study shows that patients selected to receive prokinetic agents, not surprisingly, had a lower initial success rate for feeding. The apparent improvement with prokinetic drugs was modest, although more than 50% of the patients who received these agents had an increase in delivery of feed. However, as this was not a randomised study, the choice and timing of prokinetic drug administration were left to the discretion of individual clinicians, and the interpretation of these data is therefore limited. It is also not possible to determine the relative effect of individual agents. A more standardised approach to the use of such agents could improve the delivery of enteral feed in view of the reports of enhanced gastric emptying during routine use of cisapride (Spapen et al., 1995).

Post pyloric placement of feeding tubes has been reported to improve delivery of enteral nutrition. The one patient in this study who had a post pyloric tube achieved an average of 94% of their nutritional goals over the 7 day study period. However, as discussed in chapter 7, positioning of these tubes can be difficult and may require endoscopy or other placement techniques. In addition, although jejunal feeding may reduce the complications associated with enteral feeding it does not eliminate these entirely (Lien et al., 2000).

Fasting prior to procedures or investigations was another major reason for interrupting delivery of enteral nutrition. Although little can be done to prevent these situations, fasting times can be minimised to prevent prolonged delays in nutrient delivery. In addition, the formula can be restarted at the rate reached immediately prior to fasting to avoid further delays in establishment of the feed volume.

Accurate assessment of the nutritional requirements for critically ill patients is difficult. In the current study, basal energy expenditure was calculated using the Harris – Benedict equations and the value increased by between 20% for single organ dysfunction, such as pneumonia, to 100% for severe burns. Studies using indirect calorimetry suggest that energy requirements of the critically ill are similar, or even reduced when compared to healthy subjects, as the hypermetabolic nature of many disease states is offset by inactivity (Robertson et al., 1984). In addition, clinical interventions, such as early debridement of a focus of infection or the maintenance of body temperature for patients with severe burns, may result in a reduction in energy expenditure. It is, accordingly, possible that feeding goals in the current study were initially set too high. However, other studies have suggested that energy requirements may increase during prolonged admissions to intensive care units (Uehara et al., 1999). However, as delivery of feeds reached a plateau at only about 50% of the calculated requirements, these data suggest a degree of underfeeding even if goals were excessive.

The effect of feeding on outcome in critically ill patients is uncertain. Currently feeding goals calculated using the Harris-Benedict equation are widely used in practice and it is intuitively likely that prolonged restriction in energy or protein administration would be deleterious.

In summary, this study demonstrates that the delivery of nutrition by the enteral route in critically ill patients in a level 3 Australian intensive care unit is frequently inadequate. There is thus a clinical need to explore the reasons for this deficiency and develop strategies to improve it.

10.3 Gastric emptying in the critically ill

10.3.1 Introduction

Although the rate of gastric emptying has been reported to be reduced in a number of subgroups, the overall prevalence of delayed GE in critically ill patients remains uncertain. This reflects the heterogeneity of the admission diagnoses, the lack of consistent methodology, and the possible effects of drugs commonly required for sedation in the previous studies. In traumatic brain injury, delayed GE (measured by scintigraphy) has been reported to occur in 50-80% of patients (chapters 4 & 5) (Kao et al., 1998; Ott et al., 1991). GE has also been measured using the paracetamol absorption test in two mixed groups of critically ill patients (Heyland et al., 1996b; Tarling et al., 1997). These studies demonstrated marked variability in GE. Tarling et al reported that GE was delayed in 60% of the patients (Tarling et al., 1997). Factors previously associated with slow GE in the critically ill (chapter 5) include; raised intracranial pressure (McArthur et al., 1995; Power et al., 1989), reduced Glasgow coma score (Kao et al., 1998), age (Heyland et al., 1996b; Kao et al., 1999), administration of dopamine (Tarling et al., 1997), time between traumatic brain injury and measurement of GE (Kao et al., 1998), and the height of a spinal cord lesion (Kao et al., 1999). There are conflicting observations in relation to the effects of the administration of opiates (Heyland et al., 1996b; McArthur et al., 1995), and gender (Heyland et al., 1996b; Kao et al., 1998). Also one study suggested that reduced illness severity is associated with delayed GE (Tarling et al., 1997), however this is intuitively unlikely.

The aim of this study was to determine the prevalence of delayed gastric emptying in a group of critically ill patients using scintigraphy which is considered to be the most accurate method of measurement. A secondary aim was to assess possible risk factors for delayed emptying.

10.3.2 Materials and Methods

Subjects

Twenty seven mechanically ventilated patients who were receiving, or eligible to receive, nasogastric feeding were enrolled in the study. This is the identical patient cohort to that included in the studies described in chapters 9 and 12 (see 9.1.2 and table 9.1 for details).

Data were compared to 14 healthy volunteers all of whom had participated previously in studies involving nasogastric intubation.

Protocol

Following aspiration of the stomach via the nasogastric tube, 100 ml of Ensure (standard liquid feed – 1kcal/ml) labelled with ^{99m}Tc sulphur colloid was infused into the stomach over 5 minutes. The study was performed using the methodology described in chapter 8. Gastric emptying was measured over the subsequent 4h using scintigraphy. The parameters used to evaluate GE are also described more fully in chapter 8. After the study period, nasogastric feeding and routine aspiration of the nasogastric tube were recommenced in the patients, as indicated clinically.

Normal range was defined as the range of normal values in the healthy cohort.

10.3.3 Results

The demographics of the study subjects are shown in table 9.1. Studies were performed 9 (range 1-22) days after admission to the ICU. 14 patients were receiving morphine infusions at a rate of between 1 and 30 mg/hr. Twenty patients had been fed prior to the study at a median rate of 72ml/h (range 40-120 ml/h) and 7 patients were considered suitable for nasogastric feeding. Complete data were obtained in the healthy cohort. Two patients did not complete the study because of regurgitation or vomiting. Technical difficulties resulted in loss of scintigraphic data in a further patient. GE data were thus available for analysis in 24 patients. Scintigraphic $t_{1/2}$ could not be calculated in 5 patients because 50% emptying had not been achieved by the end of the 4 hour period.

10.3.3.1 Gastric emptying

Gastric emptying was significantly reduced in the ICU group compared to the healthy cohort ($P < 0.001$) (figure 10.3.1 and table 10.3.1).

10.3.3.2 Prevalence of delayed gastric emptying in the critically ill

The prevalence of delayed GE in the critically ill varied between 33 and 54% depending on the scintigraphic parameter chosen (table 9.2). If normal GE was defined as scintigraphic $t_{1/2} < 86$ min (longest in the healthy cohort), 10 (42%) patients were slower than this range. If normal was defined as $< 10\%$ retention at 240 minutes then 12 of the 24 patients (50%) studied had abnormally slow emptying. Two subjects had abnormally rapid GE at 60 minutes (figure 10.3.1).

10.3.3.3 Determinants of gastric emptying in the critically ill

The relationship between GE and diagnosis is shown in table 10.3.2. Patients with trauma and sepsis had the slowest rate of GE. In the critically ill patients, there was a relationship between GE and length of stay in ICU prior to the study, so that GE was faster if the study was performed later in the patient's admission (retention at 60 min (%); $r = -0.429$, $P = 0.041$). There was no relationship between GE and the APACHE II score on the day of study, age or gender. There was also no relationship between GE and the dose of morphine, catecholamines or propofol. In addition, there was no difference between GE measurements in those who had, and had not, been receiving prokinetics (retention at 60 minutes (%); 64 (+/- 31) vs. 51 (+/- 22); $P > 0.05$). There was also no difference in the GE in those patients who had and had not been fed prior to the study. Baseline BGL had no relationship with GE in either cohort.

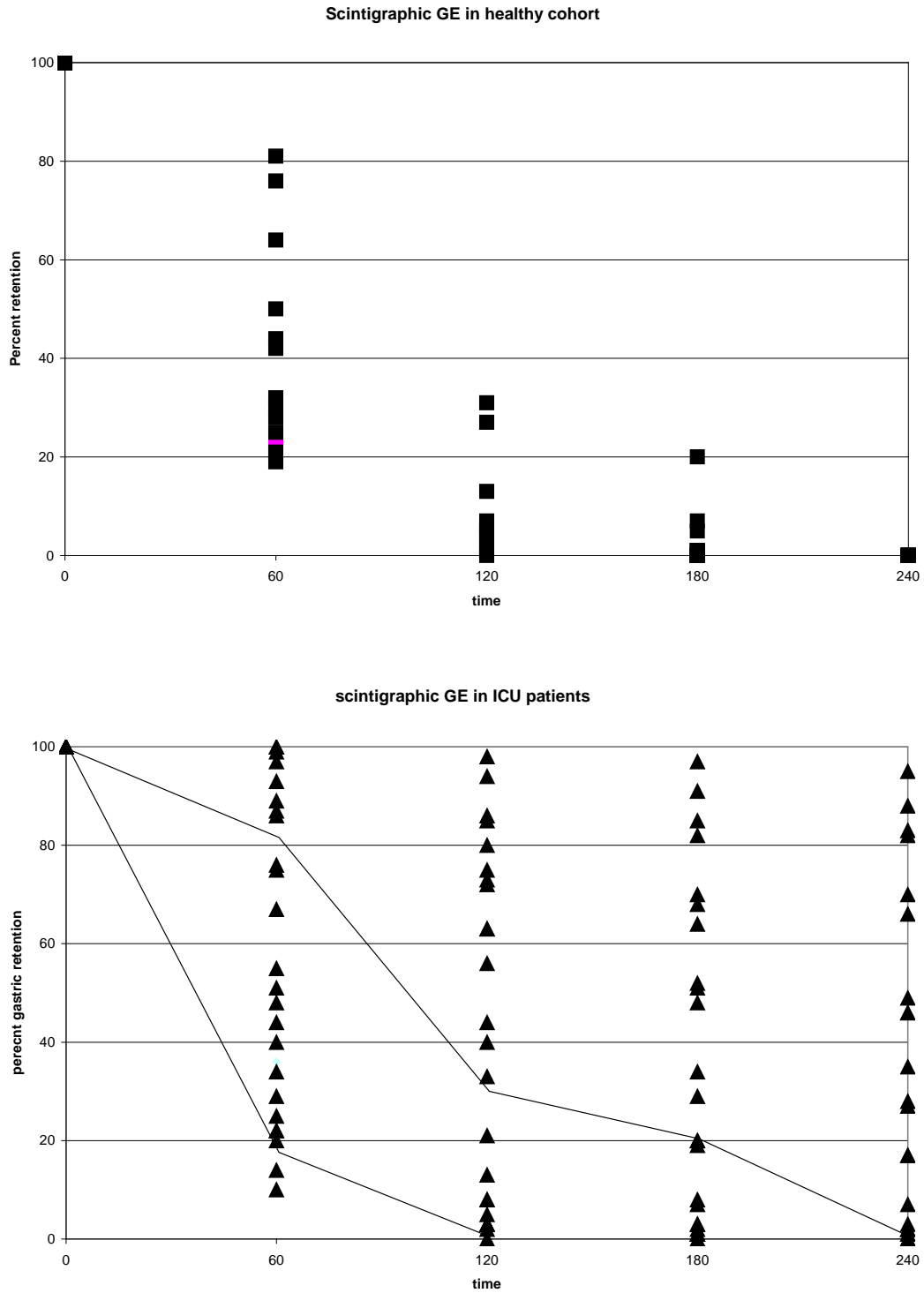


Figure 10.3.1 Scintigraphic measurement of GE showing individual results for gastric meal retention over time for healthy subjects (n=14) and ICU patients (n=24). The normal range from this healthy cohort is shown in the enclosed area on the ICU graph. At 240 min 12 patients were outside the normal range (ANOVA $P < 0.001$).

Median (range)	Controls (n=14)	Patients (n=24)	P value
Scintigraphic t _{1/2} (min)	37 (12-86)	N/A	
Retention at 60min (%)	31 (19-81)	51 (10-100)	0.08
Retention at 120min (%)	5 (0-31)	40 (0-98)	0.005
Retention at 180min (%)	1 (0-20)	20 (0-97)	<0.001
Retention at 240min (%)	0 (0-0)	17 (0-95)	<0.001

Table 10.3.1 Gastric emptying in patients and healthy subjects.

	GE (% Retention at 60 minutes)
Trauma n=6	81% (+/-16)
Sepsis n=6	74% (+/- 37)
Respiratory failure n=4	46% (+/-20)
Intracranial Haemorrhage n=5	27% (+/-13)

Table 10.3.2 The effect of diagnostic group on gastric emptying in the critically ill patients

10.3.4 Discussion

This study is the first to examine the prevalence of delayed GE in a heterogeneous critically ill population using the 'gold standard' technique for measurement i.e. scintigraphy. These results show that approximately 50% of patients have incomplete gastric emptying after 4 hours when compared to healthy subjects, where emptying was complete in all cases. The prevalence of delayed GE may have been underestimated as the two subjects with vomiting and regurgitation were also likely to have had delayed GE. Trauma and sepsis appear to be risk factors for delayed emptying.

These observations are consistent with previous, limited, scintigraphic measurements of GE in the critically ill (see chapter 4). Spapen et al reported that GE of a nutrient liquid was significantly delayed in a small mixed ICU group (Spapen et al., 1995). Although scintigraphic $t_{1/2}$ was prolonged in the critically ill patients in this study, gastric retention of marker (see chapter 6.3.2.2) and the prevalence of delayed GE were not reported. Gastric emptying of non-nutrient liquid was reported to be delayed in 50-80% of patients with severe head injury (Kao et al., 1998; Ott et al., 1991), but interpretation of these studies is limited by the difference in meal ingestion between the healthy subjects, who swallowed the marker, and the patient group where the test meal was infused via a nasogastric tube. In the study by Ott et al, historical controls were used, and the technique for measurement of GE was not described. As GE may be affected by the presence or absence of a nasogastric tube (Read et al., 1983), this could have confounded the results. Nevertheless, the previous data are in concordance with those from the current study where GE was retarded in 12 (of 24) patients, such that residual feed was still present in the stomach at 4 hours.

The data from this study are also consistent with previous studies that used other techniques to measure GE. The study by Tarling et al reported an incidence of delayed GE of 60% in a mixed group of ICU patients (Tarling et al., 1997), which is similar to the 50% reported in this study. In that group the paracetamol absorption technique was used to measure GE. In contrast, Heyland et al, also using the paracetamol absorption technique, did not demonstrate any difference in the AUC of paracetamol concentrations, however a difference was demonstrated in maximal concentration and time to maximal concentration (Heyland et al., 1996b). That study did not comment on the prevalence of delayed emptying. An estimation of the prevalence of delayed GE may be a more useful parameter to quantify GE in the critically ill because the marked variability in GE makes statistical comparisons between groups difficult to interpret. The variability in GE was evident in the current study with 2 patients having abnormally rapid GE at 60mins (figure 10.3.1). GE has also been noted to be highly variable in health (Tougas et al., 2000).

It is not clear which parameter of GE measurement is best used to describe GE in the critically ill. However the use of percentage retention at 4h gives a clear differentiation between normal and delayed GE. The GE demonstrated in this study correlates with an emptying of about 0.5kcal/min over the first hour of the study in the critically ill subjects while the healthy subjects emptied at a rate of more than 1kcal/min.

When measuring GE in a healthy cohort using a nasogastric tube, it is probably important that subjects have been accustomed to the positioning of a nasogastric tube prior to the study. The rate of gastric emptying is exquisitely sensitive to stress or discomfort (Roland et al., 1990).

Anxiety and discomfort in the placement of nasogastric tubes, or other devices is likely to give an impression of falsely slow gastric emptying in the control group. All the subjects in this study had had nasogastric tubes placed previously and were apparently unaffected by the process. The use of a 'gold standard' for measurement and careful duplication of process in both groups renders this the best study to date for determination of the prevalence of delayed gastric emptying in the critically ill. However, although this is the largest study to date using scintigraphy in a heterogeneous group of critically ill patients, it is still limited in size. The prevalence of delayed GE in certain diagnostic subgroups remains to be further evaluated.

Several other potential limitations of this study should be recognised. It is unlikely that the group studied was truly representative of a general ICU population. The logistical difficulties of obtaining consent and performing a 4-6 h study meant that there was bias in the type of patients recruited. The median length of stay in the ICU at the Royal Adelaide Hospital is 48-72h whereas the median length of stay in this group was 9 days prior to the study. It is, therefore, likely that the group sampled in this study were sicker and stayed longer in the ICU than is usual. In less acute patients, who stay in the ICU for shorter periods, the prevalence of delayed GE is likely to be less, although this premise is not supported by the study of Tarling et al (Tarling et al., 1997) who reported that GE was slower in less acute patients. However, examination of the individual data points suggests that the patients who had GE measured in the 24-48h after admission following elective surgery had markedly delayed emptying, possibly reflecting the effect of general anaesthesia. Thus, while the group in the current study cannot be considered as an ideal sample of mixed ICU patients, it is unclear how this may have affected the measured prevalence of delayed GE.

In summary, GE is delayed in approximately 50% of critically ill patients and markedly delayed in about 20%. Patients with trauma and sepsis appear to be most at risk.

Chapter 11

Gastric and small intestinal motility in critical illness

11.1 Introduction

A study was performed to examine the abnormalities in gastric and small intestinal motility underlying delays in GE and feed intolerance in the critically ill. As described in chapter 4, previous studies in the critically ill have documented absent fasting antral activity fronts (Bosscha et al., 1998; Dive et al., 1994b), and reduced postprandial antral activity (Bosscha et al., 1998), with more frequent duodenal activity fronts (Bosscha et al., 1998; Dive et al., 2000), and relatively normal numbers of duodenal pressure waves (Bosscha et al., 1998; Dive et al., 1994b). Fasting motility frequently persists in the duodenum during feeding (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Moore et al., 2001; Toumadre et al., 2001). Furthermore, although the duration of the duodenal migrating motor complex appears to be relatively normal, the relative contribution of the quiescent period (phase 1) to the total cycle length is increased and the contribution of phase 2 decreased (Dive et al., 1994b; Miedema et al., 2002). Abnormally propagated (retrograde or stationary) activity fronts in the duodenum also occur (Dive et al., 1994b); (Dive et al., 2000; Miedema et al., 2002; Toumadre et al., 2001).

The cause(s) and implications of these abnormalities on GE and feed tolerance are uncertain. Bosscha *et al* demonstrated that gastric residual volumes were negatively correlated ($r^2=0.44$; $P < .01$) with antral motor activity (Bosscha et al., 1998) but more quantitative relationships between GE, measured more rigorously, and upper gastrointestinal motility have not been investigated. To date, no studies have evaluated pyloric motility in the critically ill. Importantly, the potential role of enterogastric feedback in the pathogenesis of delayed GE has not been examined in this group.

The studies described in this chapter were designed to examine the effect of critical illness on antral and duodenal motility and pyloric pressures, during fasting, during GE of nutrient and during intraduodenal infusion of nutrient and to investigate the relationship between GE and abnormalities in motility.

11.2 Materials and methods

Subjects

Fifteen mechanically ventilated patients suitable for, or receiving nasogastric feeding were enrolled in the study.

Patients were excluded from participation if they had any of the following:

1. Cervical spine injury,
2. Increased intracranial pressure,
3. Compromised coronary perfusion,
4. Contraindication to the passage of an enteral tube,
5. Requirement for opiate analgesia,
6. Contraindication to the use of propofol.

Data were compared to 10 healthy volunteers.

In the patients, opiate administration was ceased on the day prior to the study and sedation was provided by a propofol infusion. Recordings of antro-pyloro-duodenal (APD) pressures were performed during fasting (6h), small intestinal infusion of enteral feed (Ensure™; Abbott Australasia Pty. Ltd., Botany, NSW; 1 kcal/ml; 37.2 g/l fat (corn oil); 37.2 g/l protein (sodium and calcium caseinates); 145 g/l carbohydrate (corn syrup/sucrose); 50ml/h; 6h) and following a gastric bolus of 100ml enteral feed (4h). The 3 study periods were randomised and allocated by sealed envelope. In the critically ill the study periods were consecutive, with a 4h fast between each study period, while the volunteers were studied on 3 separate days. All subjects were studied supine at 30° head elevation.

Measurements

The methods of measurement are described in chapter 8. Antro-pyloro-duodenal motility was measured by manometry (chapter 8). Gastric emptying was measured by the ¹³C octanoic acid breath test technique (chapter 8). The organisation of the wave sequences was only examined for the first 2 h of the study periods.

Statistical Analysis

As the antral wave frequency data were not normally distributed, the data were log transformed for statistical analysis and are presented as medians and ranges. Analysis of wave frequency was by mixed model ANOVA to allow for missing data. Pearson correlation coefficient was used to examine the relationship between GEC and isolated pyloric pressure waves (IPPWs), antral waves and pyloric tone. For the propagated pressure wave outcomes, healthy subjects and patients were compared using linear regression adjusting for clustering of patients. When many of the values were zero, the outcomes were assessed as binary, and the binomial generalised estimating equation was used, again to allow for clustering of subjects.

11.3 Results

Demographic characteristics of the patient cohort are shown in Table 11.1 and 11.2. The healthy subjects were younger than the patients (21 years (19-40); P<0.001). The median rate of

feed prior to the study was 63 ml/h (range 0-80 ml/h). Eight of the fifteen patients were intolerant of feeds (GRV>250ml- see chapter 6) at some time in the preceding 24 h. No patient had undergone abdominal surgery, or had known diabetes mellitus. Ten of the 15 patients had received opiates within the 48 hr period (mean 20.5h) prior to commencing the study. The patients were studied after fasting a mean of 8 h (\pm 3). One patient had not commenced feeding prior to the study. The study was well tolerated by both patients and volunteers. One patient experienced minor bleeding as a result of a pharyngeal abrasion. The sleeve was positioned correctly 98% of the time in healthy subjects and 87% of the time in the patients. In three patients, data were not available for one of the study periods as a result of tube malposition. An example of the motor patterns recorded is demonstrated in Figure 11.1.

11.3.1 Burst activity

In the healthy subjects all burst activity fulfilled the criteria for phase 3. In patients, 38% of episodes of burst activity were “atypical”, usually because they were not followed by quiescence. The results are shown in Table 11.3. The periodicity of duodenal burst activity during fasting tended to be less in the patients than in the healthy volunteers (68 (\pm 20) vs. 122 (\pm 21) minutes; $P=0.08$). The proportion of time spent in quiescence, irregular activity and burst activity is shown in Table 11.4.

