THE RELATIONSHIP BETWEEN DISTURBED GASTRIC MOTOR FUNCTION AND ENTERAL NUTRITION IN CRITICALLY ILL PATIENTS

A thesis submitted by

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TABLE OF CONTENTS

CHAPTER 2: PATTERNS OF GASTRIC EMPTYING AND MOTOR ACTIVITY IN HEALTHY HUMANS

CHAPTER 3: CONTROL OF GASTRIC MOTILITY AND EMPTYING IN HEALTHY HUMANS

CHAPTER 4: DISTURBANCES OF GASTRIC MOTOR ACTIVITY AND EMPTYING IN CRITICAL ILLNESS.

CHAPTER 5: NUTRITIONAL SUPPORT IN CRITICALLY ILL PATIENTS

CHAPTER 10: IMPACT OF PRE-EXISTING TYPE 2 DIABETES MELLITUS (DM) ON PROXIMAL GASTRIC MOTILITY, GASTRIC EMPTYING AND FEED INTOLERANCE DURING CRITICAL ILLNESS

CHAPTER 11: PROKINETIC THERAPY WITH ERYTHROMYCIN FOR THE TREATMENT OF FEED INTOLERANCE IN CRITICALLY ILL PATIENTS

THESIS SUMMARY

Delayed gastric emptying, that manifests clinically as intolerance to enteral feeding, occurs in over 50% of critically ill patients and has a major impact on patient morbidity and mortality. Despite the recognition that the proximal stomach has a major role in gastric emptying of liquids, only the motor activity of the antro-pyloro-duodenal region has been evaluated in detail. In addition, many of the proposed risk factors for the gastric dysmotility, particularly a prior history of diabetes mellitus, have not been evaluated formally but have been extrapolated from data from non-critically ill patients. The currently available prokinetic drugs, erythromycin and metoclopramide, are considered to be the first line treatment for feed intolerance. However, neither data comparing the effectiveness of these agents nor the data on the effects of combination of therapy in the treatment of feed intolerance are available. The aims of this thesis were, therefore, to examine: (i) proximal gastric motor activity and the association between proximal and distal motility; (ii) the relationship between entero-gastric humoral responses to nutrients, gastric emptying and feed intolerance; (iii) the impact of admission diagnoses, choice of sedations, timing of initiation of feeding, and pre-existing history of diabetes mellitus on gastric emptying and feed intolerance; and (iv) the efficacy of erythromycin, metoclopramide and combination of these drugs in treatment of feed intolerance in critically ill patients.

The current thesis indicates that motor activity is impaired in multiple regions of the stomach in the critically ill. When compared to healthy humans, proximal gastric relaxation was prolonged and fundic wave activity was educed during small intestinal

nutrient infusion in critically ill patients. In addition, simultaneous assessment of proximal and distal gastric motility demonstrated a possible disruption of the motor integration between the proximal and distal stomach. In light of the recent data that suggested a significantly greater proportion of meal distributed proximally in critically ill patients with delayed gastric emptying (Nguyen, *et al.* 2006), the disruption of the gastric motor integration and the prolonged gastric relaxation in response to duodenal nutrients may play a significant role in the pathogenesis of slow gastric emptying during critical illness, especially as liquid formulae.

The entero-gastric hormonal feedback responses were also disturbed during critical illness. Both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations were significantly higher in critically ill patients, particularly those who did not tolerated gastric feeds. The rate of gastric emptying of a liquid meal was inversely related to both fasting and postprandial plasma CCK and PYY concentrations, supporting the potential role of plasma CCK and PYY in the pathogenesis of gastric dysmotility in critically ill patients.

Admission diagnosis, choice of sedative drug and blood glucose control but not the timing of enteral feeds were important factors for delayed gastric emptying and feed intolerance in these patients. In particular, delaying enteral feeding by 4 days had no impact on the rate of gastric emptying, intra-gastric meal distribution, or plasma CCK and PYY concentrations. Contrary to traditional belief, critically ill patients with a pre-existing diagnosis of type 2 DM have only a minor disturbance to the proximal stomach, a relatively normal gastric emptying and are at no higher risk of feed intolerance than those

without DM, suggesting the presence of pre-existing DM 2 in critically ill patients should not influence the standard practice of gastric feeding.

Therapeutically, short-term treatment with low dose erythromycin was more effective than metoclopramide, but the effectiveness decreased rapidly overtime at similar rate as observed with metoclopramide. In patients who failed to response to either agent, treatment with both agents was highly effective in re-establishing feeding success. The use of combination therapy as the initial treatment for feed intolerance was also more effective than erythromycin alone and had less tachyphylaxis. Treatment with erythromycin and metoclopramide, either as a single agent or in combination did not associated with major cardiovascular adverse side effects. Although diarrhoea was a common side effect and was highest with combination therapy, it was not associated with *Clostridium difficile* infection and settled quickly after the cessation of the prokinetic therapy.

In summary, the work performed in the current thesis has provided substantial insights into the understanding of the nature, risk factors, pathogenesis and treatment of disturbed gastric motor function in critically ill patients. Not only do these findings stimulate further research into the mechanisms responsible for gastric dysmotility in critical illness, they also lead to the development of new strategies for optimizing the management of feed intolerance.

STATEMENT OF ORIGINALITY

The work presented 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 2004 and 2006. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution. To the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except when due reference has been made in the text.

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Nam Q. Nguyen

August 2007

DEDICATION

I dedicate this thesis to my dearest parents, Mai and Lựu Nguyễn.

To my dearest wife, Lisa Tang, I am forever grateful for your unconditional love and support.

Kính thưa Cha Mẹ,

Con cám ơn công nuôi dưỡng và dạy dỗ của Cha Mẹ bao năm qua.

Công bằng tiến sỉ này là công sức và sự thành công của Cha Mẹ.

Nguyễn Quốc Nam

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SECTION 1:

LITERATURE REVIEW

CHAPTER 1: OVERVIEW OF THE MACROSCOPIC AND NEURAL ANATOMY OF THE STOMACH

1.1 INTRODUCTION

In health, the stomach is a J-shaped, distensible bag-like organ in continuity proximally with the oesophagus and distally the duodenum. It is located just beneath the diaphragm and to the left of midline. The size of stomach varies from a few hundred millilitres to 2 litres, dependent on age, body habitus, posture and the time since meal ingestion (Langer 1975; Bisaillon and Bherer 1979; Jones 1982). More recently, the traditional anatomical division of the stomach into the cardia, fundus, body or corpus, antrum and the pylorus has been replaced by a functional division (Mayer 1994; Soybel 2005), which integrates both anatomical and functional components (Figure 1.1). Accordingly, the stomach is divided into three main regions: proximal stomach (cardia, fundus and the superior portion of the gastric body), distal stomach (remainder of the gastric body and the antrum) and the pylorus (Mayer 1994; Soybel 2005).

Following meal ingestion, the proximal stomach relaxes to accommodate the meal whilst the distal stomach grinds and triturates ingested material (Mayer 1994). Coordination between antral contractions and those in the pylorus and the duodenum results in the distal stomach emptying gastric contents into the duodenum in a regulated manner (Weisbrodt, *et al.* 1969; Rees, *et al.* 1979; Tougas, *et al.* 1992; Holle, *et al.* 1994). The specialised functions of the stomach are determined to a major extent by the distinct anatomical, electrophysiological and neural properties of different gastric regions, which will be discussed in this chapter.

1.2 MUSCULAR ANATOMY

In keeping with other regions of the gastrointestinal tract, the stomach is composed of four layers: mucosa, submucosa, muscularis propria, and serosa (Ito 1967). The most prominent of these is the muscularis propria, which is composed of 3 layers of smooth muscle that are arranged in a specific orientation (Figure 1.1) (Kelly, *et al.* 1981; Mayer 1994). The distinction between these muscle layers is least obvious proximally and none of these muscle layers completely envelops the entire stomach. Located below the serosa, the longitudinal layer is most prominent in the distal stomach and is continuous with the duodenal longitudinal layer. Proximally, this layer is sparse or absent on the anterior and posterior surfaces. The middle circular layer is prominent in all gastric regions and is electrically isolated from the duodenal circular layer by a thick fibrous septum at the pylorus (Ramkumar and Schulze 2005). Both longitudinal and circular muscle layers thicken as they approach the pylorus (Kelly, *et al.* 1981; Mayer 1994). The inner oblique layer is the least complete and consists of two bands of muscle lying on the anterior and posterior surfaces of the stomach. These two muscular bands of the oblique layer meet proximally at the gastro-oesophageal junction and fan out to fuse with the middle circular layer in the caudal regions of the stomach.

In contrast, the pylorus is composed of two circumferential loops of specialised smooth muscle, the proximal pyloric loop on the antral side and the distal pyloric loop on the duodenal side (Torgersen 1949; Keet 1982; Keet and Heydenrych 1982; Schulze-Delrieu and Shirazi 1983). The pyloric muscular loops are mainly circular smooth muscle and define the anatomical borders of the pylorus. On the lesser curvature, these loops converge into a

prominent knot, consisting of muscle, connective tissue and fat called the pyloric torus (Torgersen 1949, 1954). This structure is further reinforced by antral longitudinal muscle fibers and the mucosal connective tissue. On the greater curvature, the pyloric muscle loops are separated by a groove with a thin wall. Contractions of these pyloric muscle loops shorten and narrow the pyloric segment, leading to obliteration of the pyloric groove and closure of the pylorus (Schulze-Delrieu and Shirazi 1983).

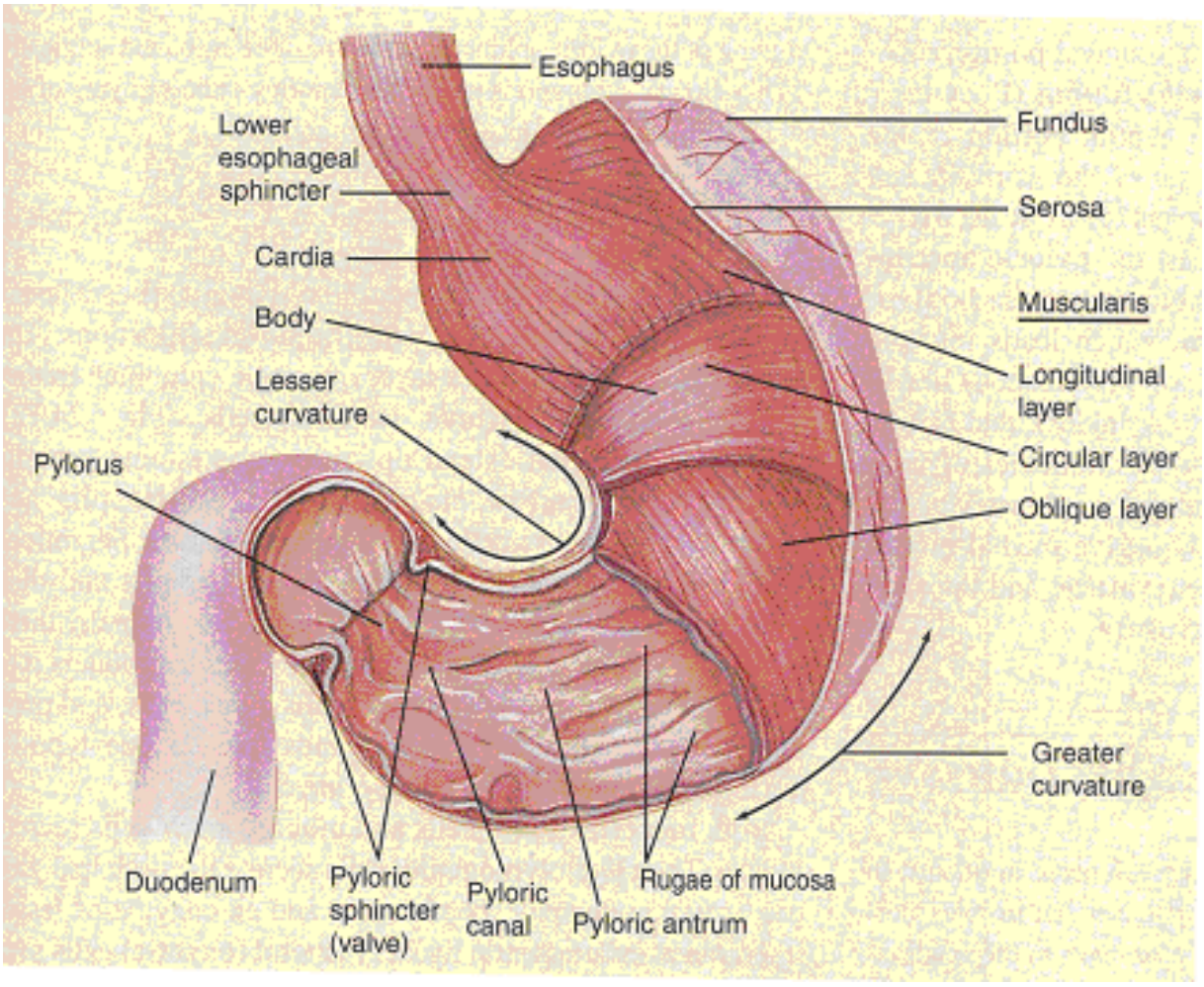


Figure 1.1 External and internal anatomy of the stomach of man (Tortora and Grabowski 1996). Permission to reproduce this figure in this thesis was given by John Wiley & Son Inc.

1.3 MUCOSAL ANATOMY

In contrast to the squamous epithelium of the oesophagus, the gastric mucosa is characterised by glandular columnar epithelium (Ito 1967). In the proximal and distal stomach, the mucosa is freely mobile on the underlying muscularis propria so that when the stomach is empty, the mucosa contracts into thick folds called rugae. As the stomach distends, the rugae flatten and eventually disappear. At the pylorus, the mucosal and submucosal tissues are closely adherent to the underlying pyloric muscle loops through sheets of fibrous tissue. The freely mobile antral mucosa, however, can slide into the pyloric ring and form a watertight mucosal plug during antral contractions (Williams 1962).

The cellular make-up of the gastric glandular epithelium varies in structure in different parts of the stomach. In the fundus and gastric body, the glands contain parietal cells that secrete acid and intrinsic factor, and chief cells that secrete pepsin (Helander 1981, 1988; Helander and Keeling 1993). In the cardia, antrum and the pylorus, the glandular epithelium is composed mainly of mucous cells, which secrete bicarbonate and mucin which protects the mucosa from gastric acid and autodigestive enzymes (Rubin, *et al.* 1968). Furthermore, the neuroendocrine G cells in the antrum secrete gastrin, which stimulate parietal cells to secrete gastric acid (Greider, *et al.* 1972). In total, the gastric mucosa secretes approximately 2500 mL of gastric juice daily containing a balanced proportion of protective mucus and digestive acid and enzymes (Ito 1967; Mayer 1994; Soybel 2005).

The duodenal epithelium is characterised by the presence of villi and crypts, and is firmly attached to the underlying muscularis propria layer by the deep penetrating Brunner's glands (Henry and al-Bagdadi 1986; Liu and Wright 1992; Takahashi 1994). The change in the epithelial cells between the stomach and duodenum gives rise to a trans-mucosal potential difference (TMPD), which can be used to determine the position of the gastro-duodenal junction (Heddle, *et al.* 1988; Houghton, *et al.* 1988).

1.4 ELECTRO-PHYSIOLOGY OF GASTRIC SMOOTH MUSCLE

There are distinct differences in the myogenic properties in the different gastric regions, resulting in different contractile properties (Szurszewski and Code 1970; Szurszewski 1977, 1985; Szurszewski 1994). Thus, in the fundus, contractions are tonic in nature whereas distally, phasic contractions predominate in the body, antrum and pylorus. Furthermore, specialised electrophysiological properties of the gastric smooth muscles allow rapid circumferential propagation of action potentials that result in peristaltic waves involving the entire muscle which migrate from the proximal stomach to the pylorus.

1.4.1 PROXIMAL STOMACH.

The resting membrane potential of the proximal gastric muscle is high (-48mV) and does not exhibit rhythmic fluctuations(Szurszewski 1985; Szurszewski 1994). Because the electrical threshold for muscular contraction is approximately -50 mV, fundal myocytes are in a state of continual partial contraction or tone. The modulation of extrinsic neural or hormonal input

results in minor depolarizations or hyperpolarizations of membrane potential that lead to an increase or decrease in fundic tone. This enables the proximal stomach to relax on the ingestion of food without significantly increasing intragastric pressure, processes known as receptive relaxation and accommodation (Cullen and Kelly 1993). In addition, the tonic fundic contractions also contribute to the redistribution and propulsion of chyme from the proximal stomach into the distal stomach for further digestion and emptying (Cannon 1898; Heddle, *et al.* 1993).

1.4.2 DISTAL STOMACH.

The electrophysiological properties of the smooth muscle in the distal stomach are more conducive to phasic activity (Cullen and Kelly 1993; Szurszewski 1994). The resting membrane potential is more negative (-71 mV), and the smooth muscle exhibits rhythmic depolarization superimposed on the resting membrane potential (El-Sharkawy, *et al.* 1978; Szurszewski 1994). This rhythmic depolarization consists of an initial rapid depolarization followed by a more prolonged plateau potential and is known as electrical control activity (ECA) or slow wave (El-Sharkawy, *et al.* 1978; Szurszewski 1994). In humans, cells along the greater curvature of the gastric body have the highest oscillatory frequency, 3 cycles per minute, and act as the dominant pacemaker that entrains the rest of the stomach (Kelly and Code 1970, 1971; Kelly and La Force 1972). Given that the stomach has no specialized electrical conduction pathway, the slow waves propagate throughout the smooth muscle (Szurszewski 1985; Szurszewski 1994). The slow waves, however, can only propagate distally, but not proximally to the fundus, because of the less negative resting membrane potential of the cells in the proximal stomach (Szurszewski 1985; Szurszewski 1994). The

distal propagation of slow waves is faster circumferentially than along the longitudinal axis (12-45 mm/sec versus 3-6mm/sec) and slightly faster along the greater curvature (Bauer, *et al.* 1985; Publicover and Sanders 1985). This results in well defined rings of depolarization that reach the pylorus simultaneously. The activity of these slow waves is modulated by neuro-humoral factors (Chapter 3).