11.3.2 Antral and pyloric wave frequency

In patients, during small intestinal nutrient infusion, antral wave frequency was decreased when compared to both fasting and healthy subjects (Table 11.3) in whom antral wave frequency increased over time ($P<0.05$ after 120 minutes; Figure 11.2). During small intestinal nutrient infusion the number of IPPWs was higher in patients when compared to both fasting and healthy subjects (Table 11.3; Figure 11.2). Small intestinal nutrient infusion stimulated pyloric tone in patients, but not in healthy subjects (Table 11.3; Figure 11.2).

11.3.3 Gastric emptying

Breath samples were unsuitable for analysis in one subject in the healthy group. Gastric emptying was slower in the patients (Table 11.3) and seven patients had a GEC that was outside (*i.e.* slower than) the normal range (see chapter 8). None of the healthy subjects had delayed GE. There was an inverse relationship between the GEC and IPPW frequency in the patients ($r=-0.56$, $P=0.03$) but not in healthy subjects ($r=-0.33$, $P=0.38$). The relationship between GEC and pyloric tone was not significant in either group (patients; $r=-0.18$, $P=0.52$, healthy subjects; $r=-0.50$, $P=0.17$); this was also the case for the relationship between GEC and antral wave frequency (patients; $r=0.37$, $P=0.17$; healthy subjects; $r=0.01$, $P=0.97$). In the patients there was no difference in the GEC in those who were receiving catecholamines from the remainder (data not shown). There was no significant relationship between blood glucose and GEC or pyloric activity (data not shown).

11.3.4 The organisation of AD motility following the intragastric nutrient bolus (Table 11.5)

In critically ill patients, following the gastric bolus of nutrient, there were fewer antegrade, more retrograde, and more mixed waves confined to the duodenum ($P<0.01$), and less antegrade and more retrograde waves involving both the antrum and duodenum ($P<0.0001$), compared to healthy subjects. In the patients, propagated duodenal and AD waves were shorter in length ($P<0.005$ for both). An example of the motor patterns demonstrating the coordination

of activity is shown in figure 11.3.

11.3.5 Relationship between GE and the organisation of AD motility

(i) Organisation of AD waves

In control subjects, there was no relationship between GE and propagated waves. In the patients, there was no correlation between gastric emptying (GEC) and propagated waves confined to the *antrum*. However, there was a relationship between GE and *duodenal* propagated waves. There was an inverse correlation between the GEC and the number of retrograde duodenal waves ($r = -0.65$, $P = 0.01$). In contrast, there was a positive correlation between GEC and the percentage of duodenal waves that propagated antegrade ($r = 0.57$, $P = 0.034$) and their length of migration ($r = 0.70$, $P = 0.005$). There was also a relationship between the GEC and the length of antegrade AD waves ($r = 0.78$, $P = 0.12$).

(ii) Propagating phase 3 waves after intragastric nutrient bolus

In 6 of the 15 patients, phase 3 activity occurred during the 2 hour period after the gastric bolus (table 11.6). In these patients, GE was slower than in those without phase 3 activity (GEC: 2.59 (0.26) vs. 3.44 (0.12); $P = 0.02$). There were 551 propagating phase 3 waves in these 6 patients and 93% were confined to the duodenum.

There was an inverse relationship between the GEC and the total number of propagating phase 3 waves ($r = -0.58$, $P = 0.03$), and the proportion that were retrograde ($r = -0.93$, $P = 0.007$). There was a strong positive correlation between the GEC and the percentage of propagating phase 3 waves that were antegrade ($r = 0.92$, $P = 0.01$). Phase 3 activity occurred in only 2 healthy subjects after the gastric nutrient bolus, and did not involve the antrum. In healthy subjects, there was no significant relationship between the GEC and number of waves involved in phase 3 activity.

When propagating phase 3 waves were excluded, there was no correlation between the GEC and duodenal waves in either the healthy or critically ill subjects.

11.3.6 Effect of duodenal nutrient infusion compared to fasting (Table 11.7 & 11.8) on the organisation of AD motility

In the healthy subjects, duodenal nutrient: (i) caused a reduction in the number of *propagated* antral waves ($P < 0.0001$), (ii) a reduction in the length of propagated antral waves ($P = 0.0002$), (iii) had no effect on propagated duodenal waves, and (iv) reduced the number of AD propagated waves ($P = 0.04$). In critically ill patients, duodenal nutrient: (i) reduced the number of *propagated* antral waves ($P = 0.02$), effects that were comparable to those seen in the healthy subjects. However, in contrast to the healthy subjects, duodenal nutrient stimulation in patients also (ii) resulted in longer ($P = 0.009$) and (iii) more mixed ($P < 0.001$) duodenal propagated waves, (iv) reduced the percentage of AD waves that were antegrade ($P = 0.02$) and (v) increased the percentage of AD waves that were mixed ($P = 0.03$).

During the first 120 min after commencing nutrient administration burst activity was reduced in healthy subjects (% of propagated waves involved in burst activity; fasting vs. gastric bolus, $P = 0.011$; fasting vs. duodenal nutrient infusion, $P = 0.06$) while it increased in critically ill patients ($P = 0.02$).

Patients	Age (y)	Sex	Fast (h)	Days in ICU	APACHE II	Outcome	Glucose	GE C	Dialysis	Insulin	Propofol
1	64	m	11	4	16	died	4.5	3.32	n	y	y
2	57	m	6	4	26	alive	11	3.48	n	n	n
3	46	m	5	10	17	died	9.1	2.9	y	y	y
4	58	f	13	11	21	alive	7.7	2.64	n	y	y
5	74	f	10	5	12	alive	8	3.94	n	y	y
6	49	m	11	4	12	alive	6.1	1.8	n	y	y
7	70	m	7	3	12	died	5	2.34	n	y	y
8	72	m	7	11	14	died	5	3.28	y	y	y
9	46	m	8	7	10	alive	5.7	3.29	n	y	y
10	38	m	7	102	13	alive	7.2	3.48	n	y	n
11	19	m	6	7	17	alive	5.8	3.31	n	n	n
12	55	m	168	7	14	alive	7.7	3.74	n	n	y
13	74	m	5	8	17	alive	7.6	2.56	y	y	y
14	31	f	6	8	20	alive	6.5	1.7	n	y	n
15	38	f	5	4	15	alive	6.7	3.01	n	y	y
median	55	4f	7	7	15	4 died	6.7	2.99	3	12	11
range	19_74		5_168	4_102	10_26		4.5_11	1.7_ 3.94			

Table 11.1 Characteristics of the critically ill patients. “Fast” refers to the period of time that the patient fasted prior to the study. “Days in ICU” are the days prior to the performance of the study. APACHE II score is the Acute Physiology and Chronic Health Evaluation Score which gives a measure of sickness severity. This was determined on the day of study. (Median admission APACHE II score was 20.) “Outcome” refers to hospital outcome. “Glucose” refers to baseline blood glucose concentration (mmol/l). GEC is the gastric emptying coefficient. The use of dialysis, intravenous insulin infusion, propofol infusion and inotropes (adrenaline and noradrenaline infusion only) are indicated. Data are median and range or number.

Patients	Diagnosis
1	brain tumour
2	sepsis
3	sepsis
4	respiratory failure/ asthma
5	respiratory failure/ aspiration
6	chest trauma
7	respiratory failure
8	ruptured thoracic aortic aneurysm
9	respiratory failure
10	pancreatitis
11	head injury
12	ruptured abdominal aortic aneurysm
13	respiratory failure
14	sepsis
15	trauma/ paraplegia

Table 11.2 Primary diagnosis of patients resulting in ICU admission

EFFECT OF DUODENAL NUTRIENT ON ANTRAL, PYLORIC AND DUODENAL WAVE FREQUENCY
IN CRITICALLY ILL PATIENTS

FIGURE 2

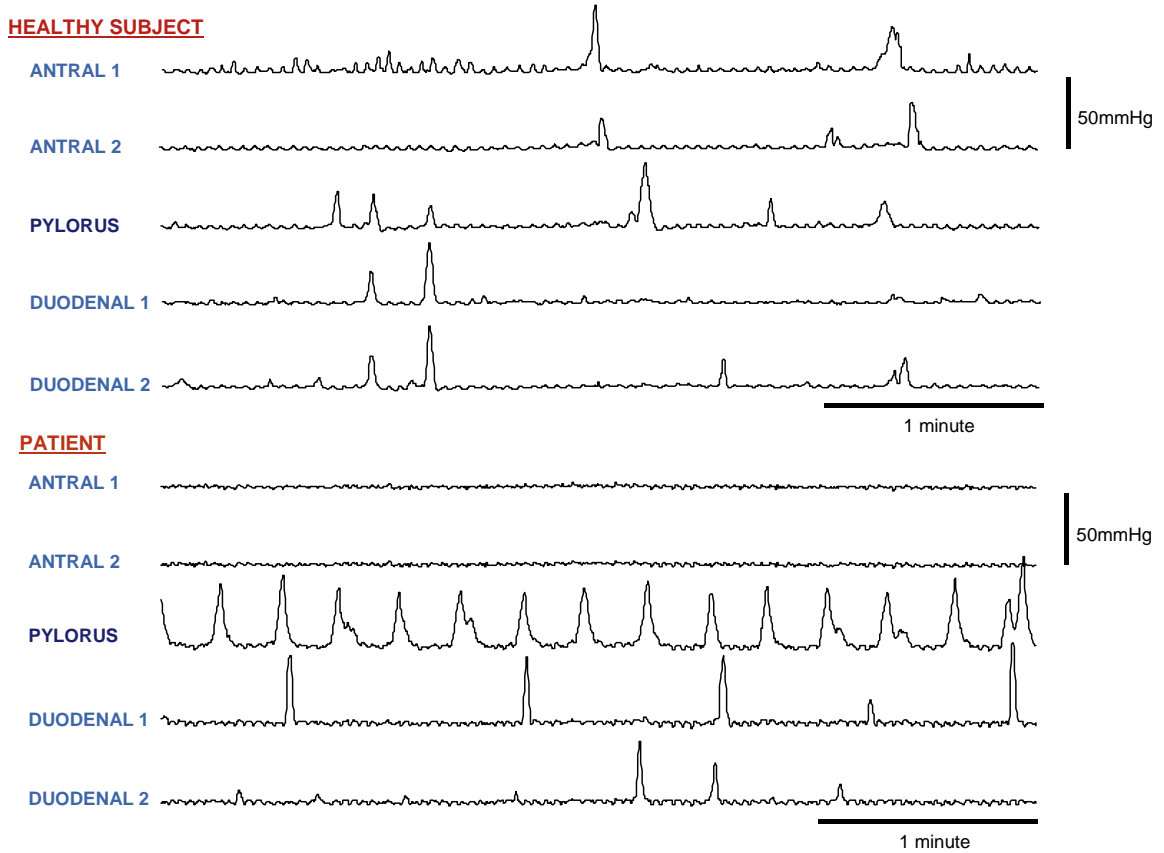


Figure 11.1 A 5 minute recording of pressure waves in two antral, one pyloric and two duodenal channels in a healthy volunteer and a patient during small intestinal infusion of nutrient. Absence of antral activity and frequent isolated pyloric pressure waves are evident in the patient.

Mean (SEM) except when stated	Fasting		ID nutrient infusion		Gastric nutrient bolus	
	Healthy	ICU	Healthy	ICU	Healthy	ICU
Antral waves/min Median (range)	0.22 (0-2.34)	0.14 (0-2.2)	0.33 (0-2.57)	0.03 [#] (0-2.47)	0.42 (0-2.67)	0.06 [†] (0-3.1)
IPPWs / min	0.23(0.14)	0.49(0.13)	0.29(0.15)	0.98(0.13) [*] #	0.22(0.15)	0.48(0.13)
Pyloric tone (mmHg)	0.30 (1.24)	-0.06 (1.05)	-0.44 (1.25)	3.12 (1.06)	1.04 (1.29)	-0.21 (1.06)
Duodenal waves / min	1.5(0.36)	1.5(0.28)	1.7(0.32)	1.9(0.27)	1.7(0.32)	2.2(0.29)
Antral phase 3 /hr	1.9(0.17)	0.14(0.15) [†]	0.3(0.17) [#]	0.06(0.14)		
Duodenal phase 3/hr	2.9(1.16)	4.33(0.96)	1(1.16)	3.33(0.95)		
GEC					3.47(0.1) [†]	2.99(0.2)

Table 11.3 APD pressures over total study period and GE during fasting, duodenal infusion of nutrient and after a gastric nutrient bolus in critically ill patients and healthy subjects. Data are mean \pm SEM or otherwise stated. ID: Intra-duodenal. ^{} $P < 0.05$ Healthy vs. ICU; [#] $P < 0.05$ fasting vs. duodenal nutrient infusion.*

Antral	Fasting			Duodenal nutrient infusion		
	Quiescence	Irregular	Burst	Quiescence	Irregular	Burst
Healthy	24(26)	74(28)	3(2)	0(5)	100(7)	0(1)
Patients	0(8)	100(9)	0(0.3)	0(1)	100(1)	0(0)
P value	0.001	0.001	<0.001	ns	ns	ns

Duodenal	Fasting			Duodenal nutrient infusion		
	Quiescence	Irregular	Burst	Quiescence	Irregular	Burst
Healthy	14(19)	82(21)	5(4)	0.5(8)	99(13)	0.5(4.5)
Patients	11(28)	72(42)	4(14)	6(29)	81(40)	4(2)
P value	ns	ns	ns	ns	0.06	0.07

Table 11.4 Percentage of time in phases of MMC (median (IQR)). Definitions are shown in text. Mann Whitney U test for analysis. Administration of duodenal nutrient to healthy subjects caused less burst activity and quiescence compared to fasting in both the antrum and duodenum ($P < 0.01$).

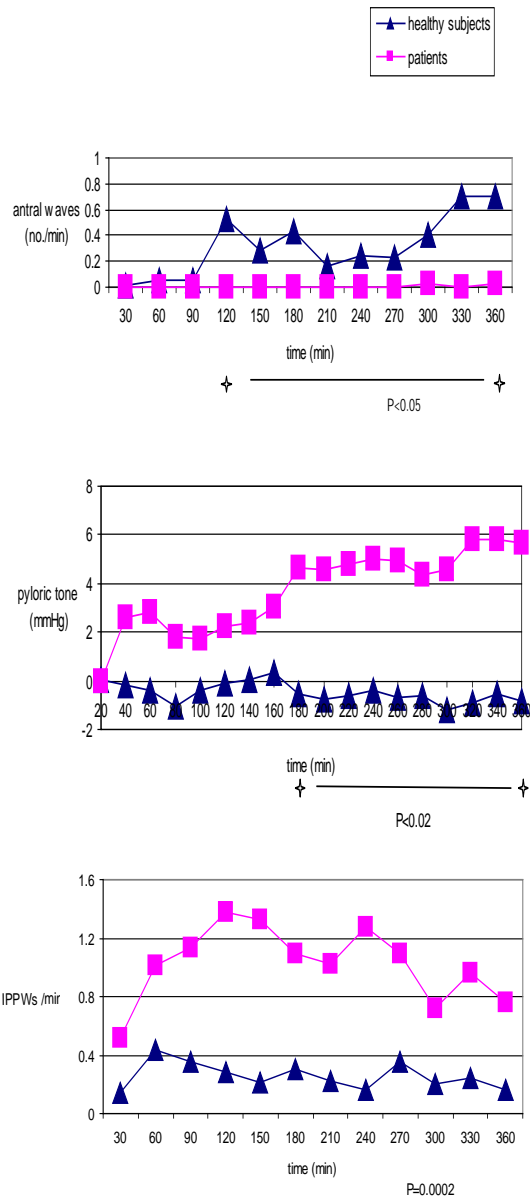
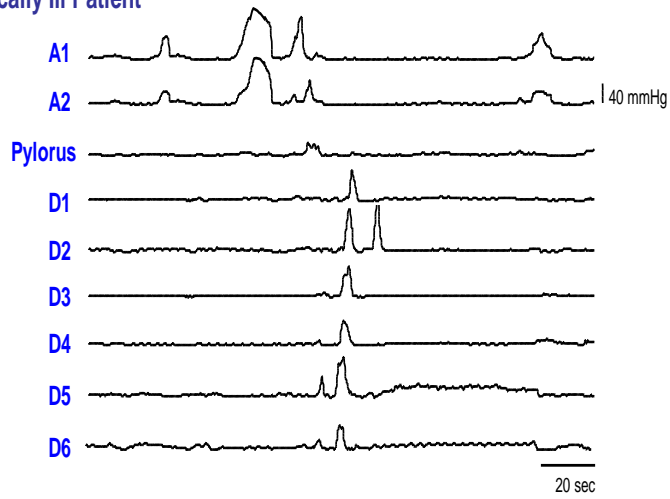


Figure 11.2 Antral wave frequency, pyloric tone and IPPW frequency over time during duodenal infusion of nutrient in patients and healthy subjects.

Critically Ill Patient



Healthy Volunteer

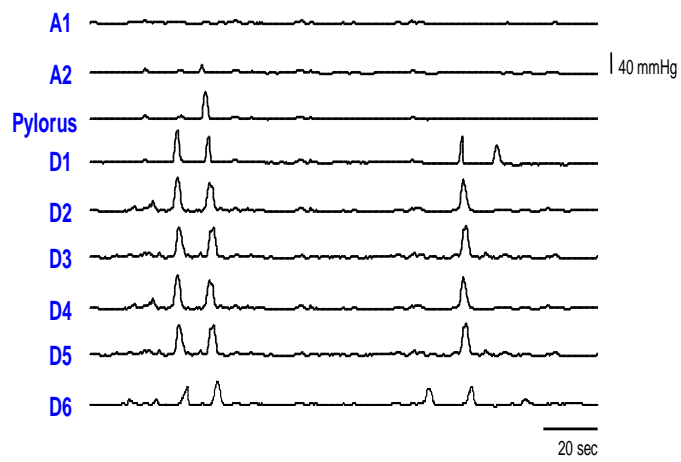


Figure 11.3. Manometric tracing demonstrating retrograde propagation of duodenal pressure wave activity in a critically ill patient.

	Waves confined to antrum		Waves confined to duodenum		Waves propagating from antrum-duodenum	
	Healthy	Patients	Healthy	Patients	Healthy	Patients
No. propagated waves / 2h Median (range)	9.0 (0-50)	7.0 (0-59)	78.0 (49-142)	66.0 (20-367)	7.0 (2-37)	2.0 (0-23)
Propagation length (cm)	3.8 ± 0.2	3.8 ± 0.2	6.0 ± 0.4	4.7 ± 0.3 [*]	10.9 ± 0.9	7.9 ± 0.6 [*]
Antegrade propagation (%)	95 ± 2	97 ± 2	83 ± 4	44 ± 6 [*]	83 ± 7	16 ± 7 [*]
Retrograde propagation (%)	4 ± 1	2 ± 2	12 ± 3	46 ± 6 [*]	4 ± 2	38 ± 11 [*]
Mixed propagation (%)	0 ± 0	0 ± 0	7 ± 2	17 ± 3 [*]	13 ± 6	45 ± 11

*Table 11.5 Propagated waves occurring in the first 2h after gastric bolus of nutrient (including phase 3 activity). Data are mean ± SEM or otherwise stated. * P<0.05 Healthy vs. patient*

	Fasting		ID nutrient infusion		Gastric nutrient bolus	
	Healthy	Patients	Healthy	Patients	Healthy	Patients
No. subjects with burst activity	7/10	4/13	2/10	7/14	3/10	6/15

Table 11.6 Number of subjects with burst activity in the first 2h of each study period. ID: Intra-duodenal

	Waves confined to antrum		Waves confined to duodenum		Waves propagating from antrum-duodenum	
	Healthy	Patients	Healthy	Patients	Healthy	Patients
No. propagated waves / 2h Median (range)	14.0 (6-39)	7.0 [*] (0-108)	97.0 (12-225)	79.0 (0-265)	14.0 (1-48)	5.0 [*] (0-19)
Propagation length (cm)	4.1 ± 0.2	3.8 ± 0.2	6.4 ± 0.5	4.6 ± 0.2 [*]	12.3 ± 0.8	8.5 ± 1.3 [*]
Antegrade propagation (%)	89 ± 4	93 ± 2	72 ± 6	41 ± 6 [*]	77 ± 8	58 ± 10
Retrograde propagation (%)	10 ± 3	6 ± 3	22 ± 5	53 ± 6 [*]	4 ± 3	28 ± 9
Mixed propagation (%)	1 ± 1	1 ± 1	5 ± 2	7 ± 2	15 ± 7	13 ± 8

*Table 11.7 Propagated waves during fasting (including phase 3 activity)
Data are mean ± SEM or otherwise stated. * P<0.05 Healthy vs. patient.*

	Waves confined to antrum		Waves confined to duodenum		Waves propagating from antrum-duodenum	
	Healthy	Patients	Healthy	Patients	Healthy	Patients
No. propagated waves / 2h Median (range)	3.0 # (0-40)	1.0 # (0-9)	67.0 (37-105)	80.0 (21-269)	3.0 # (0-18)	4.0 (0-11)
Propagation length (cm)	3.4 ± 0.2 #	4.0 ± 0.3	5.9 ± 0.4	5.4 ± 0.3 #	10.3 ± 1.0	8.0 ± 0.7
Antegrade propagation (%)	89 ± 5	93 ± 4	82 ± 3	41 ± 6 *	66 ± 12	26 ± 10 *#
Retrograde propagation (%)	10 ± 4	7 ± 4	12 ± 3	42 ± 6 *	7 ± 4	19 ± 9 *
Mixed propagation (%)	1 ± 1	0 ± 0	5 ± 1	12 ± 3 *#	27 ± 11	55 ± 11 #

*Table 11.8. Propagated wave sequences during duodenal nutrient infusion (including phase 3 activity) Data are mean ± SEM or otherwise stated. * P<0.05 Healthy vs. patient; # P<0.05 Duodenal nutrient infusion vs. fasting*

11.4 Discussion

This study represents the first evaluation of pyloric motility in critical illness. It is also the first to examine the effects of small intestinal nutrients on APD motility, as well as the relationship between GE and motility, in the critically ill. The major novel observation is that duodenal nutrient infusion, at a rate of energy delivery which approximates 50% of that which occurs during normal GE, (Brener et al., 1983) suppresses antral pressure waves and stimulates both tonic and phasic pyloric pressures in critically ill, but not healthy, subjects. This study also confirms that GE of a liquid nutrient is delayed in about 50% of critically ill patients. Several abnormalities were found to be associated with delayed GE. An inverse relationship between GE and phasic pyloric activity was demonstrated. The persistence of phase 3 activity in the first 2h after nutrient administration, and the presence of retrograde phase 3 activity, were also associated with delayed GE.

This study provides several important insights into the pathophysiology underlying delayed GE in the critically ill. As described in chapter 3, GE is controlled by feedback from small intestinal nutrient receptors acting via neurohumoral pathways, limiting GE to an overall rate of 2-3 kcal/min (Brener et al., 1983). The delivery of glucose at or above this rate into the small intestine suppresses gastric contractile activity and stimulates pyloric activity to retard transpyloric flow (Heddle et al., 1988c). This study establishes that nutrient delivery at a rate of only 1 kcal/min triggers mechanisms which retard pyloric flow in the critically ill, but not in healthy subjects.

Small intestinal feedback on APD motility and GE may be dependent on the type of nutrient administered (Lin, 1994). In a study reported by Heddle et al, 1 kcal/min infusion of fat in the form of Intralipid 10% (10g soybean oil/100ml) reduced antral, and increased pyloric activity in healthy subjects (Heddle et al., 1988a; Heddle et al., 1988c; Lin, 1994). In the healthy subjects in this study, 1 kcal/min of Ensure, which is made up of 3.7% fat (3.7g corn oil/100ml), had no effect on antral or pyloric activity. The different responses observed in these studies are likely to be attributable to the differences in the composition of the nutrient. It would be of interest to evaluate the response of GE in the critically ill to a nutrient with a lower fat content as this may potentially result in less gastric inhibition and, thereby, increase the success of feeding.

An inverse association between pyloric activity and GE, in keeping with our understanding of the motor control of GE (Heddle et al., 1989), was demonstrated. The motility of the distal stomach and proximal duodenum in critical illness was also characterised. There was no significant relationship between antral activity and GE. This may be because the study was underpowered to demonstrate a relationship. However, the results suggest that pyloric contractile activity is more important than antral contractions, or pyloric tone as a determinant of GE in this population. Proximal stomach function, and its contribution to the delays in GE, remain to be examined. Our observations introduce a novel explanation for the delays in GE seen in the critically ill, which is that GE in these patients is hypersensitive to feedback from small intestinal nutrient. Thus, the presence of small amounts of liquid nutrient in the duodenum causes marked pyloric contractions which retard further emptying.

This is the first study to evaluate the organisation of antro-duodenal (AD) pressure waves and their relationship to GE in the critically ill. In critically ill patients, there were less antegrade, and more retrograde, propagated waves, with a shorter length of propagation, compared to healthy controls. Propagated waves were less likely to originate from the antrum. In healthy subjects, the infusion of 1 kcal/min of duodenal nutrient was associated with a reduction in

phase 3 activity and shorter propagated waves. In contrast, duodenal nutrient infusion in patients resulted in an increase in phase 3 activity, longer propagated duodenal waves and abnormal propagation, with more mixed, and less antegrade, AD waves. In addition, in the patients, increased antegrade activity was associated with more rapid, and retrograde activity with slower GE. Accordingly, this study demonstrates that the organisation of AD pressure waves is frequently abnormal in critically ill patients, and suggests that this is a major determinant of delayed GE.

While it is logical that GE would be facilitated by coordinated antegrade propagated waves in the stomach and duodenum and hindered by retrograde activity, there is relatively little information about the relationship between GE and the organisation of pressure waves in health or disease. Indeed, in the small number of healthy subjects in this study we were unable to demonstrate a significant relationship. However, possibly because of the greater proportion of waves that propagated in a retrograde direction in the critically ill patients, there was a clear relationship between GE and the direction and length of propagated waves in this group.

The observations relating to interdigestive motor activity complement those from previous studies (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Dive et al., 1994b; Toumadre et al., 2001) in that critically ill patients have less antral MMC activity with similar, or a tendency to more frequent but atypical, duodenal MMC activity and a lack of inhibition of fasting motility by nutrient. Manometric studies have rarely been performed in the critically ill population (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Dive et al., 1994b; Toumadre et al., 2001). Duodenal MMC intervals are highly variable in both health and critical illness but appear to be shorter in the latter (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Dive et al., 1994b; Toumadre et al., 2001). In the critically ill, the mean MMC duration during fasting has been reported to range between 32 to 91 minutes (Bosscha et al., 1998; Dive et al., 2000; Dive et al., 1994a; Dive et al., 1994b; Toumadre et al., 2001). It may be shortened by the use of opiates (Bosscha et al., 1998), or dopamine (Dive et al., 2000), and increases as patients recover (Bosscha et al., 1998). In this study, the duodenal MMC interval fell within this range and tended to be shorter than in the healthy subjects. In the critically ill, it has been reported that proportionally more time is spent in phase 1 (quiescence) and less in phase 2 (irregular activity) than in the healthy (Bosscha et al., 1998; Dive et al., 1994b; Toumadre et al., 2001). This latter observation was not evident in our study. This lack of concordance with previous data may reflect the effect of opiate administration in the earlier studies. Further studies are indicated to examine this issue in greater depth. In the critically ill, it has been reported that MMC activity is not suppressed by the introduction of nasogastric nutrition (Dive et al., 1994a; Toumadre et al., 2001). This is supported by our study, even though the nutrient dose was sufficient to reduce activity fronts in healthy subjects. It is unclear why a small dose of duodenal nutrient suppresses GE by reducing antral activity and increasing pyloric activity, but does not reduce fasting MMC activity, in this patient group. This may imply different mechanisms for the regulation of postprandial motility and GE.

While it has been reported that fasting motor patterns persist during feeding in the critically ill (Dive et al., 1994a; Toumadre et al., 2001), and that the propagation of these may be retrograde (Miedema et al., 2002), the significance of this has been unclear. This study has now demonstrated a strong inverse relationship between GE and phase 3 or burst activity in these patients, so that both an increased total number of propagated waves involved in phase 3 activity and the proportion of waves moving retrograde, were associated with slower GE; accordingly, it appears plausible that the persistent phase 3 activity observed during feeding in the critically ill has a negative impact on GE. While it has been reported that duodenal phase 3 activity is frequently retrograde in health, resulting in the movement of intestinal contents into

the stomach (Castedal et al., 2000b), Andrews et al (Andrews et al., 2002), showed that approximately 60% of duodenal pressure waves propagated in an antegrade direction during phase 3 activity. The current observations in the control subjects concur with the latter report, and contrast with the patients in whom only one-third of phase 3 waves were antegrade. Furthermore, there was no relationship between GE and pressure wave sequences that were *not* involved in phase 3 activity. Hence, both the occurrence and characteristics of phase 3 activity appear to have a strong influence on GE in the critically ill. There is little information regarding abnormalities in MMC activity in other disease states (Hveem et al., 1996; Peters et al., 2002).

Previous reports in the critically ill describe major abnormalities in motility in the distal stomach, and the pylorus and suggest that the frequency of duodenal motor activity is relatively normal (Dive et al., 1994a). The current study indicates that increased pyloric activity is associated with reduced GE in this group, and that while the absolute numbers of duodenal waves in the critically ill are comparable to healthy subjects, their organisation is not, and this is associated with delays in GE. This information provides a better understanding of the disordered antro-pyloro-duodenal motility which contributes to delays in GE. It is unclear from these data which aspect of disordered motility has the greater influence over GE. Increased pyloric activity and uncoordinated APD peristaltic activity may be additive but this is purely speculative. The relationship between wave propagation and GE appears stronger ($r=0.9$ vs. $r=-0.6$), but it is likely that a number of factors contribute to transpyloric flow and the determinants may vary in individual patients.

Other limitations of the study should be recognised. Antro-duodenal motility was determined in critically ill patients during fasting and after a gastric bolus of nutrient, which allowed the assessment of the motor responses to the usual route of nutrient administration in these patients. It also enabled GE to be measured concurrently. The AD response was also quantified during a low-dose duodenal nutrient infusion, which standardised the rate of nutrient delivery into the small intestine. For logistical reasons, the study periods were performed consecutively in the patients, in a randomised order, while in the healthy volunteers the studies were conducted on different days, approximately one week apart. Although unlikely, this time difference may have affected the study results.

In summary, this study has characterised the abnormalities in upper gastrointestinal motility associated with critical illness. Reduced antral and increased pyloric activity were demonstrated. Duodenal motility appeared to be quantitatively normal but coordination was abnormal, with a high rate of retrograde activity. Delayed GE in the critically ill was strongly associated with increased phasic pyloric activity and retrograde duodenal activity. Furthermore, there was hypersensitivity to small intestinal nutrient leading to the motility changes which resulted in reduced GE. This observation provides an important insight into the pathogenesis of delayed emptying in critical illness. The presence of small amounts of nutrient in the small intestine suppressed antral activity, and stimulated pyloric activity, but did not suppress fasting motor activity. The resulting persistent phase 3 activity was comprised of a high rate of abnormally propagated (retrograde) waves. These motor factors appeared to have a strong negative influence on GE.

Chapter 12

Glucose absorption and gastric emptying in critical illness

12.1 Introduction

Delayed gastric emptying occurs frequently in the critically ill and is associated with impaired tolerance to nasogastric feeding. By slowing the transfer of food from the stomach into the small intestine and, thereby, reducing or delaying exposure of small bowel mucosa to nutrient, gastric stasis has the potential to affect both the rate, and extent, of nutrient absorption adversely. Conversely, prolonged small intestinal transit will increase the exposure of the mucosa to nutrient and, potentially, improve absorption. Absorption may be compromised by factors other than motility/transit, including mucosal villous atrophy, mucosal oedema and reduced splanchnic perfusion. There is limited information about nutrient absorption in the critically ill (see chapter 4) and the relationship between gastric emptying and intestinal absorption has hitherto not been evaluated.

Postprandial blood glucose concentrations are affected by many factors, including gastric emptying and subsequent small intestinal glucose absorption. In health, the relationship between GE and blood glucose is complex. Acute hyperglycaemia, including elevations in blood glucose that are within the normal postprandial range, has been shown to slow GE (Fraser et al., 1991; Fraser et al., 1990; Hebbard et al., 1996; MacGregor et al., 1976; Oster-Jorgensen et al., 1990; Schvarcz et al., 1997), when compared to euglycaemia. However, a reduced rate of GE will also slow the rate of carbohydrate absorption (Daumerie and Henquin, 1982) and, thereby, attenuate the rise in blood glucose (Gonlachanvit et al., 2003; Horowitz et al., 2002). Thus, in health and in type 2 diabetics the rate of gastric emptying is both a determinant of, as well as determined by, the blood glucose level (Rayner et al., 2001). The relationship between blood glucose concentration and gastric emptying in the critically ill has not been evaluated. Hyperglycaemia due to insulin resistance and elevated glucagon concentrations is known to occur frequently, even when there is no history of diabetes (Dahn and Lange, 1982). This could contribute to the delayed GE observed in some patients with critical illness. Conversely delayed GE may limit the degree of hyperglycaemia in patients fed by the nasogastric route. There is evidence that maintenance of blood glucose concentrations in the euglycaemic range improves outcomes in ICU patients (van den Berghe et al., 2001). An improved understanding of factors influencing blood glucose is, therefore, important.

The evaluation of absorption of any substrate necessitates quantification of both the rate, and extent, of absorption. The rate of absorption is indicated by the time taken to reach maximum concentration in the blood. The maximum concentration achieved after a dose of substrate (e.g. 3-OMG) reflects both of these factors, whereas the area under the concentration curve reflects the extent of substrate absorbed over that time period.

The aim of this study was to quantify glucose absorption, and assess the relationships between gastric emptying with glucose absorption and with glycaemia in critically ill patients.

12.2 Materials and methods.

Subjects.

Twenty seven mechanically ventilated patients who were receiving, or eligible to receive, nasogastric feeding were enrolled in the study. This is the same patient cohort referred to in the studies described in chapters 9 and 10 (see 9.1.2 and table 9.1 for details). However, the 6 patients with pre-existing type 2 diabetes mellitus were excluded from this analysis leaving 19 subjects for analysis. A further 3 patients were receiving actrapid insulin and these were excluded from analysis of blood glucose data (n=16).

Data were compared to 19 healthy volunteers. This is not the same cohort as described in chapters 9 and 10. These 19 healthy subjects were recruited originally for gastric emptying measurements, but several subjects were found to have delayed GE (see below). The delay in gastric emptying in some subjects was attributed to anxiety and/or discomfort, particularly as many of them had not experienced placement of a nasogastric tube previously. Following this observation, healthy subjects who had been subjected to nasogastric intubation on at least one occasion in the past were recruited for prevalence studies (chapter 9.1.2). Hence, while the group was considered unsuitable for determining the prevalence of delayed gastric emptying, the data were used to quantify glucose absorption and determine the relationship between gastric emptying, glucose absorption and glycaemia in health and critical illness.

Protocol.

Following aspiration of the nasogastric tube, 100 ml of Ensure (standard liquid feed – 1kcal/ml) labelled with ^{99m}Tc sulphur colloid and 2g 3-O-methyl glucose was infused into the stomach over 5 minutes. The study was performed over the subsequent 4h in accordance with the methods set out in chapter 8. Gastric emptying was measured using scintigraphy (see section 8.3.1) and glucose absorption was measured using 3-OMG (see section 8.5). Blood glucose concentrations were also measured (see section 8.5).

The relationship between glucose absorption and GE was examined using the peak, and time to peak for both 3-OMG and glucose concentrations, and the area under the 3-OMG concentration curve to gastric emptying measurements. The relationship between baseline blood glucose concentrations and GE was also examined. Data are shown as means and standard deviations.

12.3 Results

Demographics of the patients are shown in Table 9.1 and other information are included in 9.1.3 and 10.3.3. The demographics of the healthy group were as follows; n=19; 12 female; age 24 (21-51); $P<0.001$. In 2 healthy subjects blood sampling was not possible for the full 4h, (60 and 150 min), as intravenous access was lost and further insertion of an intravenous cannula was declined. Blood glucose data were mislaid in 1 patient.

12.3.1 Glucose absorption

3-OMG concentrations over time in the 19 patients and 19 healthy subjects are shown in figure 12.1. There was a significant increase in 3-OMG concentration in both groups. The mean area under the 3-OMG concentration curve was markedly less in critically ill patients than healthy subjects (AUC_{240} : 26.2 ± 18.4 vs. 66.6 ± 16.8 ; $P<0.001$). The peak concentration of 3-OMG

was also less (0.17 ± 0.12 vs. 0.37 ± 0.098 mmol/l; $P < 0.001$) and the time to peak was longer (151 ± 84 vs. 89 ± 33 minutes; $P = 0.007$). In 6 patients the maximum 3-OMG concentration recorded was at 240 minutes (i.e. the end of the sampling period). 3-OMG concentration had not returned to baseline by the end of the 4h period (figure 12.1) in any subject.

12.3.2 Blood glucose concentrations (figure 12.2).

Nine patients with pre-existing diabetes mellitus and/or a requirement for insulin during the period of the study were not included in analyses involving blood glucose concentrations leaving data on 16 subjects for analysis. The baseline blood glucose concentrations were higher in the patients (8.0 ± 2.1 vs. 5.6 ± 0.23 mmol/l; $P < 0.001$) and peak levels following nutrient administration were also greater (10.0 ± 2.2 vs. 7.7 ± 0.2 mmol/l; $P < 0.001$) than in healthy subjects ($n = 19$). The time to peak blood glucose was longer in the patients (116 ± 90 vs. 39 ± 17 min; $P < 0.001$).

12.3.3 Gastric emptying.

The gastric emptying of the 2 groups is shown in figure 12.3. Gastric emptying was slower in the patients compared to the healthy subjects, but this difference was only significant at 180 and 240 min. Seventeen healthy subjects and 8 (42%) critically ill patients had $< 10\%$ meal retention at 240min (i.e. normal gastric emptying) (Tougas et al., 2000).

12.3.4 Relationships between plasma 3-OMG, blood glucose concentrations and gastric emptying.

Plasma 3-OMG and GE

In the patients, there was a close relationship between all parameters of 3-OMG absorption (AUC_{240} , peak concentration, time to peak) and gastric emptying (retention at 60 min - %) (figure 12.4). There was a negative correlation between the percentage meal retention (at all time-points) and 3-OMG absorption in critically ill patients (AUC ; $r = -0.77$ to -0.87 ; $P < 0.001$; peak concentrations; $r = -0.75$ - -0.81 ; $P \leq 0.001$). There was a strong positive relationship between GE and time to peak concentration and GE ($r = 0.89$ - 0.94 ; $P < 0.001$) In the subset of 9 patients with normal gastric emptying ($< 10\%$ retention at 240 min), 3-OMG absorption was still less than in the healthy subjects (figure 12.5) (AUC_{240} : 44.4 ± 4.6 vs. 65.9 ± 4.8 ; $P < 0.005$; maximum 3-OMG concentration 0.26 ± 0.11 vs. 0.37 ± 0.098 mmol/l; $P = 0.008$; no difference in the time to maximum concentration; 90 ± 51 vs. 89 ± 34 minutes; $P > 0.05$).

In the healthy subjects there was a relationship between time to peak 3-OMG concentrations and gastric emptying (scintigraphic $t_{1/2}$ $r = 0.58$; $P = 0.012$; retention at 60 min $r = 0.64$; $P = 0.004$; retention at 120 min $r = 0.75$; $P < 0.001$).

Blood glucose concentrations and GE

Baseline blood glucose concentrations were related to GE in the 16 patients who were not diabetic and not on insulin. Higher blood glucose concentrations at baseline were associated with a slower subsequent GE (retention at 60, 180 & 240 min - %) ($r = 0.51$ - 0.54 ; $P < 0.05$) (figure 12.6). No relationship was demonstrated between any of the parameters of GE and peak, time to peak and increment in blood glucose concentrations.

In the healthy subjects there was no relationship between blood glucose concentration at baseline and GE. However, there was a weak relationship between the change in blood glucose

and GE, such that the increment in blood glucose was smaller with slower GE (blood glucose vs. % retention at 60 min, $r = -0.45$; $P=0.04$). There was no relationship between time to peak blood glucose and GE.

Glucose absorption and plasma glucose concentrations

There was no relationship between baseline blood glucose concentrations and 3-OMG absorption in either the healthy subjects or the patients. However, in the patients there was a relationship between the increment in blood glucose concentration and 3-OMG concentrations (AUC_{240} $r=0.70$, $P=0.004$; peak 3-OMG $r=0.73$, $P=0.002$; time to peak 3-OMG $r=-0.62$; $P=0.01$) (Figure 12.7).

In the healthy subjects, there was a relationship between time to peak blood glucose and time to peak 3-OMG concentration and ($r=0.52$; $P=0.001$). There was no significant relationship demonstrated between any other parameters.

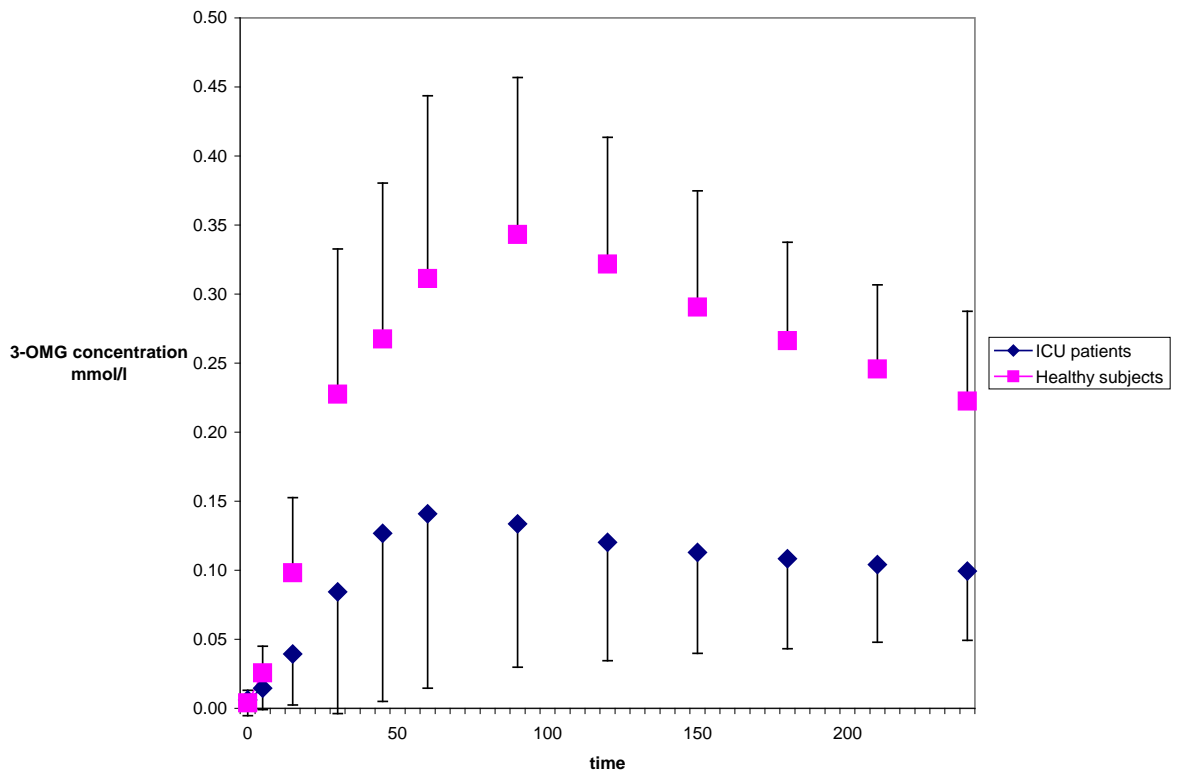


Figure 12.1 3-OMG concentrations over time in 19 ICU patients (who did not have pre-existing diabetes mellitus) and 19 healthy subjects. Glucose absorption was markedly reduced in critically ill patients compared to healthy subjects. (3-OMG AUC₂₄₀: 26.2 ± 18.4 vs. 66.6 ± 16.8; P<0.001; peak 3-OMG 0.17 ± 0.12 vs. 0.37 ± 0.098 mmol/l; P<0.001; time to peak 151 ± 84 vs. 89 ± 33 minutes; P=0.007).