1.4.3 PYLORUS.

The electrical characteristics of the pylorus differ from those of both proximal and distal stomach. Although there are fewer gap junctions between smooth muscle cells in the pylorus (Daniel, *et al.* 1989; Daniel, *et al.* 2001), there is a dense network of interstitial cells of Cajal (ICC) (Allescher, *et al.* 1989; Daniel, *et al.* 1989), which interact closely with pyloric muscle cells. The frequency of the pyloric slow wave is similar to that of distal stomach (3 cycles per minute). Most antro-pyloric slow waves, however, do not propagate into the duodenum due to the thick fibrous septum (Ramkumar and Schulze 2005).

1.5 INTERSTITIAL CELLS OF CAJAL

Interstitial cells of Cajal are specialised cells that generate electrical slow wave activity in the gastrointestinal tract and are also known as the pacemaker cells (Thuneberg 1982; Thuneberg, *et al.* 1982; Rumessen and Thuneberg 1996). In the stomach, these cells undergo rhythmic depolarizations at an oscillatory frequency of 3 cycles per minute and act as the dominant pacemaker to entrain the rest of the stomach. Interstitial cells of Cajal can be classified into

three groups, based on their location and functions: myenteric, intramuscular and connective tissue septae (Thuneberg 1982; Rumessen, *et al.* 1993; Rumessen and Thuneberg 1996; Song, *et al.* 2005).

Located between the circular and longitudinal muscle layers and most prominent in the gastric corpus and antrum, the network of myenteric ICC is considered to be responsible for the initiation of gastric slow waves that spread into adjacent electrically coupled muscle layers (Cousins, *et al.* 2003). On the other hand, intramuscular ICC form a parallel lattice of cells interspersed between nerve endings, smooth muscle cells in the circular and longitudinal muscle layers and the myenteric ICC network (Burns, *et al.* 1996). This network of intramuscular ICC plays an important role in the cholinergic and nitrergic neuro-transmission from the extrinsic neural modulation onto the pacemaker activity of the myenteric ICC. In mice, the absence of intramuscular ICC in gastric muscles leads to little or no cholinergic and nitrergic neurotransmission (Sivarao, *et al.* 2001). Recently, a regional variation in the density of intramuscular ICC has been observed within the murine stomach, which may explain the regional variation in gastric pacemaker response to neural modulation and thus, the differences in contractile patterns during gastric emptying (Song, *et al.* 2005).

The last group of ICC is located along the surface of circular muscle bundles in the connective tissue septae that separate the muscle bundles (Ward, *et al.* 1990). These septal ICC have been proposed to provide an active propagation pathway for the distribution of slow waves from the myenteric ICC to the muscle layers (Horiguchi, *et al.* 2001).

1.6 NEURAL ANATOMY

The stomach receives two types of innervations (Kyosola, *et al.* 1980; Spencer, *et al.* 1989; Tanaka, *et al.* 2001). Extrinsic innervation relays both motor and sensory information to and from the central nervous system and spinal cord, mainly via the vagus nerve (Spencer, *et al.* 1989; Siaud, *et al.* 1990; Raybould, *et al.* 1991). Intrinsic innervation, on the other hand, is provided by the enteric nervous system and consists of the myenteric and submucosal plexuses (Tanaka, *et al.* 2001; Ward, *et al.* 2004).

1.6.1 INTRINSIC INNERVATION

In the absence of extrinsic input, the enteric nervous system can initiate many physiological motor and feedback reflex responses for the stomach via the submucosal and myenteric plexuses (Reiche, *et al.* 1998; Schemann, *et al.* 2001; Bertrand and Thomas 2004). Each neural plexus consists of a network of afferent neurons, inter-neurons and motor neurons, which contain numerous neuro-transmitters. Excitatory neurons contain acetylcholine, substance P and neurokinin A, whereas inhibitory motor neurones contain nitric oxide and vasoactive intestinal polypeptide (Bornstein, *et al.* 1986; McConalogue and Furness 1994; Johnson, *et al.* 1996; Reiche, *et al.* 1998; Reiche, *et al.* 2000; Schemann, *et al.* 2001). Both excitatory and inhibitory neurons in the myenteric plexus interact closely with the ICC, a mechanism by which the intrinsic nervous system exerts its modulatory action on gastric motor function (Reiche, *et al.* 1998; Schemann, *et al.* 2001; Ward and Sanders 2001).

In contrast to the other regions of the stomach, the myenteric plexus in the pylorus is richly supplied with large ganglia that extend into the duodenum and contain large vesicles of neurotransmitters (Daniel, *et al.* 1983; Wattchow, *et al.* 1987; Wattchow, *et al.* 1988; Daniel, *et al.* 2001). The submucosal plexus in the pylorus, however, does not cross the pylorus into the duodenum, probably due to the thick fibrous septum (Ramkumar and Schulze 2005).

1.6.2 EXTRINSIC MOTOR INNERVATION

The stomach receives innervation from both parasympathetic and sympathetic neurons which comprise the autonomic nervous system (Grundy 1988; Spencer, *et al.* 1989; Raybould, *et al.* 1991; Lefebvre 1993). Parasympathetic innervation from the dorsal motor nucleus of the medulla is provided by the vagus nerve, which divides into posterior and anterior vagal trunks as it enters the abdomen. The anterior vagal trunk divides into anterior gastric and hepatic branches, which innervate the cardia and pylorus respectively (Raybould, *et al.* 1991; Mayer 1994). Similarly, the posterior vagal trunk divides into coeliac and posterior gastric branches. Both anterior and posterior gastric branches give off branches to form the anterior and posterior nerves of Latarjet along the lesser curvature, which provide innervation to the fundus, corpus and antrum (Skandalakis, *et al.* 1980; Skandalakis, *et al.* 1993). Almost all parasympathetic efferent fibers have a low threshold to electrical stimulation, synapse with gastric cholinergic and peptidergic neurons in the wall of the stomach and increase gastric motor activity (Tsubomura, *et al.* 1988; Berthoud and Powley 1993; Travagli, *et al.* 2006). A few efferent fibers, however, have a high threshold to electrical stimulation and release the nitric oxide and vasoactive intestinal polypeptide, which inhibit gastric motor activity

(Furness and Costa 1974; Grundy, *et al.* 1981; Grundy and Scratcherd 1982; Westerman, *et al.* 1989; Furness, *et al.* 1991).

The sympathetic innervation of the stomach originates from neurones locates in the gray matter of the anterior column, from spinal thoracic segments T7 to T8 (Scharoun, *et al.* 1984; Grundy 1988; Mayer 1994). The preganglionic efferent fibers unite to form the greater and lesser splanchnic nerves, which then synapse in the coeliac ganglia. The post-ganglionic efferent fibers follow the left gastric artery to the stomach and form the perivascular intramural autonomic plexuses which generally inhibit excitatory myenteric transmission. A smaller number of sympathetic fibers project directly to the smooth muscle and inhibit gastric motor activity.

1.6.3 EXTRINSIC SENSORY INNERVATION

In the stomach, afferent neural fibers comprise 90% of vagal neurons and outnumber the efferent fibers by tenfold. Similarly, afferent fibers comprise 75% of splanchnic neurons. Together, these afferent fibers provide important feedback information for the regulation gastric function (Grundy 1988). The vagal afferent fibers project sensory input from two types of mechanoreceptors to the Nucleus Tractus Solitarius (NTS) and Area Postrema (AP), which are then relayed to the Dorsal Motor Nucleus (DMN) of the vagus, nucleus ambiguus and other higher cerebral centres (Andrews, *et al.* 1980; Andrews, *et al.* 1980; Andrews, *et al.* 1980; Andrews and Scratcherd 1980). Stimulation of intra-muscular mechanoreceptors by gastric distension activates the NTS and the DMN of the vagus, and is involved in the mediation of gastric tonic activities (Andrews, *et al.* 1980; Andrews and Scratcherd 1980).

On the other hand, the functions of vagal afferent endings from myenteric plexus, also known as intra-ganglionic laminar endings (Nonidez 1936), are less well understood. Integration of the sensory input from these mechanoreceptors has been suggested to enable the central nervous system to incorporate information on gastric wall tension into propagative motor programs during peristaltic sequences or emptying (Berthoud, *et al.* 1991; Berthoud and Powley 1992).

Afferent feedback from the splanchnic nerves carries sensory input from gastric mesenteric and serosal mechanoreceptors to the dorsal horn of the spinal cord (Morrison 1972). In addition to relaying information about the tension on the viscera and forceful contractions, these afferent fibers also mediate perception of visceral pain and extended neural reflexes such as vagovagal, vagosplanchnic and splanchnosplanchnic reflexes (Grundy 1988).

1.7 CONCLUSION

Differences in the anatomical, electro-physiological and neural properties of the proximal stomach, distal stomach and the pylorus underlie the generation of specialised patterns of motor activities in these regions. These patterns are responsible for gastric functions of accommodation, trituration and emptying of ingested food, which occur simultaneously.

CHAPTER 2: PATTERNS OF GASTRIC EMPTYING AND MOTOR ACTIVITY IN HEALTHY HUMANS

2.1 INTRODUCTION

In health, gastric motility is responsible for four activities: (i) reception and storage of ingesta, (ii) mixing of the ingested food with gastric secretions, (iii) trituration of solid components of the ingested food, and finally (iv) transfer of chyme into the duodenum in a tightly regulated fashion (Mayer 1994). These tasks result in optimal digestion and absorption of nutrients by the small intestine, and require closely coordinated and integrated motor activity between the gastric regions and the duodenum (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Houghton, *et al.* 1988). A series of complex neural and hormonal networks are present and interact with each other to ensure that motor activity of various gut regions are regulated carefully.

The aim of this chapter is to describe the patterns of gastric emptying and motor activity in health that occur during fasting and post-prandial states.

2.2 PATTERNS OF GASTRIC EMPTYING

Studies that have examined transpyloric flow in both animals and humans suggest that the stomach empties its contents in a pulsatile fashion (Heddle, *et al.* 1988; Treacy, *et al.* 1990; Anvari, *et al.* 1995; Anvari, *et al.* 1998), and that the characteristics of the flow pulses are modulated by the intra-gastric volume and small intestinal feedback mechanisms (Azpiroz

and Malagelada 1985; Heddle, *et al.* 1989; Lin, *et al.* 1990, 1990; Fone, *et al.* 1991; Heddle, *et al.* 1993; Lin 1994).

2.2.1 PATTERN OF GASTRIC EMPTYING – AN OVERVIEW

With the exception of non-nutrient liquids, gastric emptying of a nutrient meal, either liquid or solid, exhibits a "biphasic pattern" which is characterised by a highly variable 'initial lag phase' and followed by a more consistent 'steady-state phase' (Kelly 1980; Horowitz and Pounder 1985; Houghton, *et al.* 1987; Mayer 1994).

The 'initial lag phase' represents the time required for the stomach to redistribute the ingested content and to grind solids into smaller particles (< 1mm) (Kelly 1980; Ehrlein and Akkermans 1984; Mayer 1994). Thus, the duration of this phase is highly variable and dependent on the properties of the meal, particularly the texture (liquid or solid), viscosity, particle size, specific gravity and nutritional density (Kelly 1980; Ehrlein and Akkermans 1984; Mayer 1994). Without the need to liquefy the meal and its ability to redistribute rapidly throughout the stomach, a liquid meal has much shorter 'initial lag phase' (< 30 minutes) than that of solid meal (Kelly 1980; Ehrlein and Akkermans 1984; Mayer 1994).

Thereafter, during the steady-state phase, regardless of the texture of the meal, the rate of gastric emptying of caloric meals of identical volume become similar (Kelly 1980; Ehrlein and Akkermans 1984; Mayer 1994). This phase is under the control of entero-gastric feedback reflexes and its onset indicates that nutrients begin to empty into the duodenum at a tightly controlled rate of 2-3 kcal/min (Kelly 1980; Ehrlein and Akkermans 1984; Lin, *et al.* 1989; Mayer 1994).

2.2.2 SPECIFIC PATTERNS OF GASTRIC EMPTYING

2.2.2.1 Non-nutrient liquids.

Gastric emptying of isotonic liquids is rapid and obeys first order kinetics with a rate of emptying that is directly proportional to the ingested volume (Hunt and Spurrell 1951; Smith, *et al.* 1984). Thus, the fractional emptying remains fairly constant over the emptying time course, in pulsatile manner (Hunt and Spurrell 1951; Malbert and Mathis 1994; Anvari, *et al.* 1995).

2.2.2.2 Nutrient liquids.

As described above, gastric emptying of nutrient liquids may exhibit a short 'initial lag phase', lasting 5 to 30 minutes, which is followed by a slower steady state phase (Hunt and Spurrell 1951; Smith, *et al.* 1984). The overall rate of liquid nutrients delivered into the duodenum is regulated tightly to a rate of 2-3 kcal per minute and is dependent on the caloric density, osmolarity, viscosity and acidity of the meal (Hunt and Knox 1972; Hunt and Stubbs 1975; Meyer, *et al.* 1985; Meyer, *et al.* 1986; Lin, *et al.* 1989; Lin, *et al.* 1993; Lin 1994). Liquids with high caloric density empty more slowly than those with fewer calories per unit volume, regardless of macronutrient content (Hunt and Stubbs 1975).

A hyper-osmolar liquid meal, consisting mostly of carbohydrates and amino acids, also regulates gastric emptying by its action on intestinal osmo-receptors (Troncon, *et al.* 1983; Lin, *et al.* 1993). Hypertonic glucose solutions have been shown to empty more slowly than iso-caloric, hypotonic glucose polymer solutions (Cooke and Clark 1976; Cooke 1978). Similarly, high viscosity also slows the rate of gastric emptying. Intra-duodenal acid,

particularly large quantities of a weak acid, is also a potent inhibitor of liquid emptying but only in the presence of an intact pylorus (Hunt and Knox 1972; Allescher, *et al.* 1989; Lin, *et al.* 1990).

2.2.2.3 Digestible solids.

The rate of gastric emptying for digestible solid is significantly slower than for liquids, and is related to the more prolonged initial lag phase, up to one hour, during which little or no ingested solids leave the stomach (Weiner, *et al.* 1981; Siegel, *et al.* 1988). Under fluoroscopic imaging, this phase is characterised by extensive mixing and retropulsion in which food particles are ground into smaller particles (Weiner, *et al.* 1981; Siegel, *et al.* 1988). During the subsequent steady-state phase, the rate of emptying follows a linear, zero-kinetic order and gastric contents are emptied into the duodenum at a constant rate, independent of the volume remaining in the stomach (Meyer, *et al.* 1976).

2.2.2.4 Fat.

Although fat exists in liquid form at body temperature, its pattern of emptying is distinct from that of liquids and resembles more that of solids (Meyer, *et al.* 1986; Meyer, *et al.* 1994; Meyer, *et al.* 1996). Using combined scintigraphic and phase-specific labelling techniques to examine the emptying pattern of a mixed meal containing liquid, solid, and fat, the liquid component of the meal was the first to be emptied rapidly out of the stomach (Meyer, *et al.* 1986; Meyer, *et al.* 1994; Meyer, *et al.* 1996). Emptying of solid and fat components of the meal was equally slow and both followed the characteristic initial lag phase of solids (Meyer,

et al. 1986; Meyer, *et al.* 1994; Meyer, *et al.* 1996). Using magnetic resonance imaging, there were marked to-and-fro movements in the antrum during the lag phase that may serve to enhance emulsification of fat (Boulby, *et al.* 1999). Overall, compared to liquid and solid components, there is preferential distribution of fat in the proximal stomach.

2.2.2.5 Indigestible solids.

The patterns of gastric emptying for indigestible contents are determined primarily by the particle size (Meyer, *et al.* 1985). Emptying of indigestible spheres of less than 1 mm in diameter closely resembles that of liquids, whilst emptying of particles between 1-3 mm in diameter is similar to that of solids (Meyer 1980; Meyer, *et al.* 1985; Meyer, *et al.* 1988). Particles larger than 7mm in diameter do not empty during the fed pattern and can only clear from the stomach during gastric late phase 2 and phase 3 of fasting, when the pylorus is widely open.

2.3 PATTERNS OF GASTRIC MOTILITY

The motility patterns of the stomach are complex and differ between the fasting and post-prandial states. In particular, post-prandial motility is tightly regulated to accommodate and store the ingested meal, triturate solid particles, and then progressively empty the meal content into the duodenum (Hunt and Knox 1968; Cooke 1975; Kelly 1980; Mayer 1994). The ability of the stomach to achieve these multiple tasks simultaneously relates to the

distinct differences in the anatomical, electrophysiological and functional properties of various regions of the stomach (Chapter 1), resulting in different patterns of gastric motor activity within the stomach. In general, the tonic characteristics of motor activity in the proximal stomach are tailored to the accommodation and storage of ingested food (Kelly 1980; Mayer 1994), whilst the intense 'contractile' property of the distal gastric motility triturates food particles and empties gastric contents into the small intestine (Kelly 1980).