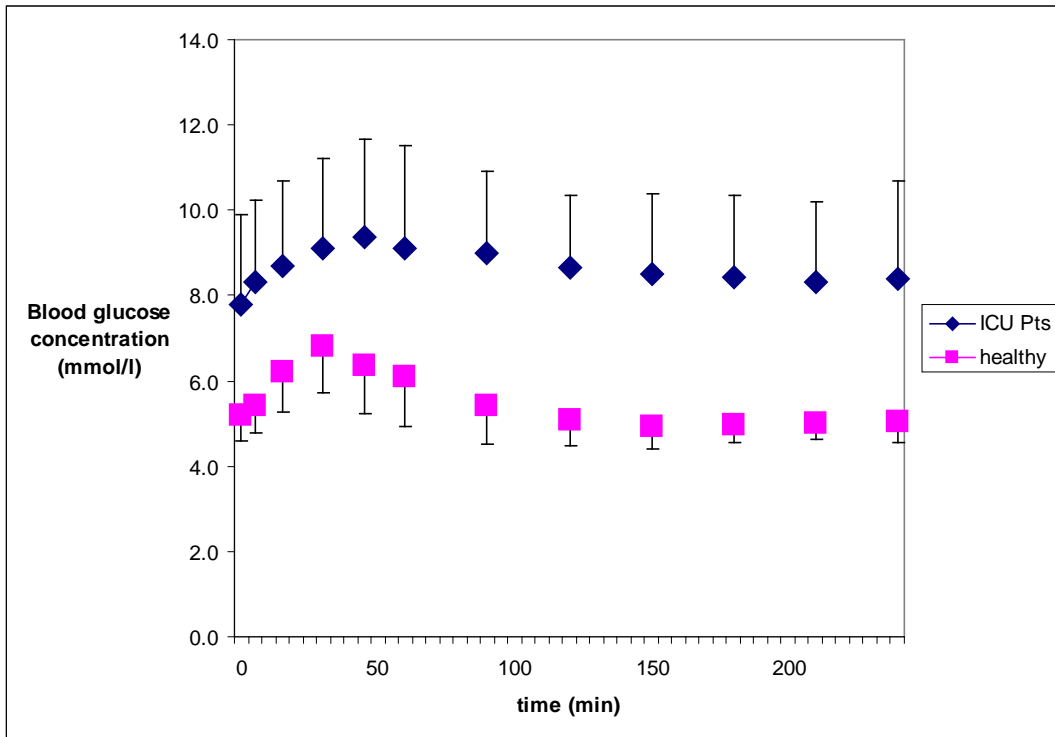


Figure 12.2 Blood glucose concentrations over time in patients (n=16 - not previously diabetic or receiving insulin) and healthy subjects (n=19). Blood glucose concentrations were elevated in the ICU patients ($P < 0.001$ for each time point) with a delayed peak (time to peak 37 ± 18 min in healthy vs. 105 ± 87 in patients; $P = 0.01$).

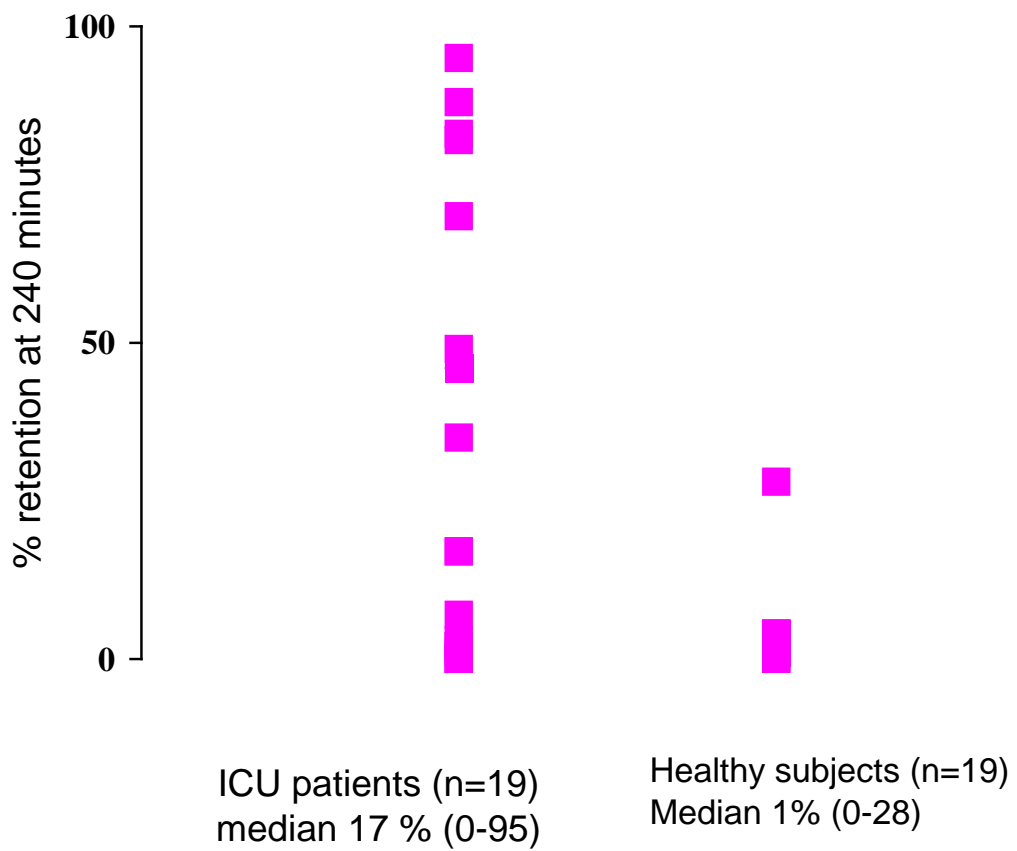


Figure 12.3 Gastric emptying was delayed in the patients at 240 minutes after intragastric nutrient bolus; $P=0.03$.

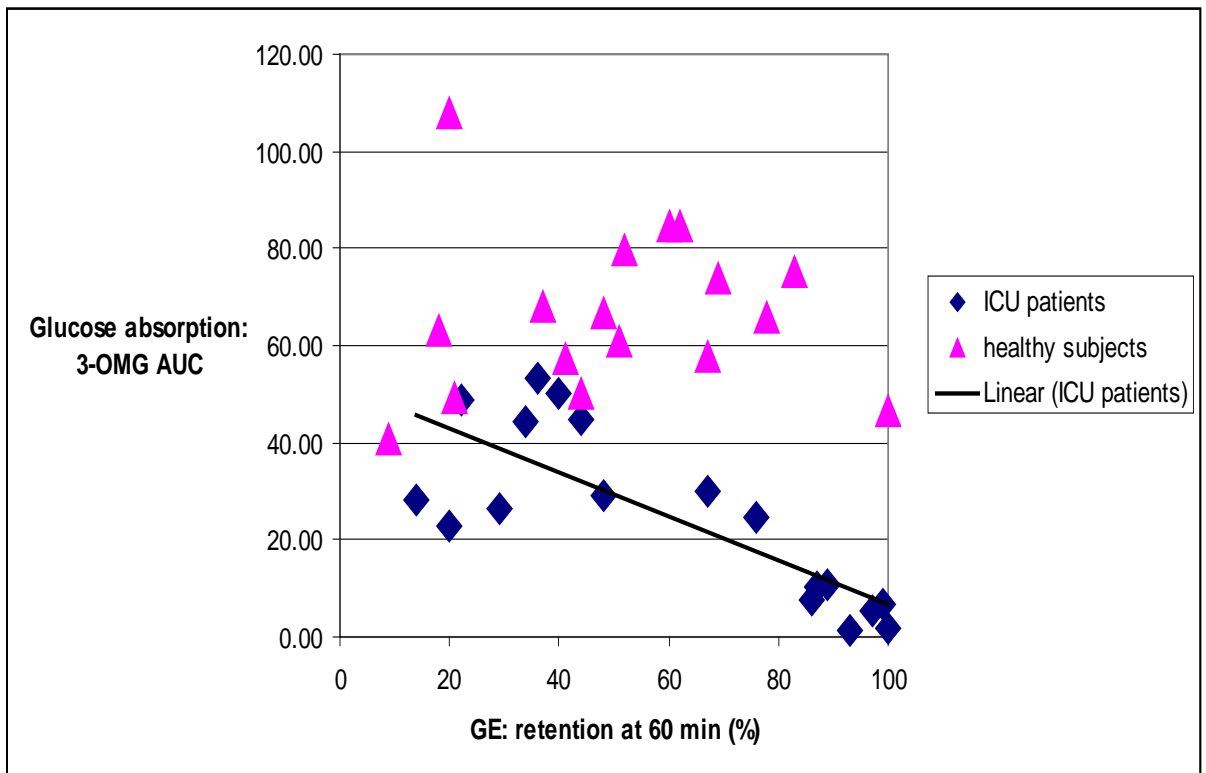


Figure 12.4 Relationship between gastric emptying (retention of marker at 60 min) and glucose absorption (AUC_{240} 3-OMG concentrations) in 19 critically ill subjects (excluding subjects with pre-existing diabetes) and 19 healthy subjects. In the ICU subjects there was a strong relationship between GE and glucose absorption ($r=-0.8$; $P<0.001$) which was not present in the healthy subjects. Of importance is that, in the ICU patients, even when GE was normal, glucose absorption was still reduced.

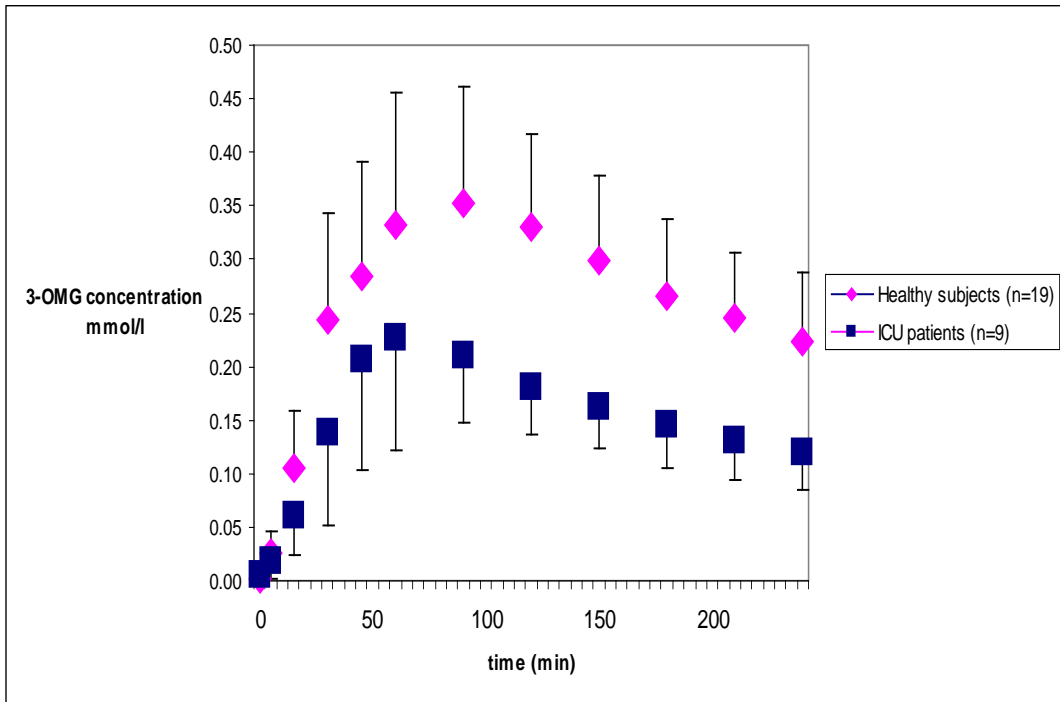


Figure 12.5 Glucose absorption was also markedly reduced in the critically ill subjects (excluding diabetics) who had normal gastric emptying (retention at 240 min <10% - n=9).

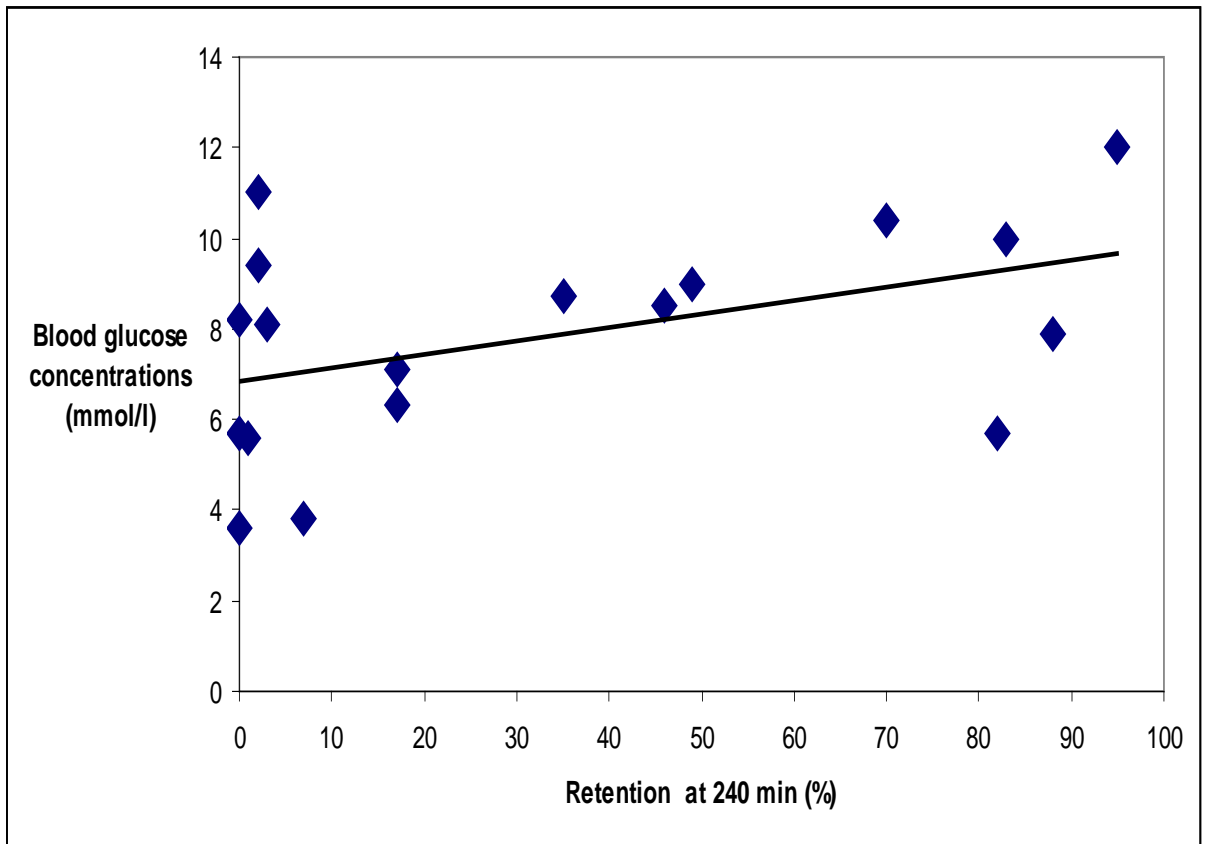


Figure 12.6 Relationship between baseline blood glucose concentrations and GE in critically ill patients. Elevated baseline blood glucose concentrations are associated with subsequent slowing of GE ($r=0.54$; $P=0.037$).

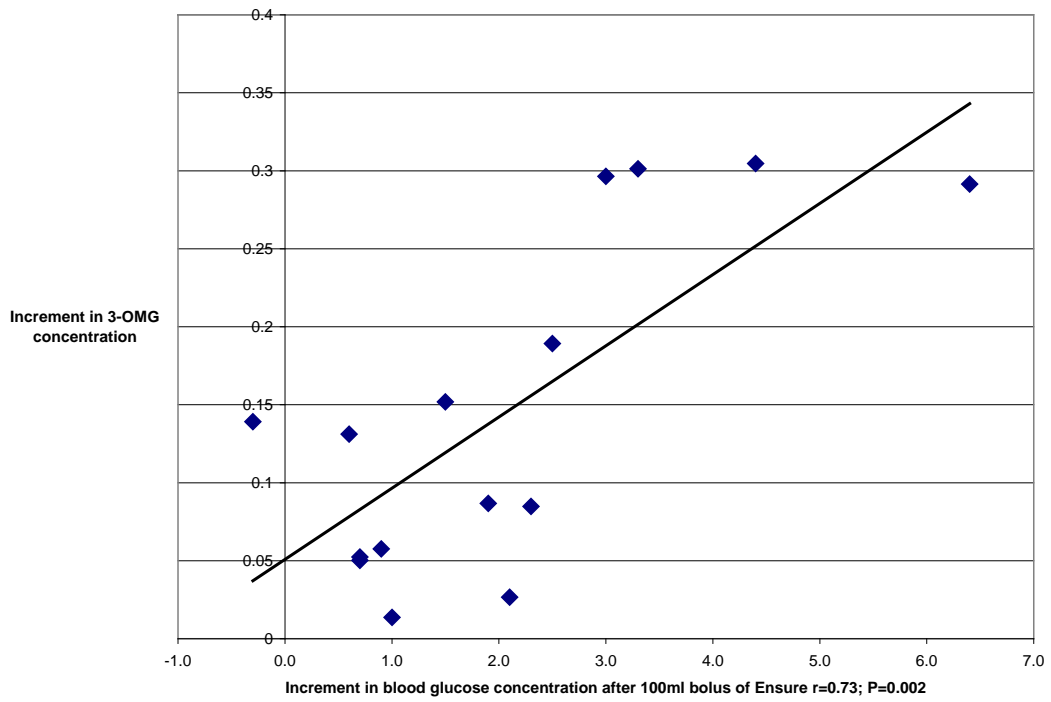


Figure 12.7 Relationship between the increment in blood glucose after a bolus of Ensure and the increment in 3-OMG concentrations suggesting that blood glucose concentrations relate at least in part to glucose absorption in the critically ill.

13.4 Discussion.

This study indicates that glucose absorption is markedly reduced in the critically ill as has been suggested previously (Chiolo et al., 2003; Hadfield et al., 1995; Singh et al., 1994) and establishes that there is a close relationship between glucose absorption and gastric emptying in the critically ill such that slow gastric emptying is associated with a reduced rate and extent of absorption. Furthermore, in the subset of critically ill patients with normal gastric emptying, the *rate* of glucose absorption appears to be normal, but the *extent* of glucose absorption is still reduced, suggesting that there are additional causes for impaired absorption in this setting. A relationship was also demonstrated between the increment in plasma glucose after the nutrient bolus and glucose absorption (figure 12.6).

These data are consistent with results from previous studies. Singh et al demonstrated that plasma xylose levels were markedly reduced 1 hour after administration in patients with severe sepsis and trauma, suggesting that xylose absorption is either markedly delayed or reduced (Singh et al., 1994). Similarly, measuring a single plasma level at 120min, Chiolo et al demonstrated reduced or delayed absorption of xylose in a mixed group of intensive care patients (Chiolo et al., 2003). These studies do not differentiate between rate and total absorption. The current study demonstrated that both the rate and extent (over 4h) of glucose absorption is reduced in critical illness. Rate is indicated by the time to achieve maximal concentration of 3-OMG. Extent is related to the AUC, but can only be ascertained for the time period of the measurements, in this case 4h. It is possible that, had the blood sampling continued, complete absorption may, eventually, have occurred. However, this is unlikely. The maximal concentration was also markedly reduced and this reflects both rate and extent of absorption. Hadfield et al assessed total 3-OMG absorption in a critically ill cohort by measuring urinary levels and found it to be reduced to approximately 20% of normal (Hadfield et al., 1995). It is thus likely that both rate and total glucose absorption are affected. However, when the rate of GE is normal the rate of glucose absorption also appears to be normal.

The results of this study have important implications for the clinical management of critically ill patients. Firstly, the close relationship between gastric emptying and glucose absorption suggests that, if gastric emptying is accelerated by the use of prokinetics, or if the stomach is bypassed and nutrient is placed directly into the small intestine, then the rate of glucose absorption will be increased. This could have the undesirable effect of increasing blood glucose concentrations. This premise needs to be confirmed. At present absorption is not routinely measured. It is possible that some critically ill patients have significant malabsorption and cannot be fed enterally. This needs further investigation and, if confirmed, methods to identify these patients clinically need to be established.

Glucose absorption across enterocytes takes place predominantly in the proximal small intestine, via the sodium-glucose cotransporter (SGLT 1) at the luminal membrane and the GLUT2 at the basolateral membrane (Levin, 1994). Increased blood glucose concentrations are associated with increased glucose absorption (Rayner et al., 2002). In the rat, hyperglycaemia increases glucose uptake by increasing the activity of intestinal disaccharidases (Murakami and Ikeda, 1998) and the number or activity of carriers at the basolateral membrane (Philpott et al., 1992). In the current study no relationship was observed between baseline blood glucose concentrations and glucose absorption.

The rate and/or extent of glucose absorption depends on a number of factors that include;

gastric emptying, the presence of pancreatic enzymes, contact time with the small intestinal mucosa (transit), contact surface area (length of intestine, surface villi, enzyme content of brush border, and function of carrier molecules), and the depth of the diffusion barrier of the absorptive epithelium (unstirred layer). The underlying causes of reduced glucose absorption in critical illness are unclear. This study has demonstrated a relationship between delayed gastric emptying and reduced rate of absorption. However in the subjects who had normal gastric emptying but reduced absorption the abnormality is likely to be in the small intestine. Abnormalities in structure or function could be responsible. Small intestinal mucosal abnormalities are known to occur in the critically ill and are most likely to be an important cause of reduced absorption. Villous height and crypt depth are reduced in association with a period of fasting (Hernandez et al., 1999). This is associated with increased permeability (Hernandez et al., 1999) and it is possible that this would also reduce absorption. Mucosal atrophy could also be associated with disruption in the amount, or function of digestive enzymes. In addition, mucosal oedema and reduced splanchnic blood flow may contribute to reduced absorption. Abnormal motility is also possible and accelerated transit can reduce the time for absorption.

Despite the markedly reduced glucose absorption, blood glucose concentrations were elevated in the critically ill and there was a higher peak glucose concentration after nutrient administration, although this was delayed. Hyperglycaemia is frequently observed in critical illness and is due to insulin resistance, as well as abnormalities in the release and action of other regulatory hormones and the presence of inflammatory cytokines (Dahn and Lange, 1982). In health and other disease states, gastric emptying is determined by, and a determinant of, blood glucose concentrations. Acute elevations in blood glucose concentrations slow GE in healthy humans, and patients with type 1 diabetes mellitus (see chapter 5). Severe hyperglycaemia (> 15 mmol/l) markedly slows gastric emptying (Fraser et al., 1991; Fraser et al., 1990; Hebbard et al., 1996; MacGregor et al., 1976; Oster-Jorgensen et al., 1990) but even changes in blood glucose concentrations within the normal postprandial range (4-8mmol/l) can have a significant impact (Andrews et al., 1998; Jones et al., 1999; Schvarcz et al., 1997). In this study, there was an association between baseline blood glucose concentrations and subsequent GE in the patients such that higher blood glucose was associated with slower GE. The baseline blood glucose concentrations in the patients ranged from 3.8 to 11.5 mmol/l. No relationship was demonstrated in the healthy subjects but the range in baseline blood glucose was only 4.2 to 6.4 mmol/l. Slower GE was associated with a smaller increment in blood glucose in the healthy subjects. This finding is similar to that described by other authors (Gonlachanvit et al., 2003; Horowitz et al., 2002; Meier et al., 2003) where pharmacological modification of gastric emptying in patients with diabetes was associated with changes in glucose absorption and postprandial glucose concentrations. In the current study no relationship was demonstrated between blood glucose and GE however the study may not have had adequate power to demonstrate this. Increasing gastric emptying by the use of prokinetics or post pyloric tubes is likely to have the unwanted side effect of increasing blood glucose. Agents that reduce GE such as glucagon-like peptide – 1 may be helpful in the control of blood glucose in critical illness (Meier et al., 2004).

There are several limitations of this study which need to be considered when interpreting the results. Blood glucose and 3-OMG samples were taken from an arterial line in the patients and a venous line in the healthy subjects (see chapter 8). There is likely to be a difference in blood glucose concentrations between arterial and venous samples but this difference is generally believed to be small (Bartlett et al., 1989; Larsson-Cohn, 1976). As 3-OMG is not metabolised by the tissues there is unlikely to be a difference between arterial and venous samples but this

has not been documented. In 6 patients the maximum 3-OMG concentration recorded was at 240 minutes (i.e. the end of the sampling period), suggesting that the peak may have been higher and more delayed, so these values may not give a true indication of the rate and extent of absorption. The number of subjects recruited into this study was small, but nevertheless highly significant differences were observed between healthy subjects and the critically ill suggesting that a study with greater numbers is unlikely to generate different results. Six of the 25 patients enrolled in this study had pre-existing type II diabetes. These patients were noted to have a higher peak blood glucose and were excluded from analyses. Longstanding diabetes could result in autonomic dysfunction causing slow gastric emptying but this was not observed in this small group. Diabetes mellitus per se should not affect 3-OMG absorption (Rayner et al., 2002).

In summary; delayed gastric emptying appears to slow the rate of absorption of glucose in the critically ill. The use of therapeutic agents to stimulate gastric emptying would therefore be expected to facilitate nutrient absorption in these patients but, this could result in unwanted hyperglycaemia. Thus, the reduction in glucose absorption associated with delays in GE may have an important beneficial impact on glycaemic control in the critically ill. Factors other than slow GE also appear to limit absorption in the critically ill. Further investigation into small intestinal abnormalities may identify reversible causes for reduced absorption. The identification of patients with severely compromised absorption may allow nutrient delivery by an alternative route.

Chapter 13

Erythromycin for the treatment of delayed gastric emptying and unsuccessful feeding in critical illness

13.1 Introduction

The primary aim of treating delayed gastric emptying (GE) in the critically ill is to improve the delivery of nutrition and, thereby, prevent weight loss during ICU stay and improve outcome. An additional benefit is the possible reduction of gastroesophageal reflux, limiting oesophageal mucosal damage and subsequent bleeding, and also possibly reducing the incidence of ventilator-associated pneumonia. GE can be stimulated by a number of drugs known as prokinetic agents. These are covered in detail in chapter 6. The gastrokinetic properties of erythromycin have only recently been recognised and it has been used to treat gastroparesis of diverse causes, including diabetes mellitus (Annese et al., 1997). It has been shown to increase antral motility and accelerate GE in critically ill patients (Dive et al., 1995). As it is available for parenteral use, and as its safety profile is well known due to its longstanding use as an antibiotic, it may be a suitable prokinetic for use in the ICU population.

The studies described in this and subsequent chapters were designed to examine the effects of measures aimed at improving the success of feeding in the critically ill. Although erythromycin has been demonstrated to accelerate gastric emptying in the critically ill its place in the clinical management of feed intolerance has not been explored. The first study examines whether a single intravenous dose of erythromycin was effective in reducing gastric residual volume in critically ill patients, and thus improving the success of feeding. The optimal dose of erythromycin for gastric prokinetic activity is also not clear, but use of a smaller dose with adequate prokinetic effect is likely to reduce the incidence of adverse events. The second study compares the effect of 2 different doses of erythromycin on gastric emptying.

13.2 The effect of erythromycin on the success of feeding critically ill patients

13.2.1 Introduction

Erythromycin is a macrolide antibiotic, which stimulates gastric motility by acting as a motilin agonist on receptors in the smooth muscle of the antrum and, at lower doses, on neuronal receptors, acting by a cholinergic effect (Parkman et al., 1995). This effect has been utilised clinically in diabetics with gastroparesis unresponsive to other treatment (Annese et al., 1997). Erythromycin has been shown to accelerate GE and increase antral motility in an unselected group of critically ill patients (Dive et al., 1995). In that study 200mg erythromycin was delivered intravenously over 30 minutes and gastric emptying was measured with the paracetamol absorption technique. The effect of erythromycin on feed tolerance in critically ill patients with delayed GE is unclear.

In this study the author investigated whether a single 200 mg dose of erythromycin, given intravenously, could increase the success rate of gastric feeding in patients intolerant of gastric feeding.

13.2.2 Materials and methods

Subjects

Twenty mechanically ventilated patients with no history of gastrointestinal surgery who had failed enteral feeding were enrolled in the study. Failure was defined as a gastric aspirate ≥ 250 ml at least 6 hours after commencing feed (Ensure-Abbott, Australasia Pty Ltd) of at least 40 ml/hour.

Patients were excluded if:

3. They had received prokinetic drugs (metoclopramide or cisapride within 72 hours, or erythromycin within 14 days, prior to the study).
4. They were known to be allergic to a macrolide antibiotic.
5. They were receiving any drugs known to interact with erythromycin (carbamazepine, cyclosporin, theophylline, aminophylline, digoxin, oral anticoagulants)
5. They had evidence of severe liver dysfunction *i.e.* any of the following measurements more than 3 times the upper end of normal range-bilirubin, gamma glutamyl transferase, aspartate transaminase, alanine transaminase, lactate dehydrogenase.

A 14 French or larger nasogastric tube was insitu in the stomach. The distal tip was either 10 cm below the gastro oesophageal junction, or clearly visualised in the stomach on plain abdominal radiograph. Following enrolment, patients received either erythromycin (n=10) or placebo (n=10) in a randomised, double blind fashion. The initial aspirate was discarded and the feed was continued at the same rate as previously for 4 hours. Three hours after the initial gastric aspirate, patients received a 20 minute intravenous infusion of either erythromycin (David Bull Laboratories, Mulgrave, Victoria, Australia) 200 mg in 20 ml normal saline or placebo. 1 hour after the infusion was commenced the stomach was again aspirated and the volume noted. GE was calculated as volume infused into the stomach over 4 hours minus residual stomach volume removed at the end of 4 hours. Successful enteral feeding was defined as a gastric volume < 250 ml and feeding was continued.

Statistical analysis

A power calculation was performed on data derived from the study performed by Dive *et al* to determine the numbers enrolled in the study (Dive *et al.*, 1995). All data are mean \pm SEM. Student's t test was used to examine independent samples. The success of feeding was analysed by a chi-squared test. P values ≤ 0.05 were considered significant.

13.2.3 Results

There was no difference in the demographics of the 2 groups (*i.e.* age, sex, admission Acute Physiology and Chronic Health Evaluation II Score, diagnoses) (table 1). There was also no difference between the 2 groups in terms of risk factors for delayed GE (table 2). Volumes of feed infused and measurements of GE are shown in table 3. The mean volume of GE was 139 ml \pm 37 ml after erythromycin and -2 ml \pm 46 ml after placebo (P=0.027). Nine out of ten patients in the erythromycin group had successful enteral feeding one hour after infusion compared to 5/10 in the placebo group (chi squared P = 0.05) (Graph 1). At 12 hours after infusion enteral feeding was successful in all patients treated with erythromycin compared with only 5/10 in the placebo group (P<0.05). 24 hours after infusion there was no significant

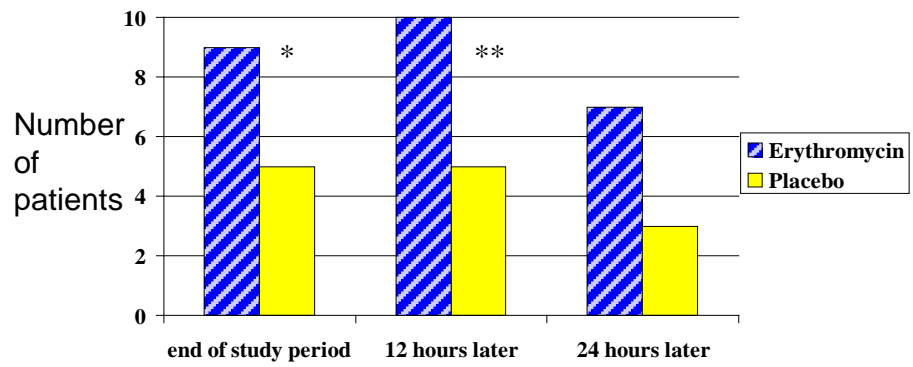
difference between the 2 groups. There was no correlation between blood glucose concentration and volume emptied over 4h.

	Erythromycin (n=10)	Saline (n=10)	P-value
Age (yrs)	46 ±17	46±16	NS
Gender (M/F)	7/3	9/1	NS
APACHE II	17±5	15±4	NS
Diagnoses	4 head injury 3 sepsis, 1 burn 1 other trauma 1 ICH	4 head injury 3 sepsis, 1 burn 1 other trauma 1 ICH	
Outcome	2 died	2 died	
Days on feed prior to study	1.6±0.2	1.4±0.1	NS
Patients on inotropes	5	5	NS
Patients on narcotics	8	8	NS
Patients with diabetes mellitus	2	0	NS
Blood glucose level	11.1±0.5	9±0.3	NS
Patients receiving neuromuscular blocking agents	1	0	NS

Table 13.2.1 Patient demographic data. (ICH – intracranial haemorrhage.) (The process of randomisation resulted in the patients in the 2 groups having identical diagnoses.)

Erythromycin					
Patient Number	rate ml/hr	volume infused over 4 hours (ml)	aspirate before drug (ml)	aspirate after drug (ml)	volume emptied over 4 hours (ml)
1	80	320	500	250	70
4	60	240	400	48	192
5	40	160	250	10	150
11	80	320	255	100	220
14	40	160	290	200	-40
16	40	160	280	10	150
17	40	160	480	130	30
18	60	240	410	120	120
19	100	400	290	10	390
20	80	320	620	210	110
Mean	62	248	378	109	139
St Dev	22	88	126	90	117
Placebo					
Patient Number	rate ml/hr	volume infused over 4 hours (ml)	aspirate before drug (ml)	aspirate after drug (ml)	volume emptied over 4 hours (ml)
2	40	160	420	280	-120
3	40	160	300	210	-50
6	60	240	350	120	120
7	40	160	280	260	-100
8	40	160	300	280	-120
9	80	320	600	250	70
10	40	160	400	3	157
12	60	240	320	0	240
13	40	160	400	160	0
15	40	160	340	380	-220
Mean	48	192	371	194	-2
St Dev	14	56	94	124	146

Table 13.2.2 Rates of feed administered, volumes of gastric aspirate and calculated volumes emptied from the stomach into the duodenum in each group. Volume emptied = volume infused over 4 hours - aspirate after dose of drug or placebo.



*Figure 13.1 Effects of erythromycin on the success of feeding. Erythromycin was more effective than placebo in promoting successful feeding after 1 and 12h but not at 24h after iv infusion * $P=0.05$, ** $P=0.01$. $n=10$ in both groups.*

13.2.4 Discussion

This study is the first to establish that a single dose of erythromycin reduces gastric residuals in critically ill patients who are intolerant of nasogastric feeding. The study also suggests that erythromycin may be used clinically to improve the success of enteral feeding in critically ill patients. Work by the author and others has shown that enteral administration of nutrition is often limited by gastrointestinal disturbance (chapter 10). (Adam and Batson, 1997; De Jonghe et al., 2001; Heyland et al., 1995; Norton et al., 1988). Underfeeding can result in delayed weaning from mechanical ventilation (Bassili and Deitel, 1981) and an increase in complications, particularly infections (Villet et al., 2005). Severe underfeeding (less than 25% requirements) increases the risk of nosocomial blood stream infections and mortality (Rubinson et al., 2004). It is, therefore, clear that efforts to improve the delivery of nutrition to critically ill patients have the potential to improve nutritional outcomes, prevent complications, prevent the need for intravenous feeding and even reduce mortality.

Erythromycin accelerates GE by causing a marked increase in the strength of antral contractions via its effect on motilin receptors located in the gastroduodenal smooth muscle. It also increases the frequency of contractions by acting via a cholinergic mechanism. Erythromycin increases antral motility and accelerates GE (measured by paracetamol absorption) in unselected critically ill patients (Dive et al., 1995). It also improves GE in diabetics refractory to other prokinetics (Annese et al., 1997; de Graaf-Strukowska et al., 1995; Okano et al., 1996), patients after gastric and nongastric surgery (Altomare et al., 1997; Mozwecz et al., 1990), and has been used to help pass nasoenteric tubes past the pylorus for enteral feeding and in preoperative patients to provide an empty stomach prior to anaesthesia (Kopp et al., 1997).

In this study, an effect from a single intravenous dose of 200mg of erythromycin was demonstrated. The optimal dose and dosage interval of erythromycin for this indication is unknown. Erythromycin has a dose-dependent effect on gastric motor activity (Otterson and Sarna, 1990). Smaller doses stimulate an antral activity front (phase III), which migrates into the duodenum while higher doses induce strong contractions of the antrum, which are not propagated, and duodenal caecal transit may actually be slower (Coulie et al., 1998). The dose of erythromycin required to increase GE is less than that used for treatment of infections. The optimal dosage for accelerating GE in the critical care setting is still uncertain. However, the suggestion by Frost *et al* that up to 500 mg QID of intravenous erythromycin may be used to accelerate GE (Frost et al., 1997) may be incorrect as doses of this magnitude are likely to disrupt electrical control activity in the stomach and small intestine. This has been associated with nausea and vomiting (Otterson and Sarna, 1990). In the current study, the effect of erythromycin on GE was still evident at 12 hours, but had reduced at 24 hours. This suggests that twice daily dosage may be sufficient to provide an ongoing prokinetic effect, but this needs confirmation in clinical studies.

The aim of this study was to assess the benefit of using erythromycin in a group of patients identified clinically as requiring a prokinetic. As expected, the inaccuracy of measurement of gastric residual volume (see chapter 6) resulted in a broad scatter of values, but despite this, erythromycin still had such a pronounced effect that statistical significance and clinical benefit could be demonstrated in this small group of patients. This is consistent with data from diabetics with gastroparesis where erythromycin is a very potent and effective agent even in patient resistant to other prokinetic therapy (Annese et al., 1997; de Graaf-Strukowska et al., 1995; Janssens et al., 1990; Okano et al., 1996).

The number of subjects included in this study was relatively small, thus, despite significant P-values, the possibility of a type I error leading to this result cannot be ruled out. However, the effect of erythromycin was marked, and consistent, and these findings are in keeping with previous results in both critical illness (Dive et al., 1995), and diabetes mellitus (Annese et al., 1997; Janssens et al., 1990; Richards et al., 1993).

Even modest hyperglycaemia has been reported to attenuate the effects of erythromycin on gastric motility and emptying (Petrakis et al., 1999a; Petrakis et al., 1999b). Hyperglycaemia is almost ubiquitous in the critically ill population. In this study, the mean blood glucose concentration was 11.1 mmol/l in the patients given erythromycin; however, there was no correlation between blood glucose concentration and response to erythromycin.

A possible limitation to the use of erythromycin as a prokinetic agent is the potential development of microbial resistance. However, at the dosages required, possibly as little as 0.5 mg/kg, the antibiotic effect is negligible. Motilin agonists without antibiotic activity are under development. Erythromycin can cause a prolonged QTc interval (Ray et al., 2004), possibly due to a direct stimulation of cardiac motilin receptors. There is thus the potential for ventricular arrhythmias to occur, particularly when erythromycin is administered in combination with other drugs with similar effects (Ray et al., 2004) such as fluconazole.

In summary, in critically ill patients intolerant of enteral feeding, a single 200 mg intravenous dose of erythromycin improves the success of feeding. These observations suggest that erythromycin can be used to enhance the delivery of nutrient to the critically ill. However the minimum dosage at which improvement of GE occurs is unclear as is the dosage interval. Given the potential for cardiac side effects and concerns about microbial resistance it would be an advantage to administer the smallest effective dose.

13.3 Comparative effects of two doses of erythromycin (70 and 200mg) on gastric emptying in critical illness

13.3.1 Introduction

Erythromycin has been shown to accelerate GE, and increase antral motility in critically ill patients (Dive et al., 1995). In the preceding study (13.2) the author showed that erythromycin reduced gastric residual volumes and improved the success of feeding when administered to critically ill patients who were feed intolerant,. Both these studies involved a single intravenous dose of 200mg. The recommended dose of erythromycin for the treatment of infection is 500mg to 1gm 6 hourly, however, the optimal dose of erythromycin for prokinetic effect is unknown. For acute treatment, most investigators have administered approximately 200mg of erythromycin intravenously over 20 to 30 minutes (Dive et al., 1995; Janssens et al., 1990). Studies in healthy subjects, however, suggest that a dose as low as 50mg may accelerate GE (Kluger, 1999). Very low doses (40mg) of erythromycin have different effects on gastrointestinal motility when compared with low doses (about 200mg). Low dose erythromycin stimulates strong antral contractions, but very low doses induce distally migrating antral activity, which is likely to accelerate GE in a very efficient way (Tack et al., 1992). Furthermore the lower dose may be associated with a reduction in adverse effects (Kluger, 1999). For the purpose of this study, the effect of 70mg of erythromycin (approximately 1mg/kg) was compared to the standard dose of 200mg (approximately 3mg/kg) on gastric emptying in a critically ill cohort. The hypothesis was that 70 mg would have an effect on GE equipotent to that of 200mg.

As discussed in chapter 6, the breath test technique for measurement of GE is a convenient, simple and highly reproducible technique, suitable for evaluating the effect of drugs on GE. In the previous study (13.2) gastric residual volume was used, but, although this is a clinically relevant parameter, it is highly variable and less suitable for precise measurement of the effect of drugs. The breath test technique avoids exposure to radiation and was thus more acceptable to the families providing consent for performance of the study than other techniques such as scintigraphy. This allowed the recruitment of greater numbers into the study.

13.3.2 Materials and methods

Subjects

Forty-four mechanically ventilated patients in a combined medical and surgical ICU were enrolled into the study. Large gastric residual volumes were not a specific inclusion criteria.

Patients were excluded if:

1. They had a history of gastrointestinal disease,
2. They had previous abdominal surgery,
3. They had received prokinetic drugs such as cisapride, metoclopramide or domperidone, during the 72 hours prior to the study,
4. They had received erythromycin during the two weeks before the study,
5. They were known to be allergic to a macrolide antibiotic,
6. They were receiving any drugs known to interact with erythromycin (carbamazepine, cyclosporin, theophylline, aminophylline, digoxin, oral anticoagulants, disopyramide, bromocriptine, ergot derivatives, terfenadine, astemizole or lovastatin).

7. They had evidence of severe liver dysfunction *i.e.* any of the following measurements more than 3 times the upper end of normal range-bilirubin, gamma glutamyl transferase, aspartate transaminase, alanine transaminase, lactate dehydrogenase.

GE was assessed using the ^{13}C -octanoic acid breath test (Ghoos et al., 1993) as described in chapter x. The test meal consisted of 100ml of a mixed nutrient liquid (Ensure; 13% protein, 64% carbohydrate, 21% fat, and caloric content of 1kcal/ml) (Ensure[®], Abbott, Kurnell, Australia) mixed with 100 μl octanoic acid (^{13}C) (Cambridge Isotope Laboratories, Andover, MA, USA).

Syringes containing erythromycin (David Bull Laboratories, Mulgrave, Victoria, Australia) in a dose of 70mg (1mg/kg) or 200mg (3mg/kg), or saline (0.9%) placebo were prepared to a volume of 20ml by the hospital pharmacy department. The investigators were blinded to the content of the syringes.

Studies were performed on two consecutive days, with patients studied in the supine position. Correct positioning of the nasogastric tube was verified by the insufflation of air and routine radiology. On both study days, enteral feeding was ceased four hours before the study. On day one, GE was measured for four hours using the ^{13}C octanoic-acid breath test. On the second day, breath testing was repeated after a 20-minute intravenous (IV) infusion of either (i) 70mg or (ii) 200mg of erythromycin or (iii) saline (0.9%) placebo, in a randomized double-blind fashion. The test meal was infused into the stomach over 5-minutes. End-expiratory breath samples were collected as described in chapter x. Breath samples were collected at baseline (immediately before the test meal), every 5 minutes during the first hour, and every 15 minutes thereafter for a further 3 hours. Gastric content was aspirated immediately before baseline and tested for pH using indicator paper (Whatman, Maidstone, England). Analysis of GE was performed prior to randomization disclosure. Enteral feeding was continued as clinically indicated between the two GE tests and upon completion of the study.

Breath samples were analysed for $^{13}\text{CO}_2$ concentration using an isotope ratio mass spectrometer (Europa Scientific, ABCA model 20\20, Crewe, United Kingdom). The values obtained were converted to % ^{13}C and expressed as the percentage of administered dose recovered per hour (% ^{13}C dose/h). The % dose/h was plotted over time and the area under the recovery curve used to calculate the GE coefficient (GEC) and gastric half-emptying time ($t_{1/2}$) (Ghoos et al., 1993).

Gastric aspirates were collected 6 hourly during the 24 hours before and after the study. The volumes obtained were averaged and used to calculate the median in each group.