2.3.1 FASTING GASTRIC MOTOR PATTERNS

During fasting, gastric motor activity consists of a recurring cyclical sequence of motor events known as the migrating motor complex (MMC) (Kelly 1992; Mayer 1994). This characteristic pattern of gastric motility during fasting is most evident in the distal stomach. Each cycle of MMC is arbitrarily divided into three phases of motor pattern with a mean total duration of approximately 100 minutes in dogs (Code and Marlett 1975) and varies from 113 to 230 minutes in humans (Dooley, *et al.* 1992). Approximately 50% of the MMC cycle consists of phase 1, a period of relative motor quiescence and characterised by 1 to 2 low amplitude antral contractions every 5 minutes (Code and Marlett 1975; Collard and Romagnoli 2000). Phase 2 is a period of increasing irregular but phasic contractions and forms 30% to 40% of the MMC cycle. The remaining 10-20% of the cycle is phase 3, characterised by a period of intense, rhythmic, luminally occlusive contractions, at a frequency that is closely related to the pacemaker electrical activity (3 contractions per minute) (Collard and Romagnoli 2000). During this phase, the contractions begin in the gastric body and propagate distally to the pylorus. Before returning to phase 1, there is a short

period of intermittent contractions that may last up to 10 minutes. This period is sometimes known as phase 4 of MMC (Dooley, *et al.* 1992).

In humans, although the proximal gastric motor activity during fasting follows the same pattern of motor event as in the antrum, the different phases of MMC are less recognizable and are separated by a transitional and intermediate period. Furthermore, the nature of proximal gastric contractions is different from those of the rest of the stomach and is characterised by two contractile patterns (Lind, *et al.* 1961; Azpiroz and Malagelada 1984, 1985). The first and predominant type of fundic contractions are slow, sustained contractions up to 6 minutes in duration (Lind, *et al.* 1961), which determine the tone of the proximal stomach and generate the basal intra-gastric pressure (Azpiroz and Malagelada 1984, 1985; Azpiroz 1994). Clinically, the variation in gastric tone is indirectly assessed by electronic barostat and is quantified by registering the changes in the volume of air with the intragastric bag maintained at a low constant pressure, usually 2 mmHg (Azpiroz and Malagelada 1985). Superimposed on these slow tonic contractions are more rapid phasic contractions up to 30 seconds in duration, also known as fundic volume waves (Azpiroz and Malagelada 1984, 1985). The precise function of these fundic volume waves is unknown, but in animals, these fundic waves contribute to the gradual transfer of gastric content to the distal stomach for further digestion and emptying (Cannon 1898).

The contractile pattern of the pylorus during fasting, on the other hand, is almost the reverse of the rest of the stomach. In dogs, the duration of pyloric opening is about 40% during phase 1 and increased to almost 100% during phase 3 of MMC (Rhodes, *et al.* 1966).

In summary, phase 1 of MMC is characterised by little or absence of fundic, antral and pyloric contractions with a partially open pylorus (Rhodes, *et al.* 1966; Code and Marlett 1975; Dooley, *et al.* 1992). In contrast, as phase 3 approaches and develops, antro-pyloro-duodenal contractions increases and high amplitude contractions propagate through the antrum across the widely opened pylorus into the proximal duodenum (Rhodes, *et al.* 1966; Code and Marlett 1975; Dooley, *et al.* 1992). During this intense contractile period, there is an increase in the basal tone of the lower oesophageal sphincter and proximal stomach to prevent reflux of gastric contents back to the fundus and the oesophagus (Gill, *et al.* 1987; Penagini, *et al.* 1996; Penagini and Bianchi 1997; Penagini, *et al.* 1998; Allocca and Penagini 2004; Penagini, *et al.* 2004). The outcome of phase 3, and probably late phase 2, motor events is to empty undigested food particles, mucus, and sloughed epithelial cells from the stomach.

MMC cycles exhibit diurnal variation and are more frequent in women than in men (Wilson, *et al.* 1994). Compared to wakefulness, sleep prolongs phase 1, shortens phase 2 and reduces the frequency of contractions in phase 3 (Wilson, *et al.* 1994). MMC activity is, however, not altered by healthy aging (Fich, *et al.* 1989).

2.3.2 POST-PRANDIAL GASTRIC MOTOR PATTERNS

Following ingestion of food, fasting motor activity is replaced by a different pattern of motility, dependent on the texture and nutrient content of the ingesta (Mayer 1994). In the proximal stomach, fundal tone and fundic waves are at first markedly reduced due to reflex gastric relaxation that maintains a stable but low intra-gastric pressure during ingestion

(Azpiroz and Malagelada 1985, 1985, 1986; Undeland, *et al.* 1998; de Zwart, *et al.* 2007). Receptive relaxation is a reflexive, short lasting relaxation of proximal stomach in response to swallowing (Ahluwalia, *et al.* 1994; Ahluwalia, *et al.* 1996). Receptive relaxation is mediated via the mechanical stimulation of the pharynx or oesophagus, rather than the transfer of food bolus into the stomach (Ahluwalia, *et al.* 1994; Ahluwalia, *et al.* 1996). As ingested food begins to fill and distend the stomach, gastric accommodation further relaxes the proximal stomach so that 80% of the ingested meal is stored in the proximal stomach (Jansson 1969; Abrahamsson 1973). Consequently, intra-gastric pressure is reduced in the first 30 minutes after ingestion with a gradual increase in gastric tone thereafter (Azpiroz and Malagelada 1985, 1986), which does not return to basal levels until all solids have emptied from the stomach (Jansson 1969; Abrahamsson 1973). The increase in gastric tone may play a role in the gradual redistribution of proximal contents to the distal stomach for trituration and in the generation of gastro-duodenal pressure gradient for emptying (Cannon 1898; Heddle, *et al.* 1993).

Post-prandially, the fasting motor patterns in the distal stomach are replaced by irregular phasic contractions of lower wave amplitude, which resemble those of phase 2 of the MMC (Cannon 1898; Kelly 1980; Fone, *et al.* 1991; Heddle, *et al.* 1993; Mayer 1994). This is known as fed motor pattern. The contractile pattern and wave amplitude of these phasic antral contractions are modulated by the consistency and nutritional composition the meal (Rees, *et al.* 1979; Heddle, *et al.* 1988; Houghton, *et al.* 1988; Houghton, *et al.* 1988; Fone, *et al.* 1991; Heddle, *et al.* 1993). More intense antral contractions with higher wave amplitude are observed after ingestion high caloric meal (De Wever, *et al.* 1978; Rees, *et al.* 1979;

Wilson, *et al.* 1994), whilst lower amplitude antral contractions but over a longer duration are elicited after ingestion of highly viscous material (Prove and Ehrlein 1982). Functionally, the outcome of these antral contractions relates to the spatial and temporal relationship between these contractions and the pyloric closure (Kelly 1980; Prove and Ehrlein 1982; Ehrlein and Akkermans 1984; Houghton, *et al.* 1988; Tougas, *et al.* 1992; Malbert and Mathis 1994). Under fluoroscopy, the direction of flow of gastric chyme depends on the depth of the antral constriction and the degree of pyloric sphincter relaxation (Prove and Ehrlein 1982). A deep constriction of the antral wave produces a strong propulsive force whereas a shallow constriction diminishes the forward flow of chyme and promotes retropulsion through the central orifice of the constricting ring (Prove and Ehrlein 1982; Mayer 1994). In particular, propulsion of gastric chyme into the duodenum occurs mainly when the peristaltic wave spreads over the middle of the antrum (Cannon 1898; Carlson, *et al.* 1966; Kelly 1980; Mayer 1994), when the pyloric sphincter and duodenal bulb are relaxed.

In general, this fed pattern persists as long as food remains in the stomach and is related to the nature and caloric content of the meal (Rees, *et al.* 1979; Heddle, *et al.* 1988; Houghton, *et al.* 1988; Houghton, *et al.* 1988; Fone, *et al.* 1991; Heddle, *et al.* 1993). However, the presence of intra-gastric nutrients without the act of swallowing does not always result in a fed motor pattern. In patients who are fed continuously via the nasogastric feeding tube, the fed motor pattern reverts to a fasting pattern in over 50% of patients (Ledeboer, *et al.* 1999). This finding suggests that inhibition of MMC by intra-gastric nutrients is self-limited.

2.3.3 RELATIONSHIP BETWEEN THE PROXIMAL AND DISTAL MOTOR UNIT

Over 100 years ago, Cannon observed in cats that after ingestion of a meal, the proximal stomach relaxed and was followed by slow sustained fundic contractions which gradually propelled gastric content distally (Cannon 1898). As the gastric content moved into the distal stomach, peristaltic antral contractions were evoked to thoroughly triturate the content and facilitate its emptying into the duodenum. Using a combination of barostat and manometric techniques, Heddle et al (1993) demonstrated an integration of fundic, antral, pyloric and duodenal motility during fasting in dogs. During both phase 2 and 3 of the migrating motor complex (MMC), approximately 64% of fundic volume waves were coordinated with clusters of antral waves, and 91% were associated with an inhibition of duodenal wave activity, although there was no relationship between these waves and pyloric contractions (Heddle, *et al.* 1993). Thus, this integrated function of fundic and antral wave activity has been hypothesized to be important in gradual distal transfer of proximal gastric contents for trituration and emptying during meal digestion (Cannon 1898; Heddle, *et al.* 1993). The role of this integration in the clearance of indigestible solids during fasting is unknown.

In humans, because of the technical difficulty in measuring motor events in the proximal stomach, antrum, pylorus and duodenum simultaneously, there are few studies which have examined this and no data regarding the functional integration of the proximal and distal stomach and its role in gastric emptying in humans.

2.4 PATTERNS OF INTRA-GASTRIC MEAL DISTRIBUTION AND ITS RELATIONSHIP WITH GASTRIC EMPTYING

A relationship between gastric emptying of a meal and intra-gastric meal distribution is suggested by observations that: (i) gastric emptying of meal, either liquids or solids, is affected by posture (Hancock, *et al.* 1974; Moore, *et al.* 1988; Horowitz, *et al.* 1993; Anvari, *et al.* 1995; Jones, *et al.* 2006; Steingoetter, *et al.* 2006); and (ii) gastric content, particularly in the distal stomach, is inversely related to the rate of gastric emptying of a nutrient liquid meal (Collins, *et al.* 1988; Urbain, *et al.* 1989).

2.4.1 SOLIDS.

Immediately after ingestion, quantitative scintigraphic examination has demonstrated that the levels of radioactivity are initially maximal in the antrum with a gradual increase in the proximal activity during the initial lag phase (Collins, *et al.* 1988; Urbain, *et al.* 1989). Thereafter in the steady state phase, the levels of radioactivity in the antrum are constant with progressive decreases in activity in fundus (Collins, *et al.* 1991). This is consistent with fluoroscopic data which indicate that solids are initially stored in the proximal stomach and then are delivered to the distal stomach at constant rates for trituration and emptying (Collins, *et al.* 1991).

2.4.2 LIQUIDS.

Liquid meals follow a similar pattern of intra-gastric distribution to that of solids, except for the non-nutrient liquid meals, of which there is less fundic but more antral retention (Pouderoux, *et al.* 1997). As discussed above, this pattern of meal distribution is associated

with rapid gastric emptying (Jones, *et al.* 1995; Pouderoux, *et al.* 1997; Jones, *et al.* 2006). On the other hand, the addition of caloric or lipid content to the ingested liquids promotes greater distribution into the fundus with associated delay in emptying (Edelbroek, *et al.* 1992; Maes, *et al.* 1998; Meyer, *et al.* 1999).

2.4.3 MIXED MEAL

When liquids and solids are consumed together, the solid fraction is preferentially retained in the proximal stomach, whereas the liquid portion is seen in the antrum (Houghton, *et al.* 1988; Collins, *et al.* 1991). Furthermore, the size of the solid meal modifies the emptying rate of liquid by retarding the movement of liquid from the proximal stomach to the antrum and delaying the delivery of liquid to the duodenum (Collins, *et al.* 1991), thereby slowing gastric emptying of the meal.

Current data, therefore, suggest a close relationship between the pattern of intra-gastric meal distribution and gastric emptying. Disturbances in this relationship and the consequences are best recognised in patients with diabetes mellitus, in whom both delayed and rapid gastric emptying have been demonstrated (Campbell, *et al.* 1980; Phillips, *et al.* 1991; Frank, *et al.* 1995; Jones, *et al.* 1996; Schwartz, *et al.* 1996; Kong and Horowitz 1999). In addition to distal gastric dysmotility, diabetic patients with delayed gastric emptying also have excessive proximal gastric relaxation when assessed concurrently with gastric barostat and scintigraphy (Samsom, *et al.* 1995; Undeland, *et al.* 1998). In contrast, in a small subgroup of patients with type 2 diabetes, rapid gastric emptying is associated with impaired proximal gastric relaxation and less proximal retention (Frank, *et al.* 1995; Samsom, *et al.* 1998).

2.5 ROLE OF PROXIMAL AND DISTAL STOMACH IN GASTRIC EMPTYING

Despite the current knowledge of the patterns of motility, emptying and meal distribution, it remains unclear whether the mechanical forces responsible for gastric emptying operate through a "pressure" or "peristaltic" pump mechanism. The "pressure" pump theory hypothesizes that the primary driving force for emptying gastric contents into the duodenum depends on the pressure gradient difference between the stomach and duodenum (Indireshkumar, *et al.* 2000), whilst the "peristaltic" pump theory proposes that propagating high-pressure waves in the distal antrum are the responsible for clearing contents from the stomach (Indireshkumar, *et al.* 2000).

2.5.1 GASTRIC EMPTYING OF LIQUIDS.

Evidence from both animal and human studies suggests the proximal stomach plays a major role in the gastric emptying of liquids. In dogs, resection of the fundus leads to a significant increase in intra-gastric pressure after a meal and a more rapid gastric emptying (Wilbur and Kelly 1973; Wilbur, *et al.* 1974), thereby supporting the "pressure" pump theory. Similarly, selective vagotomy to denervate the fundus and corpus of the stomach results in impaired gastric accommodation, higher intra-gastric pressure and more rapid gastric emptying (Wilbur and Kelly 1973). Furthermore, a linear relationship between intra-gastric pressure and the rate of gastric emptying of liquids has been demonstrated in dogs (Strunz and Grossman 1978; Kelly 1980), by concurrently studying gastric emptying while varying intra-

gastric pressures with a gastric barostat. In contrast, increasing proximal gastric relaxation and inhibition of fundic contractions with gastrin (Wilbur and Kelly 1974) and cholecystokinin (Yamagishi and Debas 1978) is associated with a reduction in intra-gastric pressure and gastric emptying of liquids.

Earlier data suggested that the distal stomach plays little role in the regulation of liquid emptying (Dozois, *et al.* 1971; Mroz and Kelly 1977; Rees, *et al.* 1979). In dogs, the rate of gastric emptying of liquids did not alter after pyloric stenting, antral and pyloric resections (Dozois, *et al.* 1971). Similarly, extrinsic denervation of the distal stomach to abolish antral motility did not alter gastric emptying of liquid (Mroz and Kelly 1977). However, more recent data indicate gastric emptying of liquids is pulsatile in nature, suggesting the involvement of either the antral peristaltic contractions or intermittent pyloric closure or both in the regulation of liquid emptying (White, *et al.* 1984; Treacy, *et al.* 1990; Malbert and Mathis 1994; Anvari, *et al.* 1995; Paterson, *et al.* 2000). Whilst the rate of gastric emptying of liquids has been reported to relate directly to the frequency and force of antral contractions (Camilleri, *et al.* 1985), a large quantity of liquid was found to empty when no antral contractions were present (Stemper 1975). Overall, current evidence suggests that the contribution of the proximal stomach to the regulation of gastric emptying of liquids is likely to be greater than that of the distal stomach.

2.5.2 GASTRIC EMPTYING OF SOLIDS.

Gastric emptying of solids depends predominantly on the distal stomach (Kelly 1980; Mayer 1994). In contrast to liquids, the proximal stomach appears to have a minor role in gastric

emptying of solids. Selective proximal gastric vagotomy does not alter gastric emptying of spheres in dogs (Mroz and Kelly 1977). However, complete gastric vagotomy, which results in denervation of the antrum and weakening of antral contractions, leads to significant impairment of trituration and delayed gastric emptying of solids (Wilbur and Kelly 1973; Mikkelsen, *et al.* 1976; Kaushik, *et al.* 1982; Lawaetz, *et al.* 1982; Shiratori, *et al.* 1985; Taylor, *et al.* 1985; Calabuig, *et al.* 1988).

2.6 CONCLUSIONS

Current data suggest that gastric emptying is a complex process in humans and involves a wide range of gastric motor patterns. These are able to process the highly variable composition of the ingested meal. Overall, liquid and solid nutrient meals elicit different gastric motor responses. The proximal stomach has a major role for the emptying of liquids whilst the distal stomach, in addition to contributing to liquid emptying, is the principle regulator of solid emptying.

The patterns of motility and emptying, however, can only be assessed separately in each gastric region due to the inability of the available techniques to concurrently measure motility from all gastric regions. Although data from animals suggest a close interaction between motor activities of the proximal and distal stomach, similar data in humans on the integration of motor activity between various gastric regions remain lacking and require further study.