Differences in GE (GEC, $t_{1/2}$ and aspirate volumes) within and between patient groups, pre- and post- treatment, were assessed. Pre-treatment (day 1) GEC values from both erythromycin groups were pooled. There was a bimodal distribution of pre-treatment GE consistent with a normal (48%) and delayed (52%) emptying group. For patients with delayed gastric emptying, comparisons were made within and between erythromycin groups.

Statistical Analysis

Data were assessed for normality (Kolmogorov-Smirnov) and the results subsequently expressed as median and interquartile range. Non-parametric analysis of variance (Kruskal-Wallis) was performed prior to group comparisons (Mann-Whitney) using Minitab[®] 13.31 software. A P-value < 0.05 was considered statistically significant.

13.3.3 Results

Forty-four patients were enrolled into the study. Thirty-five patients completed the study (25M: 10F; median age 48 years (18-79); BMI range 18-53kg/m²). Nine patients failed to complete the study for the following reasons (extubation (2), surgery (1), elevated liver enzymes (1), vomiting (2), technical difficulty with sample collection (2), and death (1)). The median duration of stay in the ICU before the study was 6 days (range 2-40 days). The median APACHE II score on admission was 19 (range 8-36). Demographic data including gender, Body Mass Index (BMI), admission APACHE II score and time spent in intensive care before the study did not differ significantly between the groups (table 1). Fifteen patients were receiving morphine. The primary diagnoses of patients were surgical (6), medical (12), neurological (8), trauma (excluding head injury) (7), and burns (2). The group given placebo was older than the group given 70mg of erythromycin (57 years (18-79) vs. 32 years (21-50), $P < 0.05$).

Collection of breath samples did not interfere with patient care. Breath samples from all 35 patients had a CO₂ level $>1\%$, indicating correct end-expiratory sampling. There were no differences in pre-treatment GE measurements between the groups (figure 1a). Both doses of erythromycin accelerated GE compared to placebo. The gastric half emptying time ($t_{1/2}$) was reduced after treatment with both doses of erythromycin (70mg: 98 min (IQR 88-112) and 200mg: 86 min (75-104)) when compared to placebo (122 min (102-190)) ($P < 0.05$) (figure 2b). Similarly, the GEC was higher after treatment with both doses of erythromycin (3.8 (3.3-4.0) after 70mg and 4.0 (3.6-4.2) after 200mg), when compared to placebo (2.9 (2.5-3.7)) ($P < 0.05$). There were no differences in the absolute values of GE following the two doses of erythromycin.

A pre-treatment GEC ≥ 3.2 was considered to be normal (Ritz et al., 2001). In both erythromycin groups, patients with a pre-treatment GEC less than 3.2 (delayed emptiers) had an improvement in GE following treatment ($P < 0.05$) (figure 2). There was no acceleration in GE following treatment with erythromycin in patients with a pre-treatment GEC greater than 3.2 (i.e. normal emptying) (figure 2). In patients with delayed emptying, the $t_{1/2}$ was reduced after treatment with erythromycin, compared with pre-treatment (70mg: 99 ± 15 ml vs. 250 ± 78 ml; and 200mg: 98 ± 31 ml vs. 226 ± 82 ml, post vs. pre treatment) ($P < 0.05$).

Despite randomising the patients using computer generated numbers, pre-treatment gastric aspirate volumes were higher in both erythromycin groups compared to placebo (table 2) ($P < 0.05$). Post treatment, there was no difference in gastric aspirate volumes between the three groups ($P > 0.05$) (table 2).

	Placebo (n=12)	70mg erythromycin (n=11)	200mg erythromycin (n=12)
Age (yrs)	59 (47-77)	32 (21-51)	46 (32-63)
BMI (kg/m²)	25 (23-31)	24 (22-28)	26 (24-31)
Gender (M / F)	9 / 3	5 / 6	11 / 1
APACHE II score (admission)	20 (14-25)	19 (13-23)	19 (15-22)
Enteral feeding rate 4h pre-study (ml/h)	58 ± 8.67	52 ± 13.4	54 ± 12.3
No. days in ICU	7 (3-8)	5 (4-7)	5 (3-12)
Patients on inotropes	2	2	5
Patients on morphine	4	6	5

Table 13.3.1 Patient demographic data (median & IQR)

	Placebo	70mg Erythromycin	200mg Erythromycin
Pre-treatment	10 (0-30)	55 (10-120)*	90 (35-195)*
Post-treatment	10 (0-20)	20 (9-120)	10 (3-20)

*Table 13.3.2 Gastric aspirate volume (ml) measured 6 hourly during the 24 hours before and after treatment. Data are median and interquartile range. * $P < 0.05$, significantly different from pre-treatment volume in placebo group*

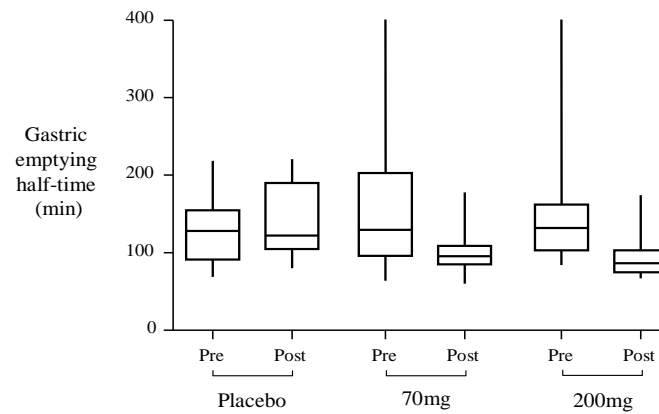


Figure 13.3.1 Gastric half-emptying time ($t_{1/2}$) (a) pre-treatment and (b) post-treatment, between placebo and erythromycin treated groups. There was no difference in gastric half-emptying times between the groups pre-treatment. The gastric half-emptying time was reduced after treatment with both doses of erythromycin compared to placebo ($P < 0.05$) and there was no difference between the 2 doses. Data are median and interquartile range.

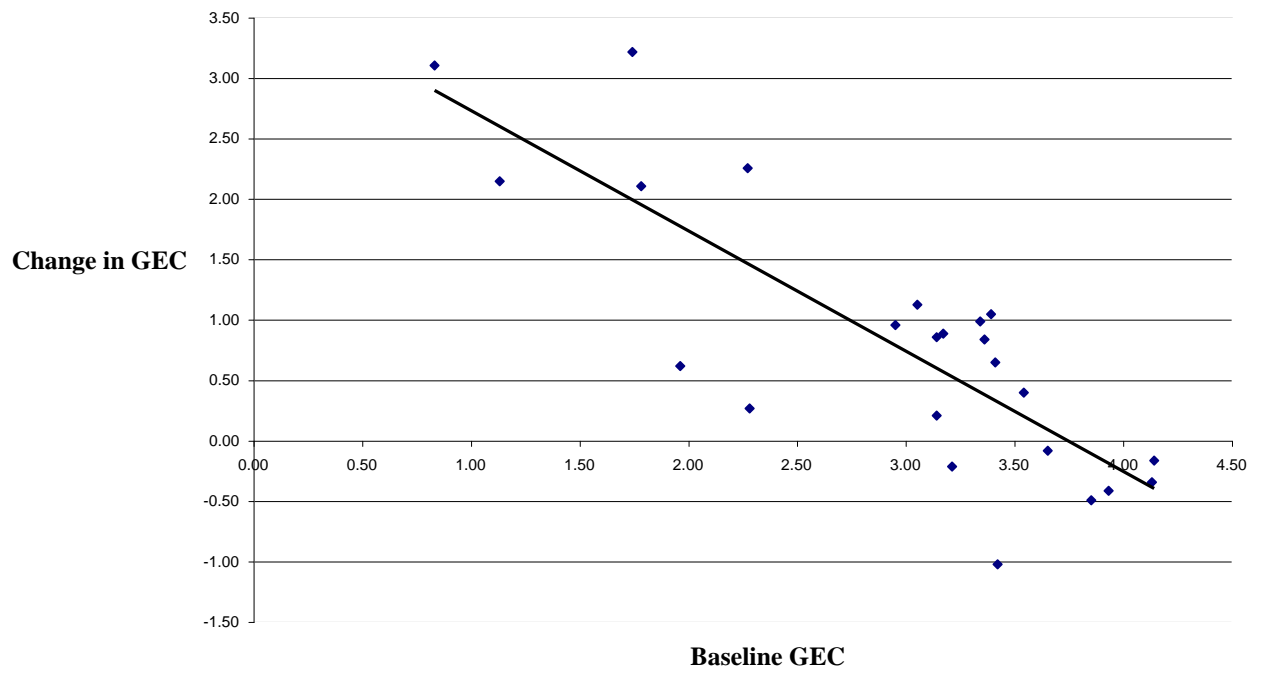


Figure 13.3.2 Relationship between the change in GEC after administration of erythromycin and the baseline GEC. Pearson correlation coefficient -0.82 $P < 0.001$.

13.3.4 Discussion

Previous studies have shown that intravenous erythromycin markedly accelerates GE in diabetic patients with gastroparesis (Janssens et al., 1990) and other patient groups with gastroparesis, such as after surgery (Kendall et al., 1997; Petrakis et al., 1998; Ramirez et al., 1994), radiotherapy (Sturm et al., 1996), anorexia nervosa (Stacher et al., 1993), and scleroderma (Fiorucci et al., 1994). The study reported in 13.2 (above) showed that a single intravenous dose of 200mg of erythromycin reduced gastric residual volumes in ICU patients who were feed intolerant. The optimal dose for erythromycin remains unclear although a dose of about 200mg of erythromycin delivered intravenously over 20 to 30 minutes has been used most frequently (Dive et al., 1995; Janssens et al., 1990). However, studies in healthy humans (Kluger, 1999) indicated that 50mg of erythromycin was as effective as 200mg in accelerating GE, and was associated with a reduction in adverse effects. For the purpose of this study, 70mg of erythromycin (approximately 1mg/kg) was compared to the standard dose of 200mg (approximately 3mg/kg), delivered intravenously over 20 minutes. The major observation was that 70mg of intravenous erythromycin was as effective as 200mg in accelerating GE in critically ill patients.

Very low doses of erythromycin (40mg) have different effects on motility when compared with low doses (about 200mg) of the drug. In healthy volunteers and diabetic patients with gastroparesis, 40mg of intravenous erythromycin induces premature antral phase III activity, which migrates down to the small intestine, whereas 200-350mg erythromycin leads to prolonged periods of strong antral contractions that do not migrate and are not followed by motor quiescence (Tack et al., 1992). The motor patterns that are reported after very low doses of erythromycin are likely to accelerate GE in a very efficient way. A reduction in adverse effects has also been reported with the lower dose (Kluger, 1999), however this was not formally assessed in the current study. As microbial resistance is an important theoretical risk of erythromycin use at low dose this would need to be investigated in the context of repeated doses over a longer time period.

The current study showed that with both doses of erythromycin, the prokinetic effect was confined to patients with delayed GE. These results apparently contradict previous studies where erythromycin accelerated GE in healthy subjects (Landry et al., 1995; Landry et al., 1996). This almost certainly reflects methodological differences, such as in the volume of nutrient delivered and the rate of administration of erythromycin. The results from the current study suggest that erythromycin should be used therapeutically when gastroparesis is evident and not for the prevention of feed intolerance.

The current study showed acceleration in GE and a reduction in gastric residuals after treatment with both doses of erythromycin, strengthening evidence that erythromycin may be a useful prokinetic in critically ill patients with feed intolerance. However, there are no data on the effectiveness of erythromycin in the management of feed intolerance over longer-term usage (e.g. more than 7 days) in the critically ill. In the treatment of diabetic gastroparesis, there is evidence that tachyphylaxis develops with chronic use of oral erythromycin (50-500mg three to four times daily for ≥ 4 weeks) (Dhir and Richter, 2004; Richards et al., 1993). It is not known whether this also occurs in the critically ill.

The placebo group was older than the 70mg erythromycin group. Age, however, is most unlikely to explain the differences in the rate of GE between the placebo and erythromycin-treated groups, as there were no differences in pre-treatment GE between the groups.

Furthermore, any effect of normal aging on GE is modest (Moore et al., 1983), and it is not known whether age affects GE in this patient group (Ritz et al., 2001).

It is possible that this study lacked sufficient power to detect a difference in the 2 doses of erythromycin. The median GEC was slightly higher in the group given 200mg erythromycin (4.02 compared to 3.68). Using this difference and the standard deviation of the GEC demonstrated in this study of 0.68, a study that would have 80% power to detect a significant difference would require 75 subjects in each group. However it is unlikely that this difference is clinically meaningful. Given the marked improvement in GE demonstrated with both doses of erythromycin, any further improvement in GE associated with the higher dose is likely to be counterbalanced by an increased rate of adverse effects. Importantly, the increment in GE was the same in the 2 groups. The absolute increase in GEC was 0.81 after 70mg and 0.78 after 200mg erythromycin (relative increase 28% and 26% respectively). Therefore the apparent trend to improved GE after 200mg may reflect a slightly higher baseline GE.

Although the breath test technique lacks the sensitivity to reliably detect delayed GE in individual subjects (see chapter x), it is a highly reproducible technique and is ideal for the measurement of a change in GE following drug administration. Thus, in this study, GE was determined at baseline and after drug administration. By chance the GRV was lower in the control group at baseline. Although this suggests that the baseline GE may have been somewhat faster in that group, this was not apparent using the breath test technique. It is therefore more likely that the baseline GRV is inaccurate, as, although the measurement of GRV is used to determine feed tolerance clinically, it is believed to be an insensitive measure of GE and is prone to inaccuracy (see chapter x).

In conclusion, the macrolide antibiotic, erythromycin, is an effective gastrokinetic drug, at doses as low as 70mg (approximately 1mg/kg) in critically ill patients. This effect is limited to patients with delayed GE suggesting against a role for prophylaxis. Future studies are required to address a comparison between prokinetic agents and to determine the interval of dose administration. Longer term studies to establish whether this prokinetic activity continues over time are also needed. Other prokinetic agents without the potential adverse effects of erythromycin would be of considerable interest.

Chapter 14

The effect of cefazolin on gastric emptying in the critically ill

14.1 Introduction

In the studies described in 13.2 and 13.3, the author has demonstrated that erythromycin improves the success of feeding, accelerates gastric emptying, and may be a clinically useful prokinetic in the critically ill. The administration of only 70mg of erythromycin appears to be effective in improving gastric emptying; however, concerns remain about the safety of this drug in the ICU population. Possible adverse effects include gastrointestinal side effects, and interactions with other medications which can prolong QT interval and induce arrhythmias. In addition, the use of erythromycin may result in the emergence of resistant microorganisms which cause nosocomial sepsis. Effective prokinetics, with fewer side effects, would thus be advantageous in the management of delayed GE in the critically ill.

The cephalosporin class of antibiotics have recently been reported to have prokinetic activity in both patients with gastrointestinal dysmotility and a mouse model (Kuo et al., 1998; Lamport, 1995). The agent with the greatest prokinetic effect and largest therapeutic window appears to be cefazolin (Kuo et al., 1998). Cefazolin (20mg/kg) accelerated GE in a mouse model to a greater degree than both erythromycin and metoclopramide. Fifty mg of cefazolin induced MMC activity and increased antral motility in patients with abnormal gastrointestinal motility. The mechanism is unknown. Whether this drug is effective in enterally fed patients in Intensive Care is unknown.

The aim of this study was to determine the effects of cefazolin on GE in critically ill patients receiving enteral nutrition.

14.2 Materials and methods

Subjects

Fourteen mechanically ventilated patients 18 years or over were recruited from a mixed medical/surgical Intensive Care Unit. All patients were considered suitable for, or were receiving enteral feeding, and had a nasogastric tube in situ. They were not selected for high gastric residual volumes.

Patients were excluded if:

1. They had previous gastrectomy or partial gastrectomy.
2. They had received prokinetic drugs (cisapride within 48 hours, or metoclopramide or erythromycin within 24 hours, prior to the study).
3. Known allergy to cephalosporins or history of anaphylaxis associated with penicillin.
4. Use of any cephalosporin within 24 hours of the study.
5. Pregnancy or breast feeding.

Studies were performed on two consecutive days in the same manner as described in 13.3. The details of breath test measurement of GE are described in chapter 8. Immediately prior to measurement of GE on day 1 the patient was randomised to receive either intravenous cefazolin (Kefzol – Aspen Pharmacare Australia) (50 mg) or intravenous saline which was infused over

20 minutes. Syringes containing cefazolin or saline (0.9%) placebo were prepared to a volume of 20ml by the hospital pharmacy department. The investigators were blinded to the content of the syringes.

Statistical Analysis

Data were assessed for normality (Kolmogorov-Smirnov) and the results subsequently expressed as mean (+/-standard deviation). Data were analysed using the paired t-test (saline vs. cefazolin). Analysis and power calculations were performed using Minitab® v13 software. A P-value < 0.05 was considered statistically significant. Differences in GE (GEC, $t_{1/2}$ and aspirate volumes) within and between patient groups, pre- and post- treatment, were assessed.

14.3 Results

Fourteen patients were enrolled into the study. In one subject breath sample collection was unsatisfactory, and another vomited during the second study, leaving 12 subjects in the final analysis.

Cefazolin had no effect on GE when compared to saline (t_{50} ; cefazolin 138 (+/-54) minutes vs. saline 122 (+/-46) minutes (Figure 1), $P=0.32$: GEC; cefazolin 3.27 (+/-0.83) vs. saline 3.55 (+/-0.6), $P=0.24$). Although not statistically significant, there was a trend for slowing of GE following cefazolin. Two patients had abnormal t_{50} following administration of placebo and 5 following cefazolin. Of the 2 with delayed GE in the placebo group one improved after cefazolin and one did not. There was no order effect of the study day on either t_{50} or GEC ($P>0.5$ for both).

Cefazolin had no effect on gastric aspirate volume (see table 2); and there was no correlation between volumes of gastric aspirates and GE as measured by breath tests.

Age (yrs)	57 (+/-16)
Gender	6M/6F
APACHE II score	0 ± 8
Diagnoses	3 neurological 2 trauma & burns 4 medical 1 surgical 2 sepsis
Patients on inotropes	3
Patients on morphine	4
Patients with diabetes mellitus	3
Patients requiring insulin infusion	4

Table 14.1 Patient demographic data

	Placebo	Cefazolin
Pre-treatment	70 (5-850)	74 (2-240)
Post-treatment	50 (12-1400)	30 (10-345)

Table 14.2 Gastric aspirate volume (ml - measured 6 hourly) during 24h before and after treatment. Data are expressed as median and range.

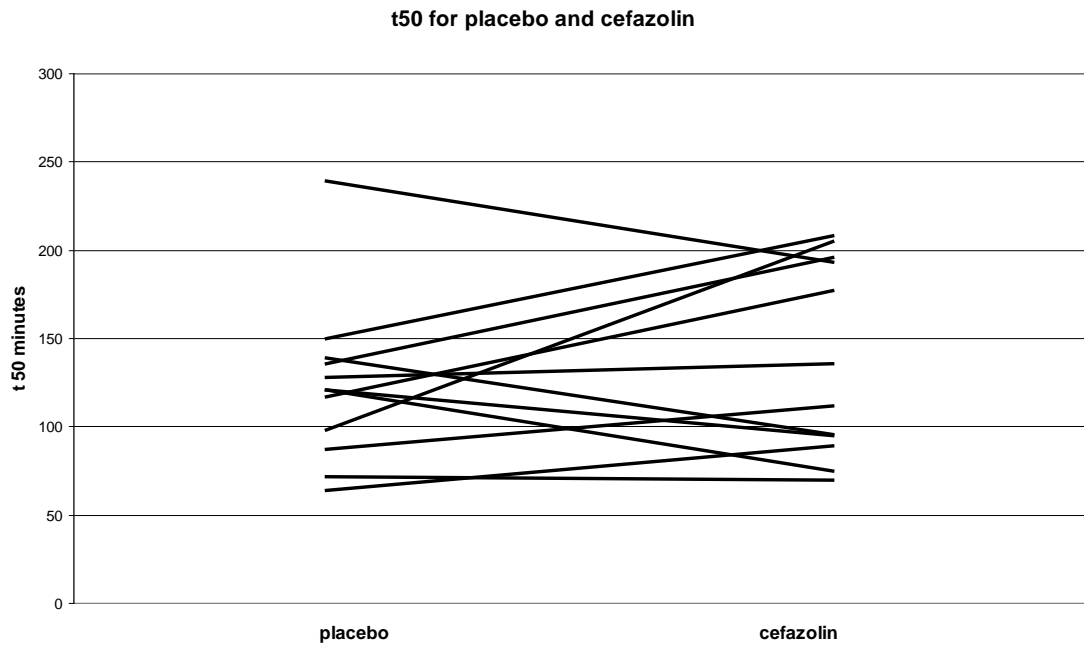


Figure 14.1 $BT_{t_{50}}$ after administration of saline and cefazolin in individual patients.

14.4 Discussion

In contrast to previous reports, this study demonstrated that this dose of cefazolin had no effect on the rate of GE in critically ill patients (Kuo et al., 1998; Lamport, 1995). This may be because the previous study showing a positive effect was in ambulant patients with gastroparesis. The underlying pathophysiology in this patient group is likely to be different. Previous studies examining the effect of cephalosporins on GE have been inconsistent. In a rat model, cefaclor delayed GE, possibly by a cholecystokinin-mediated effect (Bozkurt et al., 2000). However animal models may not be relevant to responses in a critically ill population. Also, although cefazolin has been reported to stimulate gastric motility (Lamport, 1995) it is possible for this to result in slowing of GE, as, for example, if the tonicity of the pylorus is increased (Fraser et al., 1993a).

There are a number of potential limitations of this study:

(i) Dose administered.

It is possible that the failure of cefazolin to increase GE in the current study is because the dose was sub-therapeutic. Fifty mg cefazolin is well below the dose required for antibiotic effect, but this dose was chosen because it has been reported to have a significant effect on human gastric motility (Lamport, 1995). Furthermore, erythromycin, in doses significantly lower than those required for an antibiotic effect, has a substantial gastrointestinal effect (Kluger, 1999; Landry et al., 1995). However, a further dose finding study using increasing doses could demonstrate an effect.

(ii) Patient group

In the study reported in chapter 13.3, the prokinetic effect of erythromycin was only demonstrated in the patients who had a baseline GE that was delayed. It is possible that in the design of this trial, patients who could potentially respond to a prokinetic were excluded. The prevalence of delayed GE in this study was only 17%, considerably less than the 45% reported in a previous study of unselected critically ill patients (Ritz et al., 2001). This may reflect the exclusion of patients requiring prokinetics prior to the study. As part of the aggressive feeding policy of the intensive care unit, patients receive prokinetics with the first evidence of failure to tolerate feeding. Thus patients likely to have delayed GE were unintentionally excluded from the trial. It is therefore possible that, in excluding patients on prokinetics, patients who may have demonstrated a benefit following the administration of this drug were excluded.

(iii) Breath test measurement of gastric emptying

Although it is possible that breath testing lacks sufficient sensitivity to detect changes in GE induced by cefazolin, this appears unlikely. Previous studies by our group have shown that the breath test can be used effectively in this group of patients (Ritz et al., 2001), that GE measured by this technique is delayed in the critically ill (Ritz et al., 2001), and that erythromycin improves GE in an unselected group of critically ill patients (chapter x). Also we have validated this technique against scintigraphy (chapter x). Furthermore, while this test may lack sensitivity to detect delayed GE in individual patients, it has extremely good intra-individual reproducibility (Choi et al., 1997, 1998) hence is very suitable for studying a change in GE following administration of a drug.

(iv) The power of the study

The power of this study to detect a difference between the t_{50} of the 2 groups was only 46%; however, the trend toward slowed GE following cefazolin suggests that further studies with either increased numbers or the use of a more sensitive test are not warranted.

In mechanically ventilated critically ill patients, low dose cefazolin had no effect on GE. The power of this study is limited by its small numbers; nevertheless, these data do not support the use of low dose cefazolin as a prokinetic agent in critically ill patients.

Chapter 15

A novel technique for postpyloric tube insertion in critically ill patients.

15.1 Introduction

Delivery of nutrition in patients with delayed GE may be achieved by bypassing the stomach and feeding directly into the duodenum, or jejunum. A number of approaches to positioning small intestinal feeding tubes have been described. These include placement at surgery, under fluoroscopic or ultrasound-guidance, with endoscopic assistance (Hernandez-Socorro et al., 1996; O'Keefe et al., 2003) and blind introduction at the bedside with (Di Lorenzo et al., 1990), or without prokinetic administration (Zaloga and Roberts, 1998). At the Royal Adelaide Hospital the most commonly used technique is endoscopy. This requires specialised equipment and staff. An ideal placement technique would be non-invasive, require no special training, achieve a high success rate and be performed at the bedside without expensive equipment. None of the currently available approaches fulfils all these requirements. The Cathlocator™ (Micronix Pty Ltd, Adelaide, Australia) is a novel device that generates a low energy electromagnetic field from a coil incorporated in the tip of a modified enteral feeding tube connected by wires to a proximal interface (see below). A small receiving plate placed on the patient's abdomen, enables the position and direction of the feeding tube to be determined and displayed, by detecting the electromagnetic field. A previous study showed that this device accurately determined the position of the tip of a nasogastric tube in healthy volunteers (Williams et al., 1996). This study was conducted to determine the feasibility of using the Cathlocator™ device to guide bedside placement of small intestinal feeding tubes and confirm placement of a nasogastric tubes in critically ill patients requiring post-pyloric feeding.

When prokinetics fail to improve feeding, an option is to bypass the stomach and deliver nutrient directly into the small intestine. This requires access to the duodenum which can be technically difficult. Traditional techniques include endoscopy, which necessitates a specialist gastroenterology team and equipment, or fluoroscopy, which exposes the patient to radiation and is technically difficult and time consuming. A simple and convenient method of post pyloric tube placement that could be performed by the intensivist at the bedside would represent a major advance in clinical management.

15.2 Materials and methods

Subjects

Ten nasoduodenal and nasogastric tube insertions were attempted in eight adult critically ill, mechanically ventilated patients in whom enteral nutrition was indicated. All patients had failed nasogastric feeding and had large gastric residual volumes (>250 ml). Two patients were studied twice (patients numbers 1 & 6), because they failed feeding again after completion of the first 7 day study period.

Patients were excluded if:

1. They had oesophageal obstruction
2. They had previous gastrectomy.

The Cathlocator™ System

The Cathlocator™ system comprises a modified feeding tube, an electronic interface module, a receiver and a graphic computer display (Figure 1). The nasoduodenal feeding tubes were modified 110 cm, 10F polyvinyl chloride, non-weighted feeding tubes with removable stylets (Corpak Medsystems, Wheeling, IL, U.S.A.). The nasogastric drainage tubes were modified 100 cm, 14F polyvinyl chloride, non-weighted feeding tubes without stylets (Maersk Indoplas Pty Ltd, Sydney, N.S.W., Australia). One hundred and twenty coils of 0.125 mm diameter polyester- insulated copper wire were wound around the tips of the tubes, i.e. the wire remained outside the tube and was coated by a polyester sheath such that no occlusion of the internal feeding lumen occurred. Two wires from the coil were passed along the inside of the feeding tube to a connector at the proximal end that was connected to the electronic interface module. The coil and wires were securely bonded to the tip of the feeding tube using cyano-acrylate glue. The conducting wires and coil were coated with a biocompatible silicon sealant that completely embedded the added components into a resin matrix. Electrical continuity was thus maintained throughout the duration of the tubes placement enabling serial measurements to be performed (Figure 2).

The electronic interface module generated a source signal for the coil in the tip of the feeding tube. The power output of the signal generator was 0.25 mW at a frequency of 40 kHz resulting in energy emitted at the tip of the feeding tube of less than 0.25 mW. This is well below the limit of exposure for humans recommended by the United States Food and Drugs Administration (Williams et al., 1996). The source signal was synchronised with the signal detected by the receiver (see below) to remove background noise. During the study, the passive receiver was placed on the midline of the patient's abdomen, with the xiphoid process as a reference point (Figure 1). The receiver contained three sets of three coils to detect the source signal generated by the coil in the tip of the feeding tube. Each set of coils was arranged on the apices of an equilateral triangle and the three coils within each set were at right angles to each other. This geometric arrangement enabled a measurement of the precise distance and direction of the signal source on the feeding tube tip to each set of coils using the inverse square law, which governs the relationship between the intensity of an electromagnetic signal and the distance from its source. These measurements were used to determine the relationship of the signal source in three dimensions, to a set reference point in the device and hence display the distance and direction of the tip of the tube. Using the xiphoid process as a fixed reference point, together with the surface anatomy of the stomach, the position of the tube tip within the gastrointestinal tract was determined. These data were then processed by the computer, which converted the received data into a graphical display (Figure 3). The electronic interface module, receiver and computer were powered by low voltage battery packs providing Class II electrical protection.

Protocol for Tube Placement

Prior to introduction of the assembly, each patient was placed supine and the Cathlocator™ receiver was positioned immediately caudal to the xiphoid process on the anterior abdominal wall. The nasoduodenal tube was passed through the nose into the proximal stomach by the same (two) investigators (MJ Chapman & RJ Young) and its position confirmed by the Cathlocator™ (Figure 3), aspiration of acidic gastric contents and auscultation over the left upper quadrant during insufflation of 50 ml of air. Air (500 ml) was insufflated into the stomach through the tube, which was then advanced. Using the graphic display of the Cathlocator™ for guidance the tip was viewed as it manoeuvred to pass beyond the pylorus. The tip was considered to have passed the pylorus when it advanced >2 cm to the right of the

midline and its track followed the surface markings of the duodenum (i.e. posteriorly (Basmajian, 1989)). Following placement of the nasoduodenal tube, a nasogastric tube was then passed to ensure continuous drainage of gastric contents during duodenal feeding. The tube's position was confirmed by the Cathlocator™, aspiration of acidic gastric contents and/or auscultation over the left upper quadrant of 50 ml of insufflated air. When both tubes had been placed or if duodenal placement could not be achieved, the position of the tubes was checked by plain abdominal X-ray as per standard clinical practice prior to initiation of feeding. Subjects were monitored until approximately 48 hours following removal of the enteric feeding tube for adverse events.

15.3 Results

There were no adverse events. Post-pyloric placement of the nasoduodenal tube was successful in nine of the ten attempts. In the remaining attempt the tube could not be advanced through the pylorus and the procedure was abandoned after 21 minutes.

The median time for successful insertion was 16 minutes (5-34 min). All nasogastric tube placements were successful with median insertion time 3.4 minutes from opening the packet to verification of tube position (0.8-10 min). The Cathlocator™ accurately determined the position of both tubes in all cases, when compared with plain abdominal X-ray. Successful feeding (90% of desired energy requirements for two consecutive days) was achieved in six of the eight patients.

Patient No.	Age	Sex	APACHE II	Height	Weight	BMI	Post-pyloric placement?	Admission diagnosis
	(y)			(cm)	(kg)	(kg/m ²)		
1	47	M	17	178	90	28.4	Yes	Organophosphate poisoning
2	62	M	36	185	95	27.7	Yes	Major burns
3	62	F	20	160	115	44.9	Yes	Multiple trauma
4	62	F	30	145	130	61.8	Yes	Necrotising fasciitis
5	34	M	20	177	105	33.5	Yes	Urosepsis
6	28	M	22	178	80	25.2	Yes	Multiple trauma
7	68	F	34	165	85	31.2	No	Lobectomy for lung cancer
8	77	M	22	161	90	34.7	Yes	Laparotomy for bowel obstruction
Mean	51	5M:3F	25	169	94	36		

Table 15.1 Patient demographic data, and outcome of post-pyloric tube placement using the Cathlocator™ device

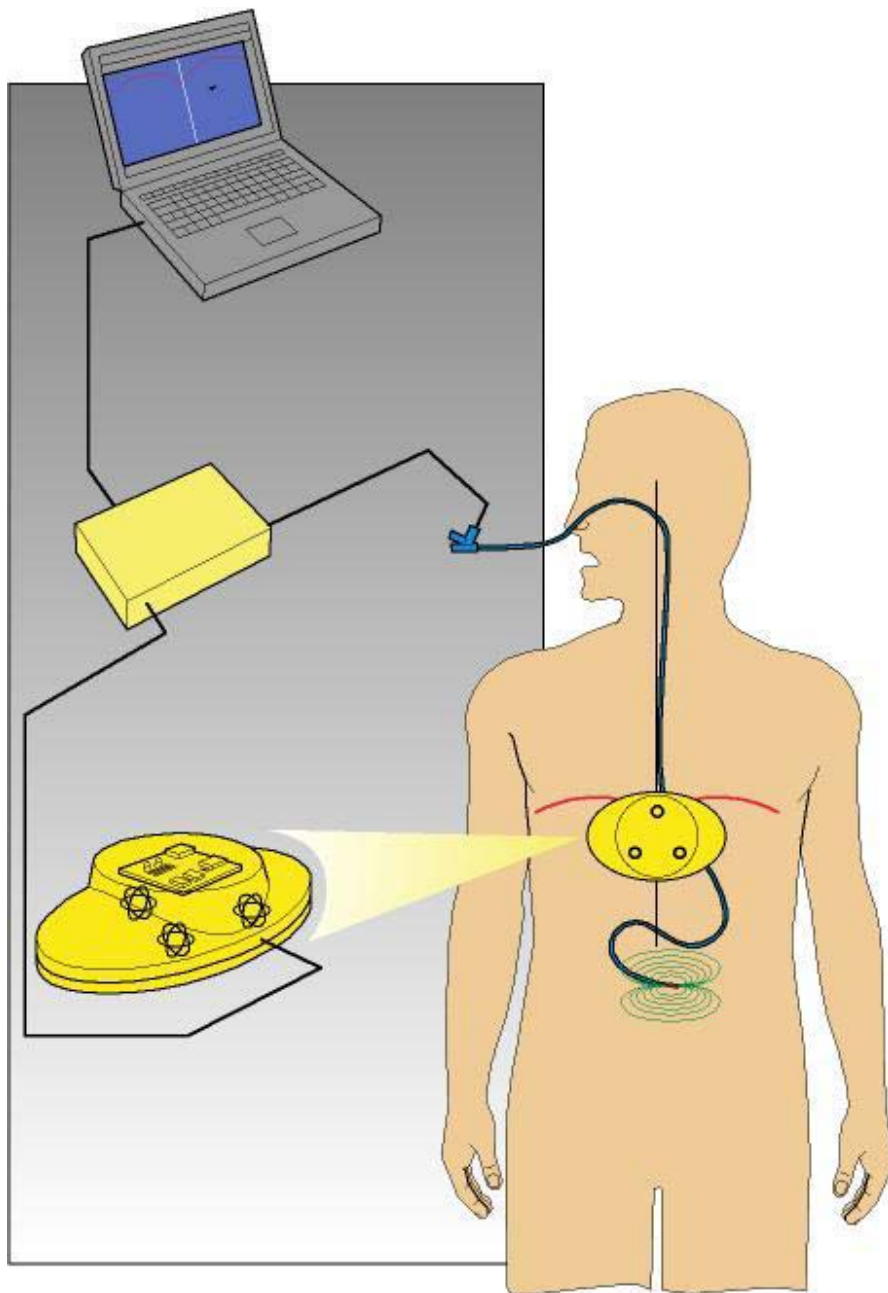


Figure 15.1 Components of the Cathlocator™ system. The receiver unit is placed on the xiphisternum to track the passage of the transmitter located on the assembly tip as it is moved along the upper gastrointestinal tract. The position is displayed on the computer screen to assist the operator in manoeuvring the tip of the nasoenteric assembly through the stomach and beyond the pylorus.

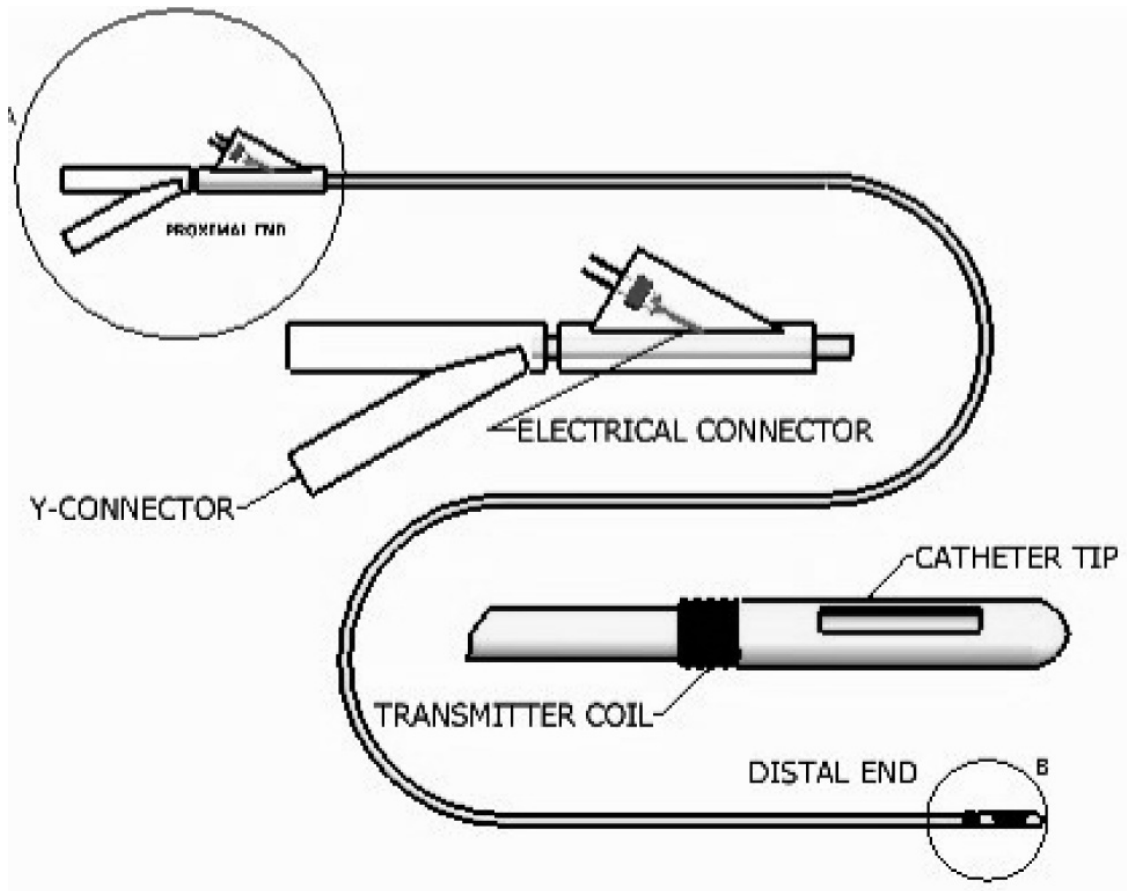


Figure 15.2 Diagram of the Cathlocator™ catheter.

Patient Number	Tube type	Time to Fundus (mins)	Time Duodenum (mins)
1	NG	5:00	
	ND		17:00
2	NG	1:28	
	ND		12:00
3	NG	0:51	
	ND		34:25
4	NG	0:00	
	ND		14:52
5	NG	0:45	
	ND		11:18
6	NG	0:39	
	ND		12:37
7	NG	1:17	
	ND		:16
8	NG	6:01	
	ND		failed
9	NG	1.25	
	ND		5.03
10	NG	3.75	
	ND		14.53

Table 15.2 Time taken to reach the fundus and the duodenum using the Cathlocator™ in critically ill patients

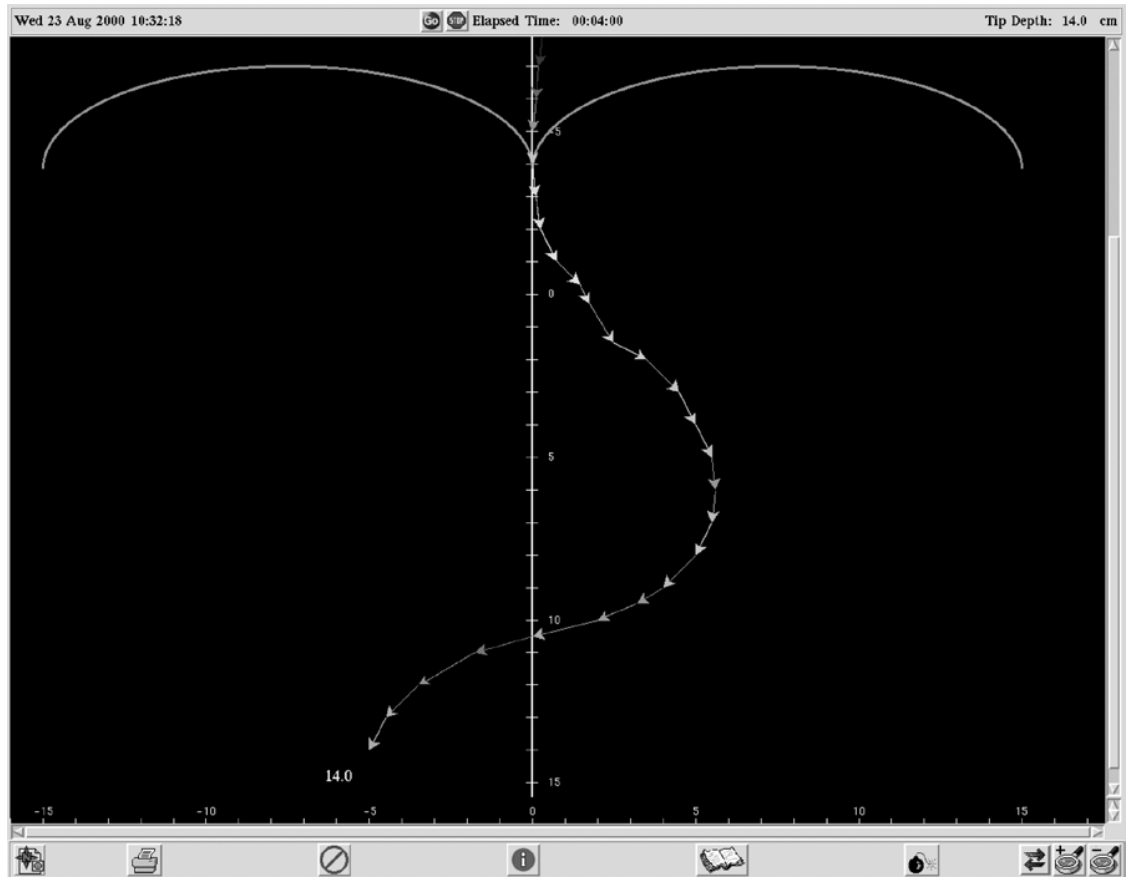


Figure 15.3 Computer screen display, showing tracking of the feeding tube relative to the diaphragm and midline. Position identified at 10 second intervals, represented by arrows.



Figure 15.4 Insertion of Cathlocator™ device into a patient in ICU with a tracheostomy.

15.4 Discussion

Using the Cathlocator™ rapid and accurate placement of post-pyloric feeding tubes was achieved in nine of ten attempts, in eight critically ill patients with large gastric residual volumes. This allowed successful feeding (90% of nutritional goals for two consecutive days (Heyland et al., 1995)) in 6 of the patients. In addition, the Cathlocator™ correctly determined the placement of nasogastric and nasoduodenal feeding tubes in all patients compared with plain abdominal X-ray. Previously, the main barrier to post-pyloric feeding has been the time and technical difficulty in placing a tube beyond the pylorus. The median time taken for transpyloric insertion using the Cathlocator™ was 16 minutes. These findings compare favourably with both the blind intubation technique described by Zaloga, (the “corkscrew” technique), (Zaloga and Roberts, 1998) and an approach utilizing gastric insufflation of air (Salasidis et al., 1998). These three techniques have the advantage of being minimally invasive, so that they can be performed at the bedside without expensive equipment. Although the gastric insufflation with air technique took only two to four minutes to perform (Salasidis et al., 1998), it had a lower success rate (60%). The corkscrew technique has been reported to allow successful placement in up to 92% of patients but is considerably more time-consuming (mean 40 minutes) (Zaloga et al., 1992). Both these techniques are likely to be operator dependent.

The Cathlocator™ appears to have the advantage of increased efficiency and reduced time of insertion. With greater familiarity with the Cathlocator™ equipment, it is likely that the insertion time could be further reduced. A further advantage to the technique is that it allows immediate verification of tube location. Williams *et al* have previously shown that the device discriminates between the positions of a feeding tube above and below the lower oesophageal sphincter (Williams et al., 1996), and that tube depth and deviation from the midline measurements also provide an accurate indication of malposition within the trachea (Williams et al., 1996).