CHAPTER 3: CONTROL OF GASTRIC MOTILITY AND EMPTYING IN HEALTHY HUMANS

3.1 INTRODUCTION

The regulatory mechanisms that are responsible for normal gastric motor function are complex and involved the interplay between the smooth muscle cells, interstitial cells of Cajal, intrinsic and extrinsic nerves, gastrointestinal hormones and circulating neurotransmitters. Myogenic control with a pacemaker property is the principle regulatory mechanism responsible for the intrinsic frequency of gastric contractions and their aboral propagation. This intrinsic contractile activity is closely monitored and modulated by the neural and hormonal regulation. The importance of intrinsic innervation, extrinsic innervation and humoral regulation are best highlighted by the intestinal feedback response to nutrients. This complexity in the regulatory mechanism reflects the needs for the stomach to perform multiple tasks simultaneously and to be able to discriminate emptying of liquid and solid. The anatomical details of most of these regulatory systems have been described in Chapter 1. This chapter focuses on the current understanding of control mechanisms that are responsible for normal gastric motor activity and emptying.

3.2 MYOGENIC CONTROL

The distinct electro-physiological properties of gastric myocytes are not only responsible for the generation of proximal gastric tone but also the rhythmic gastric motor activity. The generation of intrinsic electrical control activity (ECA), that consists of periodic electrical

oscillations in resting membrane potential that are characterised by initial depolarization, partial repolarization, a sustained plateau phase lasting up to 20 seconds and repolarization, is particularly important for the intrinsic contractile activity of the stomach (Publicover and Sanders 1985). The rate of ECA depolarization determines the maximum frequency of the intrinsic contractile activity although the contraction that result from the depolarization itself is of insignificant amplitude (Szurszewski 1985; Szurszewski 1994). As discussed in Chapter 1, differences in the frequency of intrinsic ECA within the stomach not only determine the location of the dominant pacemaker for the rhythmic activity but also the spatial and temporal organisation of the peristaltic contractions in the distal stomach (El-Sharkawy, *et al.* 1978). In humans, the intrinsic frequency of ECA is highest in along the greater curvature of the body (3.7 cycle per minute) and gradually reduced in the antrum (1.4 cycle per minute) and pylorus (0.15 cycle per minute) (Kelly, *et al.* 1969; El-Sharkawy, *et al.* 1978). This proximal to distal frequency gradient ensures that the initiation of the gastric contractions always arises in the mid-gastric body and propagates aborally. Furthermore, the propagation velocity of the ECA is greater along the circular axis than the longitudinal axis of the circular muscle layer, resulting in ring contraction (Publicover and Sanders 1985). The progressive acceleration of the ECA as it approaches the pylorus may preferentially transport smaller particle and liquids within the central stream as the bolus moves toward the pylorus. This central streaming function, according to the hydrodynamic model, plays an important role in the sieving function of solid particles and liquid-solid discriminatory emptying.

During ECA depolarization, in order for the resting membrane potential to exceed the excitation threshold and result in a contraction of significant amplitude, inputs from the

nervous and hormonal systems are required. This type of electrical activity is known as the electrical response activity (ERA) (Szurszewski 1985; Szurszewski 1994), which can only occur during the ECA depolarization of the membrane and determines the maximal contraction frequency of the stomach. The neural and hormonal modulations of ECA and ERA activities have been studied in both canines and humans (Szurszewski 1977; El-Sharkawy and Szurszewski 1978; Szurszewski 1978, 1985; Szurszewski 1994). Both cholinergic nerve activity, via acetylcholine, and hormones such as gastrin and cholecystokinin have been shown to increase the duration and amplitude of the ERA and lead to a dramatic increase in phasic contraction of gastric muscle strips (Szurszewski 1977; El-Sharkawy and Szurszewski 1978; Szurszewski 1978, 1985; Szurszewski 1994). On the other hand, sympathetic neural mediators such as nor-adrenaline, and hormones such as neurotensin and vasoactive intestinal polypeptide decrease amplitude and duration of plateau potential and therefore, reduce the amplitude of the contractions (El-Sharkawy and Szurszewski 1978).

3.3 INTRINSIC NEURAL CONTROL

As elsewhere in the gastrointestinal tract, the ‘intrinsic’ gastric motor activity is controlled by the enteric nervous system, which is abundant in the stomach and closely apposed to the interstitial cells of Cajal (Boeckxstaens 2002). Recent data suggest that the neural input responsible for most of the electrical response activity is from the intrinsic nerves (Ward, *et*

al. 2006). Most studies that have characterised the functions of enteric neurones, however, have been performed on intestinal and colonic regions.

Limited data from electrical field stimulation on gastric muscle strips suggest a regional specificity in the neuro-transmission and response of the gastric intrinsic neural activation (Barbier and Lefebvre 1993, 1995; Coulie, *et al.* 1999). In cat, EFS of fundal muscle strips leads to inhibition of nitric oxide synthase, a release of nitric oxide (NO) and an decrease in fundic tone (Barbier and Lefebvre 1993, 1995; Coulie, *et al.* 1999). In contrast, EFS of antral muscle strips increases plateau potentials via a cholinergic pathway and induces a contraction (Morgan and Szurszewski 1980; Morgan, *et al.* 1981). In humans, different responses are elicited after EFS of antral and pyloric muscle strips (Schulze-Delrieu and Shirazi 1983). In contrast to the pure contractile activity in the antrum, there was a biphasic motor response in the pylorus which may relate to the non-cholinergic, non-adrenergic innervation of the pylorus (Anuras, *et al.* 1977).

There are several intrinsic neural pathways, mainly in the myenteric plexuses, within the stomach which appear to be in continuity with the duodenum (Furness, *et al.* 1991; Reiche, *et al.* 1998; Schemann, *et al.* 2001). These ascending and descending pathways mediate several feedback responses, elicited either within the stomach or from the duodenum. The ascending intramural pathway from the duodenum carries feedback information from small intestinal luminal receptors to the stomach and plays an important role in the entero-gastric feedback regulation of antro-pyloric motility. In animals, duodenal transection, but not vagotomy, has been reported to diminish or even abolish both tonic and phasic pyloric responses to either

duodenal EFS (Allescher, *et al.* 1988) or intra-duodenal dextrose infusion (Treacy, *et al.* 1992). In humans, blockade of the entero-gastric feedback on pyloric responses by atropine and hexamethonium but not naloxone suggests that these ascending intramural pathways are cholinergically mediated (Valenzuela 1976; Fone, *et al.* 1989).

The descending intramural pathways within the stomach, on the other hand, appear to be inhibitory in nature and important in the regulation of distal gastric motility. In dogs, circumferential myotomy of the mid-stomach was associated with an increase in antral motor activity after meal ingestion, suggesting the presence of tonic inhibition on the antrum by the fundus (Holle, *et al.* 1994). Similarly, the inhibition of pyloric motility induced by antral distension or EFS can be abolished by antral transection, 2 cm above the pylorus (Allescher, *et al.* 1988). In dogs, the inhibition of pyloric activation by antral EFS is reversed by N-L-arginine-methyl-ester (Allescher, *et al.* 1992), suggesting the involvement of non-adrenergic non-cholinergic transmission, particularly nitric oxide, in the mediation of these inhibitory descending pathways.

3.4 EXTRINSIC NEURAL CONTROL

Extrinsic innervation exerts an important regulatory influence on the 'intrinsic' gastric motor activity governed by the myogenic and enteric neural controls. In particular, the enteric nervous system receives significant parasympathetic and sympathetic inputs from the vagal and splanchnic nerves, respectively.

3.4.1 VAGAL (PARASYMPATHETIC) CONTROL

For many years, the importance of vagal control on both proximal and distal gastric motor activities has been recognised through numerous animal and human studies that have examined the effects of vagotomy and vagal cooling.

3.4.1.1 Afferent vagal control.

The disproportionate amount of afferent fibres within the vagal nerve (Agostoni, *et al.* 1957) suggests that vagal sensory innervation is important in the regulation of gastric motility. In both animals and humans, the afferent output from the gastric mechanoreceptors plays a major role in the mediation of fundo-antral reflex (Andrews, *et al.* 1980; Rao, *et al.* 2002; Rao, *et al.* 2005), in which distension of the proximal stomach evokes phasic motor activity in the antrum and duodenum. Similarly, distension of the antrum, by either a balloon or fluid, is associated with a reduction in fundic tone and proximal gastric relaxation (Piessevaux, *et al.* 2001; Caldarella, *et al.* 2003). These reflexes between the proximal and distal stomach are important in the optimization of intra-gastric distribution of meal (Andrews, *et al.* 1980; Caldarella, *et al.* 2003). In diabetic patients, reduced afferent vagal conduction is associated with impaired proximal gastric relaxation, reduced gastroduodenal motility and poor gastric emptying (Tougas, *et al.* 1992; Samsom, *et al.* 1998).

The vagal afferent fibres that supply the duodenum and the proximal small intestine, on the other hand, play a central role in the enterogastric reflexes, in which the presence of duodenal nutrients, acid or distension lead to fundal relaxation, reduced antral motor activity, increased pyloric contraction and slowing of gastric emptying (Mei 1983; Azpiroz and Malagelada

1984, 1985; Treacy, *et al.* 1992; Stanghellini, *et al.* 1994; Zittel, *et al.* 1994). In response to duodenal balloon distension, the responses are partly blocked or attenuated by disrupting the afferent fibres by either surgical vagotomy or the neurotoxin capsaicin (Azpiroz and Malagelada 1986; De Ponti, *et al.* 1987). As mentioned, these negative feedback responses are unaffected by duodenal transection, supporting the more prominent role of extrinsic innervation over the intrinsic neural pathways in the mediation of these entero-gastric feedback responses (Allescher, *et al.* 1988). Available data in humans suggest that the afferent pathway of these responses is mediated by non-adrenergic, non-cholinergic neurotransmission (Azpiroz and Malagelada 1990, 1990).

3.4.1.2 Efferent vagal control.

In order to tightly regulate gastric motor function, the vagus nerve carries both excitatory and inhibitory efferent fibres to the stomach, which directly exert their output on the intrinsic gastric neural system. In rats, an immunohistochemical study of myenteric c-fos expression has shown widespread functional efferent vagal innervation of the enteric nervous system (Zheng and Berthoud 2000).

3.4.1.2.1 Excitatory input.

The excitatory efferent output of the vagus nerve is mediated by the low-threshold fibers. In dogs, the stimulation of these efferent fibres increases the proportion of ECA which is accompanied by ERA in the antrum as well as improves the antro-duodenal association (Bortoff and Davis 1968; Sarna and Daniel 1975). Consequently, vagotomy results in a

transient disruption of ECA (Kelly and Code 1969), an alteration in the shape of the ERA and a decreased in the overall amplitude of the depolarization (Stoddard, *et al.* 1975).

The impact of the excitatory efferent input is highlighted by studies that involve stimulation and disruption of vagal nerve function. In dogs and ferrets, stimulation of the low-threshold efferent fibers leads to an increase in fundic tone (Allescher, *et al.* 1988), antral motor activity (Ludwick, *et al.* 1969; Walker, *et al.* 1974; Andrews, *et al.* 1980) and pyloric contractions (Miolan and Roman 1978). Conversely, vagal cooling or vagotomy is associated with a reduction in proximal gastric motor activity, a decrease in gastric distensibility and an increase in intragastric pressure after bolus ingestion in animals (Stadaas and Aune 1970; Stadaas, *et al.* 1974; Azpiroz and Malagelada 1987). Atropine, vagal cooling or vagotomy has also been shown to block the increase fundic tone induced by nitric oxide synthase inhibitors (Dickens, *et al.* 2000; Paterson, *et al.* 2000), indicating the additional role nitric oxide in the pre-synaptic region of the vagal cholinergic efferent pathways (Paterson, *et al.* 2000).

The impact of excitatory efferent control on gastric emptying has been demonstrated indirectly through the effects of vagotomy. To date, there has been no study that has examined the effect of stimulating excitatory efferent fibres on gastric emptying. In dogs, disruption of vagal function by either atropine or vagotomy, however, has been shown to slow gastric emptying of both digestible and non-digestible solids (Wilbur and Kelly 1973; Walker, *et al.* 1974; Mroz and Kelly 1977). The mechanisms that underlie the delayed gastric emptying post-vagotomy are unclear but may relate to (i) disruption to the

organisation of antro-duodenal contractions and the onset of post-prandial motor pattern (Hall, *et al.* 1996); and (ii) disturbances to the motor activity of MMC cycles during fasting (relevant to the digestion of non-digestible solids) (Tanaka, *et al.* 2001).

3.4.1.2.2 Inhibitory input.

The structure and threshold to stimulation for these efferent fibres are different and are often referred to as "high-threshold" efferent fibres. In cats, these inhibitory fibres are smaller in diameter and have a higher threshold to stimulation than the excitatory efferent fibres (Martinson and Muren 1963).

It was first observed in dogs that firing of inhibitory fibres was associated with a reduction of gastric motility (Miolan and Roman 1984). Using electrical vagal stimulation, subsequent studies have confirmed that the activation of these high-threshold inhibitory fibres was associated with a reduction in fundic tone and antral motor activity, a decreased in pyloric motility and tone with an increased in transpyloric flow (Edin, *et al.* 1979; Andrews, *et al.* 1980; Allescher, *et al.* 1988; Malbert, *et al.* 1995; Dickens, *et al.* 2000). Consequently, disruption of these inhibitory fibres by vagotomy in dogs was associated with an increase in spontaneous pyloric motor activity with more phasic pyloric contractions (Mir, *et al.* 1977; Telford, *et al.* 1979). As the inhibition-relaxation response induced by electrical vagal stimulation was completely blocked by tetrodotoxin and vagotomy but not atropine, these authors suggested that the inhibitory effects are mediated by non-cholinergic pathways (Mir, *et al.* 1977; Telford, *et al.* 1979).

3.4.2 SPLANCHNIC (SYMPATHETIC) CONTROL

Studies which have examined the influence of splanchnic or sympathetic neural control on gastric motor activity are less numerous. As with the vagal innervation, sympathetic fibres from splanchnic nerves exert their effects on the stomach via their input to the gastric intrinsic neural system. The neural pathways of the sympathetic nervous system emerge from the spinal cord at T5 to T10 and have been highlighted in Chapter 1.

Current data suggest that sympathetic control plays an important role in the modulation of gastric motor function. Electrical stimulation of splanchnic nerves relaxes the proximal stomach and inhibits propulsive contractions of the antro-duodenal region (Kreulen, *et al.* 1983; Andrews and Lawes 1984, 1985), suggesting the inhibitory property of the sympathetic innervation. Similarly, sympathetic activation by stressful stimuli, such as cold pain, is also associated with a reduction in antral contractions (Fone, *et al.* 1990; Stanghellini, *et al.* 1994), an increased in localised pyloric contractions (Fone, *et al.* 1990), and slowing of gastric emptying of both liquid and solids (Thompson, *et al.* 1983; Fone, *et al.* 1990; Stanghellini, *et al.* 1994). The cold-induced slowing of gastric emptying, however, was prevented by a combination of alpha and beta adrenergic blockers, phentolamine and propranolol, suggesting the importance of adrenergic pathways in the mediation of the response (Stanghellini, *et al.* 1994).

Data derived from animal studies indicate a complex integration and interaction between the splanchnic and vagus nerves in the modulation of gastric motor function. Whilst stimulation of the greater splanchnic nerve inhibits vagal evoked fundal and antral contractions in ferrets

(Andrews, *et al.* 1980), splanchnicectomy augments the increase in intragastric pressure evoked by vagal activation in cats (Frankriks and Jonson 1989). Injection of capsaicin into the coeliac and superior mesenteric ganglia attenuates proximal gastric relaxation in response to duodenal balloon distension, indicating activation of vagal sensory pathways by low levels of distension and activation of splanchnic nerve pathways by more intense stimuli (Holzer and Raybould 1992). Similarly, the fundo-antral reflex has been reported to be enhanced after splanchnic nerve section, but markedly reduced after bilateral cervical vagotomy (Andrews, *et al.* 1980; Andrews, *et al.* 1980). Although data from studies of ferrets suggest that the interactions between the vagus and splanchnic nerves occur at the central level (Andrews and Lawes 1984), the complex neural interaction between parasympathetic and sympathetic innervation to the stomach in humans remains unknown. A sudden loss of sympathetic outflow in patients with acute traumatic cord transection at the level of T5 to T10 is associated with an acute gastric dilatation and small intestinal ileus, rather than an increased in gastric motor activity (Fealey, *et al.* 1984). However, the gradual normalization of gastro-duodenal motility with time suggests the compensatory influences of the central and vagal innervation on the regulation of gastric motor function (Fealey, *et al.* 1984).

3.5 HORMONAL CONTROL

Several hormones are involved in the regulation of gastrointestinal motility and gastric emptying, particularly through the entero-gastric feedback responses. Their precise role, however, is not well defined because of the difficulty in separating their pharmacologic from

physiologic effects and the effects of humorally released bioactive peptides from the effects of analogous peptides released at the tissue level, where they may act as neurotransmitters or paracrine substances (Malagelada, *et al.* 1986). The physiological role of a hormone in response to a stimulus is only established if: (i) there is a rise in plasma levels of the hormone in association with the stimulus; (ii) exogenous administration of the hormone at a 'physiological' concentration produces a similar motor response; and (iii) the response is blocked by specific hormone antagonists (Grossman 1974).

Although numerous hormonal candidates have been proposed, not many hormones are able to fulfil all of the criteria suggested by Grossman (1974). The role of some of the strongest humoral candidates involved in the control of gastric motor function will be discussed in this section.

3.5.1 CHOLECYSTOKININ

Cholecystokinin (CCK) is one of the best studied hormonal candidates for involvement in the physiological regulation of gastric motility and emptying. This peptide hormone is secreted by cells in the duodenum and upper jejunum in response to duodenal acid and nutrients, particularly lipids and proteins (Chen, *et al.* 1985; Liddle, *et al.* 1986; Guedon, *et al.* 1988). CCK exists in a number of different molecular sizes and in humans, the best characterised is cholecystokinin-octapeptide (CCK-8) (Liddle, *et al.* 1985; Liddle, *et al.* 1986; Liddle, *et al.* 1988).

3.5.1.1 Effects on proximal gastric motility.

In humans, exogenous CCK-8 infusions that mimic plasma concentrations in the post-prandial range induce significant fundic relaxation and increase proximal gastric compliance (Straathof, *et al.* 1998; McLaughlin, *et al.* 1999). In contrast, fundal relaxation induced by duodenal infusion of nutrients is strongly inhibited by a CCK antagonist, loxiglumide (Mesquita, *et al.*; Mesquita, *et al.* 1997; Zerbib, *et al.* 1998).

3.5.1.2 Effects on distal gastric motility.

Available data from animal studies suggest that the distal stomach, including the pylorus, is an important site of action of CCK. In dogs, the combination of antrectomy and pyloroplasty inhibits the effects of physiological CCK infusions on liquid gastric emptying (Yamagishi and Debas 1978). In contrast, surgical resection of the fundus prevents CCK inhibition of emptying in some studies but has no effect in others (Moran and McHugh 1982).

In animals, except for the study by Kuwahara et al (1986), current data support an inhibitory effect CCK on antral motility. Exogenous administration of CCK-8 leads to dose-dependent inhibitory effects on antral myoelectric activity and phase 3 MMC in the antro-duodenal region of sheep (Romanski 2004). Similarly, exogenous infusion of CCK-8 leads to dose-dependent increases in both frequency and amplitude of phasic and tonic pyloric contractions (Behar, *et al.* 1979; Reynolds, *et al.* 1985; Allescher, *et al.* 1989), responses that can be abolished by a specific CCK antagonist (Allescher, *et al.* 1989).

In human, the effects of CCK on distal gastric motor activity are more consistent. McLaughlin et al observed that the elevation of plasma CCK induced by intestinal lipid infusion was associated with a reduction in antral contractile amplitude, an effect that could be abolished by loxiglumide (McLaughlin, *et al.* 1999). Assessment with either direct endoscopic visualization or manometry (with both pull-through side-hole and sleeve sensor techniques to record pyloric motor activity), has shown exogenous administration of CCK-8 to inhibit antral motility, increase basal pyloric pressure and stimulate isolated pyloric pressure waves (IPPWs) (Fisher and Cohen 1973; Munk, *et al.* 1978; Fraser, *et al.* 1993; Rayner, *et al.* 2000). Antral motility is increased after administration of a specific CCK antagonist (Schwizer, *et al.* 1997).

3.5.1.3 Effects on gastric emptying.

At physiological concentrations, intravenous administration of both exogenous CCK-8 and CCK-3 is associated with a decrease in gastric emptying of both liquid and semi-solid meals in animals and humans (Debas, *et al.* 1975; Moran and McHugh 1982; Liddle, *et al.* 1986; Kleibeuker, *et al.* 1988; Muurahainen, *et al.* 1988). More recently, gastric emptying of solid was significantly delayed and proximal gastric relaxation increased after an oral dose of a novel CCK-1 agonist (Castillo, *et al.* 2004).

Studies that have examined the impact of specific CCK antagonists on gastric emptying in humans, however, have resulted in conflicting data and may related to the different formulation of the CCK antagonists used amongst the studies. All studies that used the intravenous form of the specific CCK antagonists, loxiglumide and lintitript, have reported an

accelerated gastric emptying of both liquid and solid meal, as well as nutrient and non-nutrient meal (Meyer, *et al.* 1989; Fried, *et al.* 1991; Schwizer, *et al.* 1997; Kreiss, *et al.* 1998). On the other hand, the two studies that used the orally administered CCK antagonists, MK-320 and loxiglumide, have failed to demonstrate a change in the gastric emptying rate of either solid or liquid meals, despite a positive effect on gallbladder motility (Liddle, *et al.* 1989; Corazziari, *et al.* 1990).

3.5.1.4 Mechanisms of action.

The effects CCK on gastric emptying are likely to be mediated by action on vagal afferents, because peri-vagal application of capsaicin abolishes the delay in emptying evoked by CCK (Raybould, *et al.* 1988). In rats, intra-arterial or intra-peritoneal CCK increases firing in gastric vagal mechanoreceptor afferents (Schwartz, *et al.* 1997). Furthermore, CCK has been reported to amplify vagal afferent discharges induced by duodenal nutrients, suggesting an integrated response between vagal innervation and CCK (Schwartz, *et al.* 1997). Although devazepide (CCK-A receptor antagonist) inhibits the increase in firing rates of gastric vagal afferents evoked by CCK (Wei and Wang 2000) and attenuates the inhibition of gastric emptying evoked by duodenal lipids , there was no additive effect of devazepide and vagal capsaicin on preventing the inhibitory effects of lipids (Wei and Wang 2000). These findings suggest that CCK acts solely on vagal afferent CCK-A receptors.

In addition, studies in cats have shown that CCK-evoked catecholamine release from splanchnic efferent nerves produces excitatory and inhibitory effects on gastric muscle through action on α_2- and β-adrenergic receptors, respectively (Takahashi and Owyang 1999).

In rats, serotonin receptors (5-$HT_{2A/2C}$) have been postulated to mediate the inhibitory effects on gastric emptying of endogenous CCK released by intestinal lipid infusion (Varga, *et al.* 1999).

3.5.2 PEPTIDE YY

Peptide YY (PYY), a 36-amino acid linear peptide secreted by the endocrine L cells of the small and large bowel (Tatemoto 1982; Adrian, *et al.* 1985; Taylor 1985), is another important hormonal candidate involved in the regulation of gastric emptying and intestinal transit, and is best known for its role in the "ileal-brake" response (Taylor 1985; Wen, *et al.* 1995; Lin, *et al.* 1996; Chen, *et al.* 1997; Cuche, *et al.* 2000). The main form of PYY is PYY 3-36, an N-terminally truncated form of the peptide that has a high affinity for the Y2 receptors in the hypothalamus (Grandt, *et al.* 1994).

In humans, PYY is released in response to food intake and the release is proportional to both the calorie density and meal composition, especially high lipid content (Adrian, *et al.* 1985). After an intra-duodenal meal, plasma PYY increases even before nutrients reach the PYY-containing cells in the ileum, suggesting PYY release is neurally mediated, probably via the vagus (Greeley, *et al.* 1989). In addition to nutrients, PYY release is also stimulated by gastric acid (Gomez, *et al.* 1996), cholecystokinin (McFadden, *et al.* 1992; Lin, *et al.* 2000), and insulin-like growth factor 1 (Lee, *et al.* 1999). Glucagon like peptide 1 has been shown to reduce plasma PYY concentrations (Naslund, *et al.* 1999).

3.5.2.1 Effects on gastric emptying.

In both animals and humans, PYY 3-36 has been consistently reported to inhibit gastric emptying of liquid in a dose-dependent manner (Allen, *et al.* 1984; Pappas, *et al.* 1986; Savage, *et al.* 1987; Pironi, *et al.* 1993; Chen, *et al.* 1996; Naslund, *et al.* 1998; Chelikani, *et al.* 2005). The release of PYY by small intestinal nutrients, especially lipids, is associated with a dose-dependent suppression of gastric emptying of both nutrient and inert liquids, in animals (Raybould, *et al.* 1999; Zhao, *et al.* 1999) and healthy volunteers (Pironi, *et al.* 1993). At physiological concentrations, the administration of exogenous PYY 3-36, into either the systemic circulation or into the CNS via the cisterna magna, also inhibits gastric emptying of liquids in animal (Chen, *et al.* 1996; Chelikani, *et al.* 2005; Moran, *et al.* 2005) and humans (Allen, *et al.* 1984; Pappas, *et al.* 1986; Savage, *et al.* 1987).

In contrast, there are limited data regarding the effects of PYY antagonists on gastric emptying. In rats, PYY antibodies were able to block the slowing of gastric emptying from exogenous PYY 3-36 during fasting, but failed after intestinal lipid infusion (Raybould, *et al.* 1999). Similarly, slow gastric emptying induced by duodenal fat in dogs was prevented by devazepride (CCK-A antagonist) rather than PYY antibodies (Zhao, *et al.* 1999). Together, these findings suggest that (i) there are candidates other than PYY that are involved in the mediation of lipid induced slow gastric emptying; and (ii) PYY may have less impact on gastric emptying than does CCK during nutrient stimulation.

3.5.2.2 Effects on gastric motor activity.

Unlike CCK, the motor mechanisms underlying the slowing of gastric emptying of PYY 3-36 are less well studied. The impact of PYY on proximal gastric motor activity has not been examined in either animals or humans. In pigs, the increase in plasma PYY concentration after ileal infusion of short chain fatty acid was associated with a reduction in the pressure amplitude, but not the frequency, of antral contractions (Cuche, *et al.* 2000).

In humans, elevated fasting PYY concentrations induced by jejuno-ileal bypass were associated with less frequent phase 3 activity of the MMC arise from the antro-duodenal region (Naslund, *et al.* 1998). Similarly, increased PYY levels during nutrient stimulation were associated with a reduction in the frequency of antro-duodenal contractions (Ledeboer, *et al.* 1999) and an increase in IPPW (MacIntosh, *et al.* 1999). Currently, there are no studies that have examined the impact of PYY antibody on gastric motility in humans.

3.5.2.3 Mechanisms of action.

Current data suggest that PYY acts centrally and modulates its inhibitory effects on gastric motor activity via the vagus nerve. It has been postulated that after its release from the gut, the systemic circulating PYY 3-36 crosses the blood brain barrier and exerts its effects by binding to the Y2 receptor in the dorsal vagal complex (Adrian, *et al.* 1985; Chen, *et al.* 1996; Batterham, *et al.* 2002). In rats, the inhibitory effects of PYY on gastric emptying is blocked by bilateral vagotomy (Chen, *et al.* 1996).

3.5.3 OTHER HORMONAL CANDIDATES

Motilin, a 22 amino acid peptide released from endocrine cells in the duodenum and jejunum, is thought to be important in the initiation of gastric phase 3 of MMC in humans (Janssens, *et al.* 1983). Plasma motilin concentrations fluctuate cyclically during the gastric MMC cycle and peak at the onset of phase 3 (Vantrappen, *et al.* 1979; Boivin, *et al.* 1992). Exogenous infusion of motilin induces premature gastric phase 3 activity (Vantrappen, *et al.* 1979) and increases antral contraction (Luiking, *et al.* 1998) and gastric phase 3 activity (Poitras 1984) is temporarily interrupted by motilin antibodies.

The effects of motilin on gastric motility and emptying are dose-dependent. At lower concentrations, exogenous motilin and its analogues stimulate phase 3 activity (Tomomasa, *et al.* 1986) and accelerate gastric emptying of both liquids and solids (Christofides, *et al.* 1979; Christofides, *et al.* 1981) via their action on motilin receptors located on vagal cholinergic nerves (Parkman, *et al.* 1995). Consequently, atropine has been reported to prevent both motilin induced MMC activity and plasma motilin release (McIntosh and Brown 1990). On the other hand, high doses of motilin directly activate smooth muscle motilin receptors (Parkman, *et al.* 1995), induce strong but stationary or even retrograde antral pressure waves (Tomomasa, *et al.* 1986; Tack, *et al.* 1992), and slow gastric emptying of a mannitol meal (Ruppin, *et al.* 1975). Recent data suggest that motilin may also mediate its actions via the serotonergic pathway (Wilmer, *et al.* 1993) as the stimulatory effect of motilin on inducing phase 3 activity was prevented by a co-administered selective 5-HT_3 receptor antagonist.

In humans, a number of other hormones have been proposed to participate in the entero-gastric feedback responses. At physiological doses, secretin slows gastric emptying of both liquid and solid meals via a vagal pathway (Valenzuela and Defilippi 1981; Kleibeuker, *et al.* 1988; Lu and Owyang 1995). Although insulin administration is associated with increased gastric emptying of saline meals (Aylett 1962), it is unclear whether the motor effects are due to insulin or hypoglycaemia. Similarly, exogenous infusion of somatostatin or its analogue, octreotide, has been reported to relax the proximal stomach (Mertz, *et al.* 1995; Bourgeois, *et al.* 1996), inhibit antral motility (Stolk, *et al.* 1995) and reduce gastric emptying of both solid and liquid meals (Maes, *et al.* 1995; Okamoto, *et al.* 1997). Data on the role of gastric inhibitory polypeptide in the regulation of gastric motility and emptying, however, are conflicting (Fried, *et al.* 1989; Meier, *et al.* 2004). Whilst earlier studies demonstrated a dose-dependent inhibitory effect on transpyloric flow and gastric emptying by exogenous gastric inhibitory polypeptide (Hardoff, *et al.*) infusion (Fried, *et al.* 1989; Anvari, *et al.* 1998), recent study by Meier et al (2004) failed to confirm the findings (Meier, *et al.* 2004).

3.6 REGULATION OF GASTRIC EMPTYING BY NUTRIENTS

3.6.1 INTRALUMINAL NUTRIENTS

After ingestion of a meal, the rate of gastric emptying is tightly regulated by the presence of the intra-luminal nutrients in the duodenum and small intestine, a process known as the entero-gastric reflex (Spiller 1990). This feedback response is important in preventing

excessive dumping of gastric contents into the small intestine and allows nutrients to enter the small intestine at a rate of 2 to 3 kcal per minute (Kelly 1980; Ehrlein and Akkermans 1984; Lin, *et al.* 1989; Mayer 1994). In both animals and humans, the degree of gastric motor inhibition has been reported to be dependent on the composition of the meal (Paraskevopoulos, *et al.* 1988), the caloric density of the meal, and the region as well as the length of the intestine that has been exposed to nutrient (Lin, *et al.* 1989, 1990; Lin, *et al.* 1993; Raybould, *et al.* 1998; McLaughlin, *et al.* 1999). These findings suggest that the mediation of nutrient feedback response involves activation of receptors that are specific to the types of 'nutrient' which are located at a specific region of the intestine. In humans, intestinal nutrients slow gastric emptying by inducing proximal gastric relaxation (Tack, *et al.* 1998; McLaughlin, *et al.* 1999; Tack, *et al.* 2002), inhibiting antro-duodenal motility (Heddle, *et al.* 1988; Fone, *et al.* 1989; Heddle, *et al.* 1989), and increasing both pyloric tone and the frequency of isolated pyloric contractions (Dooley and Valenzuela 1988; Houghton, *et al.* 1988; Fone, *et al.* 1989; Heddle, *et al.* 1989). Assessed by either fluoroscopy or ultrasound technique, these motor changes have been reported to be associated with reduced transpyloric flow in animals (Anvari, *et al.* 1998; Anvari, *et al.* 1998; Cuche, *et al.* 2000) and humans (Hausken, *et al.* 1998).

Both neural and hormonal pathways are likely to participate in the mediation of the enterogastric reflexes as the gastric inhibitory effects of the reflexes can be abolished by supra-diaphragmatic vagal cooling (Azpiroz and Malagelada 1986; De Ponti, *et al.* 1987), truncal vagotomy (Stadaas 1980) and the CCK antagonist, loxiglumide (Mesquita, *et al.* 1997; Zerbib, *et al.* 1998). Studies that have examined the impact of neurotransmission

blockade with capsaicin, bethanechol, and adrenergic blockers on the reflexes suggest the involvement of vagal afferent pathways and non-adrenergic, non-cholinergic efferent pathways. The role of hormonal mediation in these reflexes is further supported by observations that the gastric inhibitory effects of duodenal lipids persists even in the denervated stomach (Quigley, *et al.* 1934) and in auto-transplanted gastric pouches (Farrell and Ivy 1926). In addition, the stimulatory effects of intestinal nutrients on pyloric activity can also be diminished by naloxone (Lopez, *et al.* 1991) and specific 5-HT_3 receptor antagonists (Stacher, *et al.* 1990), indicating the involvement of opioid and serotonergic pathways.

3.6.2 INTRAVENOUS NUTRIENTS

3.6.2.1 Blood glucose concentrations

The importance of blood glucose concentration in the regulation of gastric motility and emptying has been recently recognised by the high prevalence of delayed gastric emptying in patients with diabetic mellitus (Horowitz, *et al.* 1986; Horowitz, *et al.* 1996). In humans, acute hyperglycaemia slows gastric emptying of liquids (Fraser, *et al.* 1990), solids (Samsom, *et al.* 1997; Petrakis, *et al.* 1999) and mixed nutrient meals (MacGregor, *et al.* 1976; Samsom, *et al.* 1997) by altering both proximal and distal gastric motor activity. During fasting, hyperglycemia reduces antral phase 3 activity (Barnett and Owyang 1988; Bjornsson, *et al.* 1994). Post-prandially, high blood glucose concentrations induce a greater degree of proximal gastric relaxation (Hebbard, *et al.* 1996), suppression of antral motility (Fraser, *et al.* 1991) and stimulation of pyloric tone and frequency of contractions (Fraser, *et al.* 1991).