Other approaches currently used for placement of post-pyloric feeding tubes (surgical, fluoroscopic, ultrasound-guided, and endoscopic) (Berger et al., 2002; Hernandez-Socorro et al., 1996; O’Keefe et al., 2003) have significant limitations. Surgical jejunostomy is highly invasive, and is not feasible or practical in many critically ill patients. Radiological placement utilizes expensive equipment and is not generally available at the bedside; additionally fluoroscopy is associated with patient and technician exposure to ionising radiation. Endoscopic and ultrasound-guided nasoenteric tube placement are as effective as fluoroscopy with success rates of 90-95% (Foote et al., 2004; Hernandez-Socorro et al., 1996). They can be performed at the bedside with mean insertion times comparable to those reported in this study (15-16 min). However they require expensive equipment and specialised training, and the logistics associated with finding appropriately trained medical staff frequently delays initiation of feeding. The simplicity of the Cathlocator™ would allow its potential use by other clinicians including nursing and allied health staff. Additional studies are required to ascertain the ease and accuracy with which the Cathlocator™ can be used to place post-pyloric feeding tubes by non-medical staff. There were no adverse events seen during the use of the technique. Modifications to the feeding catheter can potentially increase the risk of problems with feeding such as catheter blockages, or even intestinal perforation. However, the fine electrode does not encroach on the feeding tube and is unlikely to increase the risk of damage or blockage. In addition, once bonded the ends of the catheter are smooth. Bench testing showed that the wiring and bonding become an intrinsic part of the assembly and do not vary the flexibility or stiffness of the assembly. Given the minimal invasiveness, low power output of the equipment and the

extremely low intensity of the magnetic field generated, it is also unlikely that significant physiological effects or interference with medical equipment will occur.

Whilst this pilot study was performed in a small number of patients, the medical and surgical diagnoses of the patients who participated was mixed, suggesting that the Cathlocator™ may provide a feasible alternative for placing post-pyloric feeding tubes in a range of critically ill patients who have slow GE. Further studies are required to establish this capability. Studies involving larger numbers of patients are required to determine the role of postpyloric feeding tubes using the Cathlocator™ system in the overall management of delivery of nutrition to the critically ill patient. Current evidence does not support routine postpyloric delivery of nutrition as this approach has not been demonstrated to be superior to nasogastric delivery, either in terms of success of nutrition or a reduction in the frequency of ventilator associated pneumonia (Ho et al., 2006). Larger studies may demonstrate a benefit. Also it has been suggested that erythromycin is as successful as post pyloric feeding in patients with large nasogastric aspirates (Boivin and Levy, 2001). This also warrants a further study of adequate power. These studies will be facilitated by a more convenient method of placement of a postpyloric tube.

In conclusion, the Cathlocator™ appears to offer a successful, reliable and convenient alternative method for post pyloric tube placement system in critically ill patients. The technique is simple, safe and allows rapid initiation of enteral nutrition with an improvement in delivery of nutrition in those patients who are failing nasogastric feeding. Current evidence suggests that this system should be used to place a postpyloric tube when a patient persistently fails nasogastric feeding despite the administration of prokinetics.

Chapter 16

Conclusion and future directions

16.1 Introduction

Inadequate delivery of enteral nutrition to the critically ill occurs frequently, may adversely affect clinical outcomes, including survival, and usually results from abnormally delayed gastric emptying. The work presented in this thesis provides novel insights into the prevalence, risk factors, pathophysiology and management of suboptimal enteral feeding in the critically ill.

16.2 Previous understanding of nutritional limitations in the critically ill

It is well established that the enteral route of feeding is preferable to the intravenous, but the provision of nutrition by this route is frequently inadequate due to delayed gastric emptying. This is clinically evident by the aspiration of large volumes of residual feed from the stomach during nutrient delivery. Potential sequelae of delayed gastric emptying include malnutrition and regurgitation, pulmonary aspiration and ventilator-associated pneumonia.

While it is clear that feed intolerance is common, the exact prevalence of delayed gastric emptying in critical illness is not known. It is also unclear whether certain diagnostic groups are at higher risk and what other risk factors are important. There is limited understanding of the disturbances in gastrointestinal motility underlying the delays in gastric emptying. When this is determined possible pathogenic pathways may become evident. Finally little is known regarding the optimal methods for management. Prokinetics are widely used with little evidence of benefit.

16.3 Contribution of the work described in this thesis

The studies presented in this thesis are briefly summarised below and their implications outlined.

16.3.1 Feeding practice

An audit of feeding practice in an Australian level 3 intensive care unit (chapter 10) confirmed that the success of enteral feeding was comparable to that in other centres. Administration of nutrition was frequently inadequate, so that at the end of 7 days only about 60% of nutritional goals were achieved. This study accordingly confirmed the significance of the problem. The audit was repeated in 2007 following changes to the feeding protocol based on work presented in this thesis, with evidence of an apparent improvement in nutrient administration. In 20 consecutive ICU subjects, 80% of nutritional goals were achieved in the first 7 days.

16.3.2 Prevalence of delayed gastric emptying

The study examining the prevalence of delayed gastric emptying (chapter 10) was the first to use scintigraphy for this purpose. It is, therefore, likely to provide a more reliable estimate of prevalence than previous studies, which used the paracetamol absorption technique. In this study gastric emptying was delayed in about half of a mixed group of critically ill subjects and was markedly delayed in 20%. This study was, however, limited by relatively small numbers which precluded a comprehensive evaluation of potential risk factors. Insights into the relative importance of risk factors, such as pre-existing diabetes, use of opiates and/or catecholamines,

or hyperglycaemia would help guide the management of ICU patients in a way that would optimise nutrient delivery. There is also no information about the natural history of delayed gastric emptying in the critically ill. Repeated measures of GE during, and after, ICU stay to establish the pattern of recovery of GE and investigate the potential implications of delayed GE on clinical progress and both short and longer term outcomes would be of interest. It is possible that in some patients gastric emptying remains delayed long after ICU discharge and that this impacts on weight recovery and outcome. Repeated scintigraphic measures of GE however are limited by radiation exposure and the logistical difficulties of performing these tests.

16.3.3 Measurement of gastric emptying in the intensive care unit

Research into the prevalence, causes, implications and management of disordered gastric emptying in the intensive care unit is hampered by the capacity to measure gastric emptying simply and accurately in this setting. A breath test technique offers a convenient reproducible measure. The study reported in chapter 9 demonstrated that in this population the breath test technique correlates very well with scintigraphic measurement of gastric emptying. However, it lacks sensitivity in the identification of patients with delayed gastric emptying. Nevertheless, its reproducibility and simplicity renders it an attractive option for cross over studies or for the measurement of the effect of an intervention. The breath test is also a suitable alternative method to measure the changes in GE over time in individual patients. The ¹³C breath test has the added advantage of not exposing the patient to additional levels of radiation.

16.3.4 Antropyloroduodenal motility in the critically ill

Upper gastrointestinal motility has rarely been examined during critical illness. A study described in this thesis (chapter 11) demonstrated several abnormalities including reduced antral and increased pyloric activity, enhanced enterogastric feedback and persistent fasting motility which is comprised of an abnormal amount of retrograde activity. It is as yet unclear which of these abnormalities is the dominant mechanism accounting for slow gastric emptying. These studies are the first to demonstrate that pyloric activity is increased in the critically ill and that this is associated with slower gastric emptying of nutrient. Furthermore, the demonstration that critically ill subjects have enhanced nutrient-mediated enterogastric feedback has fundamental implications for our understanding of the pathogenesis of feed intolerance in this group. It had previously been assumed that slow gastric emptying reflected gastric 'pump' failure. This opens up an exciting area of future investigation that could lead to important therapeutic advances. The enhanced enterogastric feedback reported in this thesis (chapter 11) was in response to a nutrient with a high fat content. It may be important to evaluate the response of gastric emptying in the critically ill to a nutrient with a lower fat content as this may potentially result in less gastric inhibition and thereby increase the success of feeding. As described in chapter 3, the enterogastric feedback loop is under neural and hormonal control, a hormone of substantial interest being CCK. Subsequent to the study reported in chapter 11, CCK concentrations have been measured in the critically ill and both fasting and nutrient stimulated CCK levels are elevated in those with feed intolerance (Nguyen et al., 2007). This raises the possibility that CCK antagonism may prove therapeutically useful. Further studies are needed to determine the reason for the elevated CCK levels. As outlined in chapter 5.2.3.2, cytokines influence CCK release and may be an important cause of feed intolerance.

The observation that fasting motility patterns persist during feeding in the critically ill needs further study, given that the causes and implications of this are unclear. However, the

demonstration that a significant proportion of the phase 3 activity is retrograde in character, and that this is associated with delayed gastric emptying, suggests that the persistence of this motor pattern is deleterious to gastric emptying in critical illness.

Diarrhoea is a common problem in the critically ill, which could be the result of persistent phase 3 activity during feeding. An observational study to establish the relationship of the persistence of fasting motility to the occurrence of diarrhoea and feed tolerance needs to be performed. An investigation of possible causes would also be of interest. Possible culprits include drugs such as narcotics or erythromycin. Bacterial overgrowth is another possible cause. Motilin agonists such as erythromycin stimulate phase 3 activity but it is not known how these agents affect the organisation of APD contractions. However, as they have been demonstrated by studies described in this thesis and others to accelerate gastric emptying, it is possible that this is achieved by reducing retrograde and increasing antegrade activity.

16.3.5 Nutrient absorption

Nutrient absorption during critical illness has hitherto received little attention. The study reported in chapter 12 is the first to demonstrate that glucose absorption is affected in critical illness, independent of gastric emptying. A substantial reduction in both the rate and extent of glucose absorption was shown. This observation has important clinical implications, in particular it implies that improving motility, by using prokinetic agents or nutrient delivery directly into the small intestine, may not normalise nutrient absorption (Schwartz et al., 2002). Studies examining the impact of prokinetics on nutrient absorption are indicated as well as studies to determine if the absorption of other macronutrients are also affected. Notwithstanding the benefits of enteral over intravenous administration of nutrient, there are potentially patients in whom enteral feeding is contraindicated because of reduced absorption. An understanding of the pathogenesis underlying reduced absorption is also needed before appropriate therapies can be instituted. Studies to establish pathogenesis may need to explore histology of small intestinal mucosa particularly looking at enzyme levels.

16.3.6 Management of feed intolerance

16.3.6.1 Prokinetics – Erythromycin

Prior to the work presented in this thesis, erythromycin had been shown to increase antral motility and accelerate gastric emptying in the critically ill. The study described in chapter 13.2 was the first to demonstrate the *clinical* benefits of a single dose of this agent in patients who were intolerant of nasogastric nutrition. As there are safety concerns regarding the use of erythromycin (see chapter 7.5.2) and some evidence in other patient groups that lower doses are equally, or more effective, a further study was performed to compare the effects of 2 different doses of erythromycin. Interpretation of this study may be limited by the relatively small patient numbers. Despite this concern the results were consistent with the hypothesis that a lower dose (70mg IV) was as effective as the standard dose (200mg IV). However, the optimal dose of erythromycin remains unclear and a more precise dose finding study would be worthwhile. The timing of administration is also uncertain. Twice daily dosage is suggested based on the results of the study described in chapter 13.2, but this warrants further evaluation. Following the outcome of these studies, erythromycin administration became part of the feeding protocol in the intensive care unit at the Royal Adelaide Hospital. It is not clear whether efficacy is sustained with continued administration, as down regulation of motilin receptors may occur. A study examining the effect of erythromycin over time is also warranted.

It is still unclear how erythromycin compares to other available prokinetics, principally metoclopramide, in terms of prokinetic activity and risk of adverse effects. Finally, in critically ill patients, the impact of therapy on outcome in terms of weight gain and mortality must be determined; e.g. it is possible that, while erythromycin improves the success of feeding, an increase in the prevalence of resistant organisms, and thus untreatable nosocomial sepsis, may increase overall patient morbidity and mortality. Studies to evaluate this will need to be large and, therefore, multicentre. The potential adverse effects with the use of erythromycin, together with the likelihood that metoclopramide may have a better safety profile, suggests that it is currently prudent to use metoclopramide as the first line agent for feed intolerance in critically ill patients.

16.3.6.2 Prokinetics – Cefazolin

Animal and human studies suggested that cephalosporin antibiotics may have prokinetic effects and these drugs may have a better safety profile than erythromycin. The role of cefazolin as a prokinetic in the critically ill was evaluated and this study is described in chapter 14. Cefazolin had no effect on gastric emptying in this study. Furthermore even though the number of subjects was small, the trend was for gastric emptying to be slower after cefazolin giving little incentive to study this agent further. The dose used in this study was the same as that previously reported to have an effect in humans (Lamport, 1995) but it is possible that this dose was too small to demonstrate an effect.

The above studies reinforce the need for new prokinetic agents to treat delayed gastric emptying in the critically ill. Motilin agonists without antibiotic effect are being developed and hold future promise. As mentioned, CCK antagonists should also be investigated for this indication.

16.3.6.3 Postpyloric delivery of nutrition

A novel technique for insertion of postpyloric tubes was reported in chapter 15. This was a small descriptive study. Further evaluation of this technique may confirm its benefits over endoscopy, or alternative methods for postpyloric tube insertion. Additional research is also required to clarify the place of postpyloric nutrient delivery. In particular it is as yet unclear whether all patients should be fed into the duodenum from the time of their admission to improve nutritional outcomes and reduce the risk of regurgitation and aspiration. Current evidence suggests that if gastric residual volumes remain high despite treatment with prokinetics then a postpyloric tube should be placed, and this could easily, and conveniently, be performed with the Cathlocator™ device.

16.4 Future directions

The work summarised above raises many further questions regarding the administration of nutrition to the critically ill. Studies in this thesis have characterised abnormalities in antropyloroduodenal motility underlying delayed GE. More research is needed to fully clarify the disturbances in gastrointestinal motility associated with critical illness. Abnormalities in proximal stomach motility may contribute to delayed emptying in critical illness and this warrants evaluation. To date proximal stomach motility has not been measured in the critically ill. The coordination between the proximal and distal stomach and small and large intestinal motility are yet to be examined.

In an effort to optimise nutrient delivery, the timing and composition of nutrient should be investigated. It is possible that delays in initiation of enteral administration of nutrition affect subsequent GE (see chapter 5.6) and this should be investigated. Early initiation of feeding may improve the success of subsequent nutrient delivery.

There has recently been interest in the use of carbohydrate administered immediately prior to surgery. This reduces postoperative insulin resistance (Ljungqvist et al., 2002) as well as postoperative muscle loss (Yuill et al., 2005). The relevance of this finding to critically ill patients is unclear, but it is possible that early carbohydrate loading might reduce subsequent metabolic derangement and catabolism. The study described in chapter 11 demonstrated an exaggerated enterogastric feedback response to a high fat meal. The response of the stomach to different macronutrients, such as a predominantly carbohydrate load, may provide insights into the regulation of GE in these patients with the potential to modify nutrient composition during the ICU admission to improve gastric emptying, absorption and subsequent metabolic response.

Many basic questions relating to nutrition in critical illness remain unanswered due to a paucity of high quality clinical trials. These include the optimal timing, amount, route, and composition of nutrition. Improved insights into the pathophysiology are clearly of major relevance in addressing these fundamental clinical questions. An important issue is whether there are particular patient subgroups within the ICU that should be treated differently. For example, enteral delivery of nutrition may be beneficial for some, but not all, patients. Clinical trials to address these questions must be adequately powered and accordingly are likely to be multicentre.

The work in this thesis has contributed significantly to our understanding and treatment of feed intolerance in the critically ill. It has also opened up exciting new directions for future research.

Appendix A

Publications arising from these studies

Chapman MJ, Fraser RJ, Kluger MT, Buist MD, De Nichilo DJ. Erythromycin improves gastric emptying in critically ill patients intolerant of nasogastric feeding. *Crit Care Med.* 2000, 28, 2334-2337.

de Beaux I, Chapman M, Fraser R, Finnis M, De Keulenaer B, Liberalli D, Satanek M. Enteral nutrition in the critically ill: A prospective survey in an Australian intensive care unit. *Anaesth & Int Care* 2001. 29:619-622.

Chapman M, Fraser R, De Beaux I, Creed S, Finnis M, Butler R., Cmielewski P, Zacharkis B, Davidson G, Cefazolin does not accelerate gastric emptying in the critically ill. *Int Care Med* 2003 29:1169-1172.

Young RJ, Chapman MJ, Fraser R, Chorley D, Creed S. A novel technique for nasoduodenal feeding tube placement in critically ill patients. *Anaes and Intens Care* 2005 33; 229-34

Chapman M, Fraser R, Vozzo R, Bryant L, Tam W, Nguyen N, Zacharakis B, Davidson G, Butler R, Horowitz M. Antro-pyloro-duodenal motor responses to gastric and duodenal nutrient in critically ill patients. *Gut*, 2005;54(10):1384-90.

Ritz MA, Chapman MJ, Finnis ME, Butler RN, Cmielewski P, Davidson GP, Rea D, Fraser RL. A single, 70 mg, intravenous dose of erythromycin is as effective as 200 mg in accelerating gastric emptying in the critically ill. *Intensive Care Medicine* 2005;31(7):949-54.

Chapman M, Fraser R, Bryant L, Vozzo R, Nguyen N , Tam W, Zacharakis B, Davidson G, Butler R, Horowitz M. The organization of antro-duodenal pressures in the critically ill – relationship to gastric emptying. *Neurogastroenterology and Motility*

Abstracts:

Chapman, M, Fraser, R, Bartholomeusz, F, Creed, S, Russo, A, Jones, K , Bellon, M , Chatterton, B , Horowitz, M. (2004). Gastric Emptying in the Critically Ill: Relationship between Scintigraphic and Carbon Breath Test Measurement. *Gastroenterology* **126**, A488.

In manuscripts where Dr Chapman was not the primary author she was heavily involved in all aspects of the studies including inception, protocol design, study execution, data analysis and manuscript preparation. None of these studies have been submitted for another higher degree.

Appendix B

Other related publications during candidature

1. **Invited editorial.** Chapman MJ. Gastric Emptying and Nutrition in the Critically Ill. *Critical Care & Resuscitation*. 2003 March.
2. **Invited review.** Chapman, M. J. Nguyen, N. Q. Fraser, R. J. (2007). Gastrointestinal motility and prokinetics in the critically ill. *Curr Opin Crit Care* **13**, 187-94.
3. Ritz MA. Fraser R. Edwards N. Di Matteo AC. Chapman M. Butler R. Cmielewski P. Tournadre JP. Davidson G. Dent J. Delayed gastric emptying in ventilated critically ill patients: measurement by ¹³C-octanoic acid breath test. *Critical Care Medicine*. 2001, 29(9):1744-9.
4. Nind G, Chen W-H, Protheroe R, Iwakiri K, Fraser RJ, Young R, Chapman M, Nguyen N, Sifrim D, Rigda R, Holloway RH. Mechanisms of gastroesophageal reflux in critically ill mechanically ventilated patients. *Gastroenterology* 2005;128:600-606.
5. Nguyen, N. Q., Chapman, M., Fraser, R. J., Ritz, M., Bryant, L. K., Butler, R., Davidson, G., Zacharakis, B., and Holloway, R. H. (2006). Long-standing type II diabetes mellitus is not a risk factor for slow gastric emptying in critically ill patients. *Intensive Care Med* **32**, 1365-70.
6. Nguyen, N. Q., Fraser, R. J., Chapman, M., Bryant, L. K., Holloway, R. H., Vozzo, R., and Feinle-Bisset, C. (2006). Proximal gastric response to small intestinal nutrients is abnormal in mechanically ventilated critically ill patients. *World J Gastroenterol* **12**, 4383-8.
7. Nguyen, N., Ching, K., Fraser, R., Chapman, M., and Holloway, R. (2007). The relationship between blood glucose control and intolerance to enteral feeding during critical illness. *Intensive Care Med* **33**, 2085-92.
8. Nguyen, N. Q., Chapman, M. J., Fraser, R. J., Bryant, L. K., and Holloway, R. H. (2007). Erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness. *Crit Care Med* **35**, 483-9.
9. Nguyen, N. Q., Chapman, M., Fraser, R. J., Bryant, L. K., Burgstad, C., and Holloway, R. H. (2007). Prokinetic therapy for feed intolerance in critical illness: one drug or two? *Crit Care Med* **35**, 2561-7.
10. Nguyen, N. Q., Fraser, R. J., Bryant, L. K., Chapman, M., and Holloway, R. H. (2007). Proximal gastric motility in critically ill patients with type 2 diabetes mellitus. *World J Gastroenterol* **13**, 270-5.
11. Nguyen, N. Q., Fraser, R. J., Chapman, M. J., Bryant, L. K., Holloway, R. H., Vozzo, R., Wishart, J., Feinle-Bisset, C., and Horowitz, M. (2007). Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. *Crit Care Med* **35**, 82-8.

12. Nguyen, N. Q., Mangoni, A. A., Fraser, R. J., Chapman, M., Bryant, L., Burgstad, C., and Holloway, R. H. (2007). Prokinetic therapy with erythromycin has no significant impact on blood pressure and heart rate in critically ill patients. *Br J Clin Pharmacol* **63**, 498-500.
13. Nguyen, N. Q., Chapman, M. J., Fraser, R. J., Bryant, L. K., Burgstad, C., Ching, K., Bellon, M., and Holloway, R. H. (2008). The effects of sedation on gastric emptying and intra-gastric meal distribution in critical illness. *Intensive Care Med* **34**, 454-60.
14. Nguyen, N. Q., Fraser, R. J., Bryant, L. K., Chapman, M., and Holloway, R. H. (2008). Diminished functional association between proximal and distal gastric motility in critically ill patients. *Intensive Care Med*.
15. Nguyen, N. Q., Ching, K., Fraser, R. J., Chapman, M. J., and Holloway, R. H. (2008). Risk of *Clostridium difficile* diarrhoea in critically ill patients treated with erythromycin-based prokinetic therapy for feed intolerance. *Intensive Care Med* **34**, 169-73.
16. Nguyen, N. Q., Fraser, R. J., Bryant, L. K., Burgstad, C., Chapman, M. J., Bellon, M., Wishart, J., Holloway, R. H., and Horowitz, M. (2008). The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Crit Care Med* **36**, 1469-74.

Abstracts

17. Nguyen, N. Q., Ng, M. P., Chapman, M., Fraser, R. J., and Holloway, R. H. (2007). The impact of admission diagnosis on gastric emptying in critically ill patients. *Crit Care* **11**, R16.

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