In rats, hyperglycaemia has also been reported to impair antro-pyloro-duodenal coordination (Ishiguchi, *et al.* 2002).

Conversely, low blood glucose concentrations induced by insulin infusion have been associated with an accelerated gastric emptying in healthy volunteers (Schvarcz, *et al.* 1997), patients with peptic ulceration (Aylett 1962) and patients with type 1 diabetes mellitus (Schvarcz, *et al.* 1997). The underlying motor mechanisms for the accelerated emptying, however, are unclear. Although insulin-induced hypoglycaemia has no significant effect on antro-pyloro-duodenal motility during fasting in humans (Fellows, *et al.* 1987; Fraser, *et al.* 1991), its impact during nutrient stimulation has not been studied.

Limited current data suggest that blood glucose concentrations may mediate the gastric motor effects via the vagal and hormonal pathways. In rats, insulin-induced hypoglycaemia stimulates gastric vagal activity and increases motor activity, without increasing cardiac vagal activity (Hjelland, *et al.* 2005). High blood glucose concentrations, on the other hand, have been shown to impair vagal nerve conduction (Ward, *et al.* 1971) as well as inhibit vagal efferent activity at the level of dorsal motor nucleus (Takahashi, *et al.* 2003). In addition, acute hyperglycaemia has been reported to be associated with alterations to the plasma concentrations of several gut hormones, such as CCK, GIP, and glucagon like peptide-1(van der Burg, *et al.* 1995; Holtenius, *et al.* 1998; Chaikomin, *et al.* 2005).

3.7 CONCLUSIONS

The complex interplay between the myogenic, neural and hormonal factors in the regulation of gastric motor function is essential for the stomach to perform multiple tasks simultaneously during digestion. The combination of the gastric smooth muscle cells, interstitial cells of Cajal and the intrinsic neural plexuses form the basis for the intrinsic gastric myo-electrophysiology and motor activity. The subsequent input from extrinsic neuro-hormonal modulators, in response to stimuli from the distal gastrointestinal tract, is critical for the precise sequencing of motor patterns required to the digestion and transit of the specific meal. In particular, intact vagal function and entero-gastric hormonal response are necessary for the normal gastric motor function. Blood glucose control is also important in the regulation of gastric emptying, though the underlying mechanisms are unknown.

CHAPTER 4: DISTURBANCES OF GASTRIC MOTOR ACTIVITY AND EMPTYING IN CRITICAL ILLNESS.

4.1 INTRODUCTION

Impaired gastric motor function and slow gastric emptying are common during critical illness and manifest clinically as intolerance to gastric feeding. Gastric dysfunction in these patients is important clinically as it is associated with higher mortality and morbidity (Montejo 1999; Mutlu, *et al.* 2001). It is unclear whether the adverse outcomes reflect the nature and severity of the patient's underlying illnesses or are related to the complications of feed intolerance. Nevertheless, in order to optimize enteral nutritional support in critically ill patients, it is important to understand the nature of gastric motor dysfunctions as well as factors that are associated with impaired gut function.

This chapter summarizes the current understanding of disturbed gastric motor function in critically ill patients, and its consequences on (i) patient's outcomes and (ii) the delivery of enteral nutrition. Current strategies to overcome gastric dysmotility in this group of patients in order to improve delivery of enteral nutrition are also discussed.

4.2 PREVALENCE OF DISTURBED GASTRIC MOTOR ACTIVITY IN CRITICAL ILLNESS

Disturbances in gastrointestinal motor activity occur in up to 70% of the critically ill patients who require mechanical ventilation (Heyland, *et al.* 1996; Tarling, *et al.* 1997; Kao, *et al.* 1998; Ritz, *et al.* 2001). This has a significant impact on the success of delivery of enteral

nutrition (Montejo 1999; Mutlu, *et al.* 2001). In a large, multi-centre, prospective survey, indicators of upper gut dysmotility such as high gastric residual volumes (GRV), vomiting, reflux and aspiration occurred in two thirds of enterally fed patients (Montejo 1999). In contrast, the motility of the small intestine and colon is less commonly affected, with only between 9% and 16% of critically ill patients found to have absent bowel sounds, abdominal distension, diarrhoea or constipation (Montejo 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; Montejo, *et al.* 2002).

The percentage of critically ill patients with delayed gastric emptying varies from 40% to 80%, and depends on factors such as admission diagnosis as well as the techniques used to assess gastric emptying (Heyland, *et al.* 1996; Tarling, *et al.* 1997; Kao, *et al.* 1998; Ritz, *et al.* 2001). Using gastric scintigraphy, up to 80% of critically ill patients admitted with head injury have slow gastric emptying (Kao, *et al.* 1998). In contrast, delayed gastric emptying occurs in only 40% to 50% of patients in unselected cohort, when assessed by either the paracetamol absorption test or ^{13}C-octanoic acid breath test (Heyland, *et al.* 1996; Tarling, *et al.* 1997; Ritz, *et al.* 2001).

4.3 CHARACTERISTICS OF DISTURBED GASTRIC MOTOR ACTIVITY IN CRITICAL ILLNESS

The motor dysfunctions that underlie slow gastric emptying in critically ill patients are poorly defined and only the motility of the antro-pyloro-duodenal region has been evaluated in detail

(Dive, *et al.* 1994; Dive, *et al.* 1994; Dive, *et al.* 1995; Heyland, *et al.* 1996; Bosscha, *et al.* 1998; Dive, *et al.* 1999; Dive, *et al.* 2000; Chapman, *et al.* 2005). Based on findings from these studies, impaired gastric emptying in critical illness has largely been attributed to 'pump failure' associated with disturbed antral motility (Fennerty 2002).

4.3.1 DISTAL GASTRIC ABNORMALITIES

During fasting, gastric inter-digestive motor activity (MMC) in the antro-duodenal region is significantly shorter in mechanically ventilated, critically ill patients than in controls (32 minutes versus 101 minutes, $P<0.01$) (Bosscha, *et al.* 1998). In part, this appears to relate to a virtual absence of phase 2 of MMC and a marked reduction in antral pressure waves (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005). In these patients, the lengths of phase 1 and 3 did not differ significantly from those of healthy volunteers (Bosscha, *et al.* 1998).

Post-prandial motor activity is also abnormal in most patients during intra-gastric feeding, with persistence of gastric inter-digestive pattern and less than 10% of phase 3 of MMC originating in the stomach (Bosscha, *et al.* 1998). During an 84 kcal/hr gastric tube feed in a small observational study, a persistent fasting pattern was observed in one half of the patients and a mixed pattern of fasting and post-prandial motility was seen in the other half (Bosscha, *et al.* 1998). The number of antral pressure waves (Dive, *et al.* 1994; Chapman, *et al.* 2005) and antral motility index (Bosscha, *et al.* 1998) are also markedly reduced in critically ill patients during gastric meal. There is a negative correlation between the antral motility index and gastric retention during gastric feeds (Bosscha, *et al.* 1998).

4.3.2 PYLORIC ABNORMALITIES

More recently, fasting and nutrient-stimulated pyloric motility have been evaluated in critical illness (Chapman, *et al.* 2005). During fasting, pyloric tone and the frequency of isolated pyloric pressure waves (IPPWs) were similar between patients and healthy subjects, and did not change during bolus administration of nutrient into the stomach (Dive, *et al.* 1994; Chapman, *et al.* 2005). During duodenal nutrient stimulation, however, the frequency of IPPWs increased significantly compared to fasting and was greater than that seen in healthy subjects (Chapman, *et al.* 2005). Similarly, the pyloric tone of critically ill patients during duodenal nutrient stimulation was significantly higher than that of healthy subjects. There was an inverse correlation between pyloric motor activity and gastric emptying, as assessed by ^{13}C-octanoic acid breath test (Chapman, *et al.* 2005). These findings suggest that the increase in localised pyloric motor activity may contribute to the slowing of gastric emptying in critical illness.

4.3.3 DUODENAL ABNORMALITIES

During both fasting and duodenal nutrient stimulation, the frequency of duodenal contractions in critically ill patients is similar to that of healthy subjects (Bosscha, *et al.* 1998; Chapman, *et al.* 2005). The organisation of the duodenal contractions in these patients, however, is markedly abnormal with approximately 50% of these contractions being propagated in retrograde manner (Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005). In-coordination of duodenal motility with increased retrograde contractions has been reported to be associated with impaired trans-pyloric flow and slowing of gastric emptying (Ehrlein 1988; Fone, *et al.* 1989; Fone, *et al.* 1990). It has also been suggested that disruption

to the organization of duodenal contractions in critically ill patients may also contribute to duodeno-gastric reflux and thereby, bile induced oesophagitis in addition to the effects on gastric emptying (Dive, *et al.* 1999; Wilmer, *et al.* 1999). Consistent with this, duodeno-gastric reflux is common in patients receiving either gastric or post-pyloric feeds (Dive, *et al.* 1999; Wilmer, *et al.* 1999). Currently, there are no data regarding the impact of abnormal duodenal motility on the pathogenesis of delayed gastric emptying and bile induced oesophagitis.

4.3.4 PROXIMAL GASTRIC MOTOR ACTIVITY

To date, most studies in critical illness have focused on the distal "pump-failure" and the overall gastric emptying. Whilst enteral nutrition is delivered as a liquid formulation in critically ill patients and the proximal stomach plays a major role in liquid gastric emptying in humans (Kelly 1980), there are no data on the motor activity of the proximal stomach in these patients. Furthermore, data on intra-gastric meal distribution as well as the relationship between the proximal and distal gastric motor activity in gastric emptying of these patients are also lacking. The understanding of proximal gastric motility in these patients would not only shed light into the pathogenesis of the dysmotility but also its relationship to gastro-esophageal reflux disease during critical illness.

4.3.5 ENTERO-GASTRIC FEEDBACK RESPONSES

In humans, gastric emptying during nutrient stimulation is highly modulated by an entero-gastric feedback responses (Cooke 1975; Azpiroz and Malagelada 1985; Lin, *et al.* 1989,

1990; Horowitz, *et al.* 1994). Recently, entero-gastric feedback modulation of disturbed gastric motility in critically ill patients has been studied by Chapman and colleagues (Chapman, *et al.* 2005). While duodenal nutrient stimulation at 1kcal/min did not alter distal gastric motor activity in healthy subjects, there was a significant suppression of antral pressure waves and stimulation of both tonic and phasic pyloric pressures (Chapman, *et al.* 2005). These findings suggest that the gastrointestinal tract of critically ill patients responds to small intestinal nutrients differently from normal and the sensitivity of entero-gastric feedback response to small intestinal nutrients in critical illness are enhanced. The underlying factors responsible for the heightened sensitivity of entero-gastric feedback are unknown and warrant further investigation.

4.3.5.1 Humoral activity of entero-gastric feedback

Currently, data regarding the humoral activity of the entero-gastric feedback in response to small intestinal nutrients are limited. Recent data suggest that the concentration of gut hormones that are involved in the regulation of gastric emptying, via the entero-gastric feedback, may also be abnormal (Nematy, *et al.* 2005). In health, PYY is released from the distal small intestine in response to luminal nutrients and inhibits both gastric emptying and small intestinal transit. During fasting, plasma PYY concentrations in critically ill patients are elevated in the first week of admission and normalise after 3 weeks (Nematy, *et al.* 2005). Ghrelin is an enterogastrone that stimulates gastric motility and increases gastric emptying (Dornonville de la Cour, *et al.* 2004; Murray, *et al.* 2005; Tack, *et al.* 2005). In critically ill patients, plasma ghrelin has been shown to be reduced during fasting, and returned to normal level as the patient recovers from their illness (Nematy, *et al.* 2005).

Together, these data suggest that enhanced entero-gastric feedback response may be important in the pathogenesis of slow gastric emptying in critical illness, and the underlying mechanism may relate to the abnormal humoral factors such as gut hormones. These areas warrant further investigation in order to develop therapeutic strategies for this common problem.

4.4 POTENTIAL FACTORS CONTRIBUTING TO DISTURBED GASTRIC MOTOR FUNCTION

A number of factors including mechanical ventilation, drugs (especially opiates and catecholamines), hyperglycaemia, shock, circulating inflammatory cytokines and the admission diagnosis have been implicated in the aetiology of slow gastric emptying in critically ill patients. The majority of these factors, however, have been inferred from studies performed in either animals (Dubois, *et al.* 1975; Lodato, *et al.* 1999; Emch, *et al.* 2000) or non-critically ill population (Mittal, *et al.* 1986; Crighton, *et al.* 1998; Hammas, *et al.* 1998; Yuan, *et al.* 1998; Hammas, *et al.* 2001). Thus, the data supporting a major role of these factors in critical illness are limited (Mutlu, *et al.* 2001). In addition, dysfunction of interstitial cells of Cajal, which act as the pacemaker for gastrointestinal motor activity, has also been suggested as a primary factor underlying the dysmotility (Hagger, *et al.* 1997) as the frequency and site of initiation of MMC in critically ill patients is frequently abnormal. There are limited data to support this speculation (Fennerty 2002) and further investigations are warranted.

4.4.1 MEDICATIONS

A number of drugs used in the management of critically ill patients could potentially contribute to the dysmotility of critical illness.

4.4.1.1 Sedatives

Sedation is essential for almost all patients who receive mechanical ventilation and the contribution of agents such as morphine and midazolam is thought to be significant (Mutlu, *et al.* 2001; Fennerty 2002). Both morphine and pethidine enhance proximal gastric relaxation, increase pyloric tone and retrograde duodenal contractions, stimulate small intestinal phase 3 activity, reduce the number of antral contractions and slow gastric emptying in humans, via their actions on the μ opioid receptors (Mittal, *et al.* 1986; Crighton, *et al.* 1998; Yuan, *et al.* 1998). The benzodiazepine, midazolam, increases the duration and amplitude of phase 3 pressure waves in the duodenum without affecting phase 3 frequency and reduces gastric emptying (Inada, *et al.* 2004). In critically ill patients, the use of opioids is associated with both gastric dysmotility (Heyland, *et al.* 1996; Bosscha, *et al.* 1998) and slow emptying (Heyland, *et al.* 1996). More importantly, there is a dose dependent relationship between sedation with morphine and midazolam and an increased risk of high gastric residual volume (GRV), gastro-esophageal reflux and aspiration (Montejo 1999; Mentec, *et al.* 2001; McClave and Snider 2002; Metheny, *et al.* 2004; Metheny, *et al.* 2006). The importance of opioid sedation in delayed gastric emptying during critical illness is further supported by the reduction in gastric residual volumes, feed intolerance and the frequency of aspiration pneumonia in critically ill patients sedated with morphine and midazolam but who received

also enterally administered naloxone, a μ-opioid receptor antagonist (Meissner, *et al.* 2003; Mixides, *et al.* 2004).

Alternative sedative drugs such as propofol are commonly used but the effects of these agents on gastric emptying and motility are less well defined (Jellish, *et al.* 1995; Hammas, *et al.* 1998; Hammas, *et al.* 2001; Chassard, *et al.* 2002; Inada, *et al.* 2004; Memis, *et al.* 2006). In healthy subjects, low doses of propofol have no effect on gastric emptying (Hammas, *et al.* 1998). In critically ill patients with head injury, who have a high risk of slow gastric emptying, replacement morphine and midazolam with propofol had no effect on the prevalence of delayed gastric emptying (McArthur, *et al.* 1999). There are no studies that have examined the impact of propofol on gastric emptying, intragastric meal distribution and development of feed intolerance in critically ill patients without head injury, nor data comparing propofol with morphine and midazolam. In addition, the effect of propofol on either proximal or distal gastric motor activity is not known.

4.4.1.2 Inotropic agents

Both endogenous and exogenous catecholamines have been shown to impair upper gastrointestinal motor function of animals and humans (Dubois, *et al.* 1975; El-Sharkawy and Szurszewski 1978; Bech, *et al.* 1982; Bech, *et al.* 1984). In critical illness, catecholamines are frequently used to support blood pressure, and both adrenaline and nor-adrenaline reduce antral motility and inhibit gastric emptying in these patients via their action on β-adrenergic receptors (Bosscha, *et al.* 1998; Mentec, *et al.* 2001). Similarly, dopamine is associated with a reduction in antral contractions, a shortens MMC duration and a delayed gastric emptying

(Dive, *et al.* 2000). Therefore, inotropic therapy may also be an important contributor of gastric dysmotility in these patients.

4.4.2 NATURE AND SEVERITY OF ADMISSION DIAGNOSIS

In critically ill patients, gastrointestinal function may be influenced by the admission diagnosis. The concept that admission diagnosis is an important determinant of gastric emptying originates from the observation that the prevalence of impaired gastric emptying and feed intolerance is higher in defined groups of critically ill patients. The prevalence of delayed gastric emptying and feed intolerance in patients admitted with head injury and burns is as high as 80% (Hu, *et al.* 1993; Kao, *et al.* 1998; McArthur, *et al.* 1999; Mutlu, *et al.* 2001). These data are supported by studies in rats, in which raised intra-cranial pressure is associated with impaired gastric motility and slow emptying (Matthews, *et al.* 1988; Livingston, *et al.* 1991; Kacker, *et al.* 1999). Similarly, in rats, thermal injury relaxes the fundus, reduces antral motility and slows gastric emptying (Chen, *et al.* 1982; Alican, *et al.* 1995). These thermal effects were associated with increased sympathetic and opioid mediate neural activity, together with release of systemic inflammatory cytokines (Alican, *et al.* 1995). Apart from these well characterised patients, data on the incidence of delayed gastric emptying in patients with other diagnoses such as sepsis and multi-trauma, however, are lacking.

Although it is generally believed that patients who have a greater illness severity are at a higher risk of delayed gastric emptying and feed intolerance, the relationship between illness severity and impaired gastric emptying is controversial. Thus, illness severity, as assessed by

Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Simplified Acute Physiology score or Sequential Organ Failure Assessment (SOFA) score did not correlate with either the rate of gastric emptying or the development of feed intolerance (Heyland, *et al.* 1996; Mentec, *et al.* 2001; Ritz, *et al.* 2001). This probably reflects, at least in part, the imprecision of the measuring variables used to assess illness severity. In addition, statistical review of these trials suggests that they may not have sufficient power and the findings may reflect a type 2 error (Doig and Simpson 2005; Doig, *et al.* 2005).

4.4.3 BLOOD GLUCOSE CONCENTRATION

There has been an increased interest in the effects of elevated blood glucose concentration during critical illness for a number of reasons. First, hyperglycemia is uniformly present during critical illness (Boord, *et al.* 2001), mainly as a consequence of the excessive release of counter-regulatory hormones and inflammatory cytokines (O'Neill, *et al.* 1991; McCowan, *et al.* 2001). Second, marked hyperglycemia is associated with increased infection-related morbidity and mortality (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003; Krinsley 2004). Meticulous blood glucose control with insulin therapy has been shown to reduce in-hospital mortality of both surgical and medical critically ill patients (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003; Krinsley 2004). Third, blood glucose has been demonstrated recently to exhibit pro-inflammatory effects by increasing oxidative stress through increased free radical production and reduced nitric oxide bioavailability (Low, *et al.* 1997), which is a key transmitter in the regulation of gastrointestinal motor function (Kellow et al, 1999). Whilst hyperglycemia impairs gastric motility and slows gastric emptying in healthy subjects and diabetic patients (MacGregor, *et al.* 1976; Fraser, *et al.* 1990; Hebbard,

et al. 1996), the impact of elevated blood glucose concentrations on gastric motor function and the development feed intolerance during critical illness is unknown and warrant further investigation.

4.4.4 NUTRITIONAL DEPRIVATION

The absence of nutrients from the gut lumen can have major effects on gastrointestinal motility. In healthy volunteers, gastric emptying is markedly delayed after only 4 days of fasting (Corvilain, *et al.* 1995). This effect is seen especially in patients with anorexia nervosa (Dubois, *et al.* 1979; Saleh and Lebwohl 1980; Rigaud, *et al.* 1988; Hutson and Wald 1990), but is also observed in patients with other chronic diseases (Russell, *et al.* 1983; Stacher, *et al.* 1986; Hutson and Wald 1990). In a variety of diseases, both acute and chronic nutrient deprivation are associated with impaired gastric motor function (Russell, *et al.* 1983; Stacher, *et al.* 1986; Hutson and Wald 1990). Similarly, the chronic nutrient deprivation and malnutrition in patients with anorexia nervosa and chronic illness is also associated with slow gastric emptying (Dubois, *et al.* 1979; Saleh and Lebwohl 1980; Rigaud, *et al.* 1988; Hutson and Wald 1990). Adequate re-feeding in anorexic patients, however, is associated with normalization of gastric emptying (Rigaud, *et al.* 1988).

In critically ill patients, frequent delays in initiating enteral feeding result in nutritional deprivation being common in these patients (Adam and Batson 1997; De Jonghe, *et al.* 2001; Barr, *et al.* 2004). However, the impact of low gut nutrient exposure on gastric motor function in these patients is unknown.

4.4.5 MECHANICAL VENTILATION

Mechanical ventilation is a common factor amongst the critically ill patients and has been implicated in the pathogenesis of disturbed gastrointestinal motility (Mutlu, *et al.* 2001). The patho-physiological effects of mechanical ventilation on gastrointestinal motility are unknown. However, in humans, positive pressure mechanical ventilation leads to splanchnic vasoconstriction and gut hypo-perfusion and increased in plasma catecholamines and pro-inflammatory cytokines levels (Love, *et al.* 1995; Mutlu, *et al.* 2001). Similar findings have come from animal studies (Chernow, *et al.* 1986; Sellden, *et al.* 1986). In addition to the sedation, these vascular and humoral consequences of mechanical ventilation can all result in impaired gastric motor function.

4.4.6 PRE-EXISTING MORBIDITY

Delayed gastric emptying occurs commonly with a number of conditions. Diabetes mellitus (DM) is one of the most frequently known conditions associated with gastroparesis. Up to 50% of patients with DM, particularly those with longstanding disease, have slow gastric emptying (Horowitz, *et al.* 1996). Whilst the pathogenesis of diabetic gastroparesis remains unclear, both hyperglycemia and autonomic neuropathy are believed to play an important role in the pathogenesis of slow gastric emptying in these patients (Horowitz, *et al.* 1996). These factors have been shown to associate with motor abnormalities in both the proximal and distal stomach (Malagelada, *et al.* 1980; Tack, *et al.* 1992; Fraser, *et al.* 1994; Samsom, *et al.* 1995; Samsom, *et al.* 1998; Rayner, *et al.* 2000). It is possible, therefore, that critically ill patients with DM may be at a higher risk of slow gastric emptying than those without DM. Indeed, in critically ill patients, pre-existing diabetes mellitus is frequently suggested as a risk

factor for delayed gastric emptying and feed intolerance, but there are no data to support this assumption. Currently, there are no data on either gastric emptying or gastric motor function in critically ill patients with diabetes mellitus.

4.5 MANIFESTATIONS AND CONSEQUENCES OF IMPAIRED GASTRIC MOTILITY IN CRITICAL ILLNESS

Impaired gastric motor function in critically ill patients unusually remains unrecognised clinically until enteral nutrition is introduced. Challenging the poorly functioning stomachs of these patients results in 'feed intolerance', which has been vaguely defined as the inability to tolerate enteral feeding given at a rate to achieve the daily goal calorie requirement. Whilst the most easily recognised clinical manifestations of feed intolerance are regurgitation, vomiting and even pulmonary aspiration of feeds, these are late manifestations and the related complications are associated with adverse morbidity and mortality (Montejo 1999; Mutlu, *et al.* 2001; Ritz, *et al.* 2001; Heyland, *et al.* 2003; Hussain, *et al.* 2003; Metheny, *et al.* 2004). Furthermore, the presence of these complications can also lead to inappropriate disruption of enteral feeds and malnutrition in these patients (Adam and Webb 1990; McClave, *et al.* 1999; De Jonghe, *et al.* 2001; Heyland, *et al.* 2003). Thus, a number of strategies have been developed to reduce the risk of enteral feeding, although the clinical utility and methods of implementation of these strategies remain controversial.

4.5.1 RELATIONSHIP BETWEEN GASTRIC RESIDUAL VOLUME (GRV) AND FEED INTOLERANCE

In order to avoid the complications of enteral feeding and to guide the rate of feed delivery, regular monitoring of GRV has been adopted widely amongst intensive care units during enteral feeds. The techniques involve in the monitoring of GRV are described in detail in Chapter 6.

4.5.1.1 Rationale for monitoring gastric residue

The rationale for this technique to assess gastric emptying is based on the concept of a finite-sized stomach, which will over-fill if input exceeds output over time. Thus, in the presence of stasis, GRV is likely to be elevated and there will be an increased risk of gastro-esophageal reflux and aspiration. For many years, the presence of 'large' GRVs during enteral feeding has been considered as the most common manifestation of 'feed intolerance'.

4.5.1.2 Controversies surrounding the cut-off volume for 'large' GRV

Although GRV monitoring during enteral feeding is widely practised by intensive care units throughout the world, this practical approach has a number of weaknesses that relate to the lack of standardization of the designated cut-off volume which defines 'feed intolerance'. Principally, the data on the relationship between GRVs, gastric emptying and associated complications are limited. Thus, the cut-off volume for 'large' gastric residue is arbitrary and has encompassed a wide range of volumes, ranging from 120 mL to 500 mL (Montejo 1999;

Chapman, *et al.* 2000; De Beaux, *et al.* 2001; Mentec, *et al.* 2001; McClave and Snider 2002; Heyland, *et al.* 2004; McClave, *et al.* 2005; Metheny, *et al.* 2005).

A residual volume of 250 mL has been commonly used as the cut-off value to define 'feed intolerance' in many clinical trials (Montejo 1999; Chapman, *et al.* 2000; Berne, *et al.* 2002; Reignier, *et al.* 2002). Based on this definition, 'feed intolerance' has been shown to be associated with increased reflux, aspiration pneumonia, length of stay in ICU and mortality (Montejo 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001).

4.5.1.3 Clinical application of GRV monitoring

The most important issue for intensivists is the level of residual volume which triggers the decision to stop feeds. Recent data have suggested that cessation of feeding based on this practice may compromise enteral feeds, particularly in critical care units which use a low cut-off volume for 'feed intolerance' (McClave, *et al.* 1999; Pinilla, *et al.* 2001; McClave, *et al.* 2005; Marshall and West 2006). McClave et al (2005) have shown that the incidence of regurgitation of feeds and aspiration is similar between cut-off volumes of 200 mL and 400 mL, and have therefore suggested that gastric residual volumes between 250 mL and 400 mL should be an indication for treatment of gastric stasis with prokinetic therapy, rather than cessation of feeds (McClave, *et al.* 2005).

4.5.1.4 Current status of GRV monitoring in clinical practice

Despite the lack of standardization and uncertainty regarding the interpretation, the practice of monitoring GRVs remains a simple, convenient and inexpensive method to guide the delivery of enteral feeds that allows early institution of treatment for impaired gastric emptying, and improves patient outcomes (Heyland, *et al.* 2003).

4.5.2 CONSEQUENCES OF IMPAIRED GASTRIC MOTOR FUNCTION IN CRITICAL ILLNESS

There are a number of important consequences of impaired gastric motility in critically ill patients, especially when gastric emptying is delayed in over 50% of patient who receive enteral feeds (Heyland, *et al.* 1996; McClave, *et al.* 1999; Montejo 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; Heyland, *et al.* 2003). The most common consequence of 'upper gastro-intestinal intolerance' is the inability to deliver daily nutrient requirements, potentially leading to malnutrition (Adam and Batson 1997; McClave, *et al.* 1999; Montejo 1999; Mentec, *et al.* 2001) and resulting in an increase in morbidity and mortality. Two recent surveys reported that feed intolerance led to interruption of feeds in 73% of patients and abandonment of enteral feeds in up to 15% of patients (Adam and Batson 1997; Montejo 1999). Consequently, patients with feed intolerance received only 50% to 60% of the daily calorie requirements, whilst patients who tolerated feeds received 90% of their goal (Adam and Batson 1997; McClave, *et al.* 1999; Montejo 1999).

For intensivists, gastro-esophageal reflux and aspiration pneumonia remain the most feared complications of disturbed gastric motility (Schwizer, *et al.* 1989). Stasis of feeds caused by

gastric hypomotility significantly increases the risk of gastro-esophageal reflux (Ibanez, *et al.* 2000; Metheny 2002; Metheny, *et al.* 2004; McClave, *et al.* 2005; Nind, *et al.* 2005). Furthermore, the high incidence of duodeno-gastric reflux may result in bile-induced oesophagitis (Dive, *et al.* 1999; Wilmer, *et al.* 1999; Ibanez, *et al.* 2000). In addition, gastric stasis also promotes bacterial colonization, and may be important in the pathogenesis of ventilation associated pneumonia (VAP) in enterally fed patients (Inglis 1995). Consistent with this, the risk of VAP is double in patients with feed intolerance compared to patients who tolerate feeds (MacLaren 2000; Mentec, *et al.* 2001). This is also associated with a prolongation of the length of stay in ICU by approximately 1 week in these patients (Montejo 1999; Mentec, *et al.* 2001).

The combination of inadequate nutritional support and increased risk of VAP due to feed intolerance resulting from impaired gastric motility are, therefore, likely to contribute significantly to the increase in both ICU and hospital mortality in these patients.

Most importantly, patients with feed intolerance have significantly higher mortality. In two large cohort of critically ill patients, the mortality of patients with feed intolerance was 30% to 40%, as compared to 15% to 25% in those who tolerated feeds (Montejo 1999; Mentec, *et al.* 2001). Currently, it is unclear whether feed intolerance is a cause of poorer outcomes or simply a reflection of severity of the illness and thereby, poorer outcomes. Whilst this requires further evaluation, the overall data suggest that feed intolerance in critically ill patients is associated with poorer outcomes.

4.6 CURRENT MANAGEMENT OF IMPAIRED GASTRIC MOTILITY AND EMPTYING

The adverse impacts of disturbed gastric motility on the morbidity and mortality of critically ill patients have led to the development of a variety of strategies to overcome the gastric dysmotility and improve the delivery of nutrition to the patients. These include minimization of known risk factors, use of prokinetic drugs and implementation of post-pyloric feeding.

4.6.1 REDUCTION OF MODIFIABLE RISK FACTORS

A number of risk factors such as sedation, mechanical ventilation and hemodynamic support with inotropic agents have been proposed to impair gastric motility and feed intolerance. Data on the impact of these risk factors on gastric motility or emptying in critically ill patients, however, are lacking. Current evidence in patients with head injury suggests that avoiding opioid sedation does not result in better gastric emptying (McArthur, *et al.* 1999). Whilst tight blood glucose control in critically ill patients is associated with reduced septic complications and mortality (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003; Krinsley 2004), its effect on gastric motor function during critical illness has not been examined. Similarly, although early enteral feeding is associated with better survival, the impact of early enteral nutrition on gastric emptying has not been examined. Thus, although it is logical to optimize the gastric motility of critically ill patients by removing or reducing modifiable risk factors, further data are needed before these can be confidently recommended.

4.6.2 PHARMACOTHERAPY – PROKINETIC AGENTS

Treatment with gastro-kinetic drugs is the principal treatment for disturbed gastric motility and slow gastric emptying in critically ill patients. The three agents for which substantial data exist are metoclopramide, cisapride, and erythromycin. The benefits as well as the disadvantages of each agent are discussed below. In addition, a number of other prokinetic agents are either under development or have the potential to improve gastric emptying in critically illness.

4.6.2.1 Metoclopramide

In healthy volunteers, metoclopramide enhances antro-pyloro-duodenal coordination, propagation of duodenal contractions and accelerates gastric emptying (Behar and Ramsby 1978; Malagelada, *et al.* 1980; Ghigliani, *et al.* 1987). The precise mechanisms underlying the prokinetic effects are unclear, but metoclopramide has been shown to antagonize dopamine's inhibitory effects on gastrointestinal motility, facilitate the release of acetylcholine from gut cholinergic neurones, and is a weak 5-hydroxytrytamine (5-HT) receptor antagonist (Booth, *et al.* 2002).

In unselected critically ill patients, metoclopramide has been reported to improve gastric emptying (Jooste, *et al.* 1999; MacLaren, *et al.* 2000; MacLaren, *et al.* 2001), but its efficacy on the success of feeding in feed intolerant patients remains controversial. In small studies, no effect was seen on GRV after a single dose of enterally administered metoclopramide and only modest reductions in volume were only observed after three doses (MacLaren, *et al.* 2001). Similarly, a single intravenous (IV) dose of metoclopramide enhances migration of

nasogastric feeding tubes into the duodenum in these patients (Jooste, *et al.* 1999; MacLaren, *et al.* 2000; MacLaren, *et al.* 2001). The prokinetic effects of metoclopramide, however, are not observed in patients with head injury (Marino, *et al.* 2003). Furthermore, neither the mortality nor the development of ventilation associated pneumonia were reduced by regular administration of metoclopramide (IV 10mg four times per day (qid), for > 48 hours) in unselected enterally fed patients (Yavagal, *et al.* 2000). Currently, there are no data on the effectiveness of either short-term or long-term use of metoclopramide in patients with feed intolerance to improve the success of feeding. Despite the limited data in patients with feed intolerance, metoclopramide has been recommended as the first line therapy in these patients (Booth, *et al.* 2002; Doherty and Winter 2003).

The use of metoclopramide, however, is associated with a number of important side effects. Extra-pyramidal side effects such as dystonia, dyskinesia and tremors are especially common in both healthy subjects and critically ill patients if use in high doses (Ponte and Nappi 1981; Schapira, *et al.* 1990; Robinson 1995). In patients with traumatic head injury, metoclopramide has been reported to be associated with increased intra-cranial pressure (Deehan and Dobb 2002).

4.6.2.2 Erythromycin

Recently, low dose erythromycin has been used increasingly as a prokinetic agent in both diabetic and critically ill patients. Erythromycin, a macrolide antibiotic, acts on motilin receptors which are found on both cholinergic nerves and the smooth muscle of the stomach and small intestine (Annese, *et al.* 1992; Tack, *et al.* 1992; Coulie, *et al.* 1998; Bradley 2001).

Depending on the dose, the motility effects of erythromycin can be mediated by activation of the motilin receptor on either the vagus nerve, gastric smooth muscle or both (Annese, *et al.* 1992; Tack, *et al.* 1992; Coulie, *et al.* 1998; Bradley 2001). Low dose erythromycin (1-3mg/kg) accelerates gastric emptying by activate motilin receptors on the vagus nerve to induce gastric antral contractions, and improve antro-duodenal co-ordination (Annese, *et al.* 1992; Tack, *et al.* 1992; Coulie, *et al.* 1998). In contrast, at higher doses (5-7 mg/kg), erythromycin mediates its effects via the motilin receptors on smooth muscle of the upper gastrointestinal tract, and induces prolonged strong antral contractile activity which is not followed by a phase 1 (Tack, *et al.* 1992; Coulie, *et al.* 1998). At antibiotic doses, there is disruption of smooth muscle membrane potentials leading to chaotic antegrade and retrograde contractions (Annese, *et al.* 1992; Tack, *et al.* 1992). These are associated with reduced gastric emptying, nausea, vomiting and crampy abdominal pain.

In humans, 3 mg/kg of erythromycin has been used to enhance gastric emptying in patients with gastroparesis caused by diabetes or vagotomy (Tack, *et al.* 1992; Ramirez, *et al.* 1994; Kendall, *et al.* 1997; Petrakis, *et al.* 2000). Limited data suggest that the long-term efficacy of erythromycin in the treatment of gastroparesis may be limited by the development of tachyphylaxis due to down-regulation of motilin receptors (Tack, *et al.* 1992).

In critically ill patients, 200 mg of erythromycin as an intravenous infusion increases the number and amplitude of antral contractions during the first hour of injection (Dive, *et al.* 1995). These effects persist for up to five hours and are associated with increased gastric emptying. The effect of prophylactic erythromycin on the success of enteral feeding was

examined by administration of intravenous erythromycin (250 mg qid) in unselected critically ill patients (Reignier, *et al.* 2002). This regime, in the initial 5 days of enteral feeding, enhanced gastric emptying, reduced gastric residual volume and improved the success of feeds (Reignier, *et al.* 2002).

Whilst erythromycin consistently reduces gastric residual volume in patients with feed intolerance, its impact on improving the success of feeds in these patients remains controversial. In 20 patients with feed intolerance, administration of a single intravenous dose of erythromycin (200 mg) significantly reduced gastric residual volume and increased the success of feeds to 90% over the next 24 hours (Chapman, *et al.* 2000). In contrast, a trial of regular administration of erythromycin (IV 250 mg qid) in patients with feed intolerance over 48 hours did not improve either the amount of feed delivered or the proportion of patients who were fed successfully (Berne, *et al.* 2002). This discrepancy between these trials may relate to a lower cut-off for GRV in the definition of feed intolerance used in these studies. In addition, the higher daily dosage of erythromycin used in the later study may have resulted in disturbances in the gastric smooth muscle membrane potential (Annese, *et al.* 1992). Finally, it has been suggested that repeated use of erythromycin is associated with tachyphylaxis (Peeters, *et al.* 1992; Dhir and Richter 2004; Thielemans, *et al.* 2005).

Clinically, the use of erythromycin as a prokinetic agent has been cautious due to potential cardiac side effects and the possible development of bacterial resistance (Tonini, *et al.* 1999; Guerin and Leibinger 2002). Doses of 70 mg erythromycin have been recently reported to have a similar effect on gastric emptying to 200 mg dose, suggesting the risk of cardiac

toxicity can be minimized by using a smaller dosage (Ritz, *et al.* 2005). There are, however, no data on the effectiveness of such low dosage on either the success of feeds or the effect of prolonged use. In attempt to prevent bacterial resistance, macrolide derivatives without antibiotic properties have been developed. In patients with slow gastric emptying, the efficacy of such new motilin agonists such as ABT-229, in the treatment of gastroparesis has been disappointing, due to rapid development of tachyphylaxis and increased dyspeptic symptoms (Talley, *et al.* 2000; Talley, *et al.* 2001). The effects of motilin agonists have not been examined in critically ill patients.

4.6.2.3 Cisapride

While the current management of gastric dysmotility in critically ill patients relies on metoclopramide and erythromycin (Booth, *et al.* 2002; Doherty and Winter 2003), cisapride has been used to accelerate gastric emptying in both diabetic and critically ill patients (Spapen, *et al.* 1995; Heyland, *et al.* 1996; Goldhill, *et al.* 1997; MacLaren, *et al.* 2000; Reddy, *et al.* 2000; MacLaren, *et al.* 2001). So far, there are no data on the impact of cisapride on and the success of feed in patients with feed intolerance. However, this prokinetic agent has been withdrawn recently due to the associated lethal cardiac toxicity (Walker, *et al.* 1999), and therefore, its use will not be discussed further in this chapter.

4.6.2.4 Other potential gastrokinetic drugs

Due to the limitations of the current prokinetics, a number of novel prokinetics have been developed and are potentially useful in the critically ill patients. The development of these

agents has been based on the recent understanding that gastric motility is regulated by various neuro-humoral pathways, including the endogenous opiate (Dubois 1987) and serotonergic (Degen, *et al.* 2001) pathways and gut hormones such as cholecystokinin (Schwizer, *et al.* 1997). Opioids, act on μ-receptors, are known to impair gastric motility and slow the rate of gastric emptying (Dubois 1987). Naloxone, antagonizes the adverse impact of opioids on gastric motility, has been reported to reduce gastric tube reflux, improve the success of feeds and reduce the incidence of pneumonia in opioid-treated critically ill patients (Meissner, *et al.* 2003). Alvimopan, another opioid receptor antagonist, hastens the recovery of gastrointestinal motility and reduces the hospital length of stay after surgery (Taguchi, *et al.* 2001; Tan, *et al.* 2006). The impact of opioid receptor antagonists on the success of feeds in critically ill patients with feed intolerance, however, has not been examined.

In humans, serotonergic pathways are important in the regulation of gastrointestinal motility. Activation of the 5-HT_4 receptor accelerates gastric emptying and shortens intestinal transit time (Galligan and Vanner 2005). The 5-HT_4 receptor agonist, tegaserod, increases gastric emptying in healthy subjects (Degen, *et al.* 2001). Its effectiveness in critically ill patients is limited to a single case report. In three patients with impaired gastric emptying refractory to conventional treatment, tegaserod improved gastric hypomotility and the amount of feeds delivered over the next 5 days (Banh, *et al.* 2005). The use of this agent in critically ill patients is, however, likely to be limited because of recently reported risks of increased cardiovascular side effects (Brinker, *et al.* 2004). It has since been withdrawn from the market.

As discussed in Chapter 3, CCK is an important mediator of the entero-gastric feedback response and slows gastric emptying (Fried, *et al.* 1991; Schwizer, *et al.* 1997; White, *et al.* 2000). Although CCK antagonists (either dexloxiglumide or loxiglumide) accelerate gastric emptying in healthy subjects (Fried, *et al.* 1991; Schwizer, *et al.* 1997), but the effect of these agents on impaired gastric emptying in critical illness has yet to be determined.

4.6.2.4 Summary

In summary, both the choice and efficacy of prokinetic therapy for impaired gastric motor function of critical illness are currently limited and restricted to the use of metoclopramide and erythromycin. In addition, there are no data on the role of combining available prokinetic agents in the treatment of feed intolerance, as either first line or rescue therapy. The use of novel prokinetic agents in critically ill patients cannot be currently recommended due to a lack of data.

4.6.3 POST-PYLORIC FEEDING

Whilst the problems associated with slow gastric emptying are often assumed to be bypassed by placement of a feeding tube beyond the pylorus, current data for this practice in critically ill patients remain controversial. In particular, both randomized trials (Montecalvo, *et al.* 1992; Davies, *et al.* 2002) and meta-analyses (McClave, *et al.* 2002; Heyland, *et al.* 2003; Marik and Zaloga 2003; Ho, *et al.* 2006) have not shown an advantage in mortality for small bowel over gastric feeding in these patients. Although a meta-analysis by Heyland et al (2002) suggested that post-pyloric feeding increased nutrient delivery coupled with a shorter

time to achieve nutritional goals, a reduction in gastroesophageal reflux and a lower rate of ventilation associated pneumonia (Heyland, *et al.* 2002), subsequent meta-analyses have not confirmed these findings (Marik and Zaloga 2003; Ho, *et al.* 2006). The benefits demonstrated by Heyland et al (2002) appear to have depended largely on a study that compared early aggressive enteral feeding with standard feeding. In fact, only 34% of patients in the aggressive feeding group had a post pyloric tube inserted (Taylor, *et al.* 1999). Furthermore, data in neonates suggests that post-pyloric feeding is associated with more gastrointestinal disturbances and an increased mortality, particularly diarrhoea (McGuire and McEwan 2004). More importantly, post pyloric feeding without concurrent gastric decompression results in significant undrained gastric residual volumes potentially increasing the risk of aspiration (Metheny, *et al.* 2005). Finally, the prophylactic use of erythromycin as a prokinetic agent appears to be as effective as post pyloric tube feeds in improving delivery of nutrients to these patients (Boivin and Levy 2001).

Currently, there are no data on the role of post pyloric feeding in patients with impaired gastric emptying and feed intolerance, particularly those refractory to prokinetic therapy. Nevertheless, despite the lack of supporting data, the use of post pyloric feeding has been recommended as the best approach to maintain adequate enteral nutrition in patients who experience upper gastrointestinal intolerance (Heyland, *et al.* 2003; Davies and Bellomo 2004).

4.7 CONCLUSIONS

Despite the frequency and adverse impact of impaired gastric motor function on outcome in the critical illness, current understanding of the nature and pathogenesis of dysmotility in these patients is limited, in large part, because of the difficulties involved in performing research in this setting. Interpretation of data concerning with both the risk factors and aetiology of disturbed gastric motility is further confounded by the heterogeneity of this population and the complex interactions amongst factors that potentially disturb gastric motility. These limitations in the understanding of disturbed gastric motility may contribute to suboptimal treatment in these patients.

With these limitations in mind, the work described in this thesis will investigate following areas:

1. Characterization of the motor activity in the proximal stomach and the motor integration between the proximal and distal stomach in critically ill patients (Chapter 7).
2. Evaluation of hormonal mediators of entero-gastric feedback response to nutrients, specifically CCK and PYY (Chapter 8).
3. Evaluation of the impact of (i) admission diagnosis; (ii) type of sedation; (iii) delaying initiation of enteral feeding; (iv) blood glucose control on gastric motor functions of critically ill patients (Chapter 9).
4. Evaluation of the impacts of pre-existing type 2 diabetes mellitus on (i) proximal gastric motility; (ii) gastric emptying and (iii) the development of feed intolerance in critically ill patients (Chapter 10).
5. Comparison of the effectiveness of available gastrokinetic agents, both singly and in combination, in the treatment of feed intolerance in critically ill patients (Chapter 11).

CHAPTER 5: NUTRITIONAL SUPPORT IN CRITICALLY ILL PATIENTS

5.1 INTRODUCTION

Over the last 30 years, the importance of nutritional support in the critically ill patients has been increasingly recognised. The development of total parenteral nutrition (TPN) enabled provision of total nutritional requirements (Spanier and Shizgal 1977; Benner, *et al.* 1979; Lumb, *et al.* 1979). The subsequent introduction of enteral nutrition and recognition of the potential benefits from delivering nutrients into the gut has led to its adoption as the preferred mode of nutritional delivery in critically ill patients. These benefits include ease of administration, reduced health care cost, lower rate of sepsis, lack of requirement for central venous access, and improvements in gastro-intestinal barrier function with potential reduction in bacterial translocation (Heyland, *et al.* 1998; Heyland, *et al.* 2003; Heyland, *et al.* 2003). However, adequate delivery of enteral feeds to critically ill patients is frequently hampered by a variety of factors, the most frequent of which is gastric dysmotility (Chapter 4).

This chapter reviews the current evidence that guides the practice of nutritional support in critical care units. The potential advantages of enteral nutrition over total parenteral nutrition, the optimal time for the initiation of nutrition support and impediments to the delivery of enteral nutrition will be discussed. Strategies to overcome these difficulties and to optimise the delivery of nutrition to critically ill patients will also be reviewed.

5.2 THE IMPORTANCE OF NUTRITIONAL SUPPORT IN CRITICAL ILLNESS

For many years, it has been recognized that critical illness is associated with hyper-catabolism, resulting in sarcopenia, impaired organ function, and reduced reparative and immune function (Barton 1994). In critically ill patients, the addition of nutritional deprivation or malnutrition is associated with further impairment of immunological function, prolongation of mechanical ventilation, increased length of ICU and hospital stay, increased infective complications and ultimately higher mortality (Giner, *et al.* 1996; Chandra 1999; Harrington 2004; Slone 2004). In order to minimize the complications associated with malnutrition during critical illness, the practice of nutritional support (by either enteral or parenteral routes) has become a standard treatment in these patients. However, for many years, although considered desirable, nutritional support was frequently either not provided routinely (Berger, *et al.* 1997) or inadequately delivered to meet metabolic requirements (Heyland, *et al.* 1995; Hill, *et al.* 1995; Adam and Batson 1997; Buchman 2001; De Beaux, *et al.* 2001; De Jonghe, *et al.* 2001; Heyland, *et al.* 2003). As a consequence, it has been suggested that the incidence of malnutrition amongst long-stay critically ill patients could be as high as 50% (Giner, *et al.* 1996; Quirk 2000).

The impact of nutritional support on patients' outcomes has been examined extensively over last two decades. Whilst many studies have documented that nutritional support changes metabolic outcomes, such as amino acid profile and nitrogen balance, the impact of this intervention on clinically important endpoints such as infection, length of stay and mortality

is less clear-cut. There are a number of methodological reasons that might explain the discrepancies amongst the reported studies. Firstly, over 60% of trials that have examined this issue lacked sufficient statistical power (Heyland 1998; Heyland, *et al.* 2003; Doig, *et al.* 2005). This is further confounded by the heterogeneity of the critically ill population and differences amongst the patients between the studies (Doig, *et al.* 2005). In addition, the quality of many trials was suboptimal with a lack of randomisation, controls and blinding (Doig, *et al.* 2005).

In view of these limitations, a number of meta-analyses that examined only high quality randomised controlled (level 2) trials have been performed. Compared with patients who received standard care (ie. IV fluid support only), nutritional support via either the enteral or parenteral route has been associated with a 5% to 12% reduction in mortality (Heyland, *et al.* 1995; Heyland, *et al.* 2003; Doig and Simpson 2005). In surgical and multi-trauma patients, nutritional support improves wound healing, decreases the catabolic response to injury and reduces infective complications (Schroeder, *et al.* 1991; Kudsk, *et al.* 1992; Heyland 1998; Heyland, *et al.* 1998; Marik and Zaloga 2001; Heyland, *et al.* 2003; Martin, *et al.* 2004). Similar reductions in septic complications and a shorter length of stay in ICU and hospital have also been demonstrated in medical critically ill patients (Heyland, *et al.* 1995; Heyland, *et al.* 2003; Doig and Simpson 2005).

5.3 NUTRITIONAL SUPPORT IN CRITICALLY ILL PATIENTS

Currently, nutrition support can be delivered to critically ill patients either as total parenteral nutrition (TPN) or enteral nutrition (EN).

5.3.1 TOTAL PARENTERAL NUTRITION VERSUS ENTERAL NUTRITION

In the 1970s, the development of total parenteral nutrition (TPN) revolutionized the provision of total nutritional requirements to critically ill patients (Spanier and Shizgal 1977; Benner, *et al.* 1979; Lumb, *et al.* 1979). This technique involves the aseptic delivery of macro- and micro-nutrients directly into the circulatory system via a central venous line (Heyland, *et al.* 2003). Utilization of TPN, however, has been restricted by recognition of associated complications such as an increased risk of infective complications, over-feeding, hyperglycemia, and gut mucosal atrophy (Heyland 1998).

Currently, nutrient is most commonly delivered into the stomach, via a naso-gastric or oro-gastric tube, due to the ease of tube placement. Direct delivery of feeds into the gastrointestinal tract is considered more physiological. In animal models, this approach maintains gastrointestinal structure and function, prevents bacterial translocation, improves wound healing, and decreases catabolic response to injury (Kudsk, *et al.* 1992; Cerra, *et al.* 1997; Jolliet, *et al.* 1998; Braunschweig, *et al.* 2001; Heyland, *et al.* 2003; Martin, *et al.* 2004). These benefits, however, have been more difficult to demonstrate in humans (Peng, *et al.* 2004; Winter, *et al.* 2007).

The methods of nutritional support amongst the critical care units around the world vary widely. Depending on local factors and expertise, the use of TPN varies from 12-71% and EN varies from 33-92% (Payne-James, *et al.* 1992; Hill, *et al.* 1995; Preiser, *et al.* 2001). Whilst some trials have shown EN to be associated with a significant reduction in infective complications compared to TPN (Moore, *et al.* 1989; Kudsk, *et al.* 1992; Kalfarentzos, *et al.* 1997), this has not been a consistent finding (Adams, *et al.* 1986; Young, *et al.* 1987). The comparative data on mortality outcomes are even more variable (Adams, *et al.* 1986; Young, *et al.* 1987; Kudsk, *et al.* 1992; Borzotta, *et al.* 1994; Hadfield, *et al.* 1995; Kalfarentzos, *et al.* 1997), and may reflect the lack of power of these studies. More recent meta-analyses, however, indicate that compared with TPN, EN does not reduce the mortality (Heyland, *et al.* 2003; Doig and Simpson 2005) rate, although it may be associated with a reduction in infections . Although the reasons for the discrepancy on mortality as compared to early studies are unclear, it may relate to the recent improvements in the techniques used to administer parenteral nutrition, as well as the recognition of the importance of tight blood glucose control (Jeejeebhoy 2001; Tay, *et al.* 2002; Dudrick 2003). Furthermore, commencement of EN is frequently delayed or interrupted (Adam and Webb 1990; De Jonghe, *et al.* 2001) and the lack of adequate nutrition may contribute to poor outcomes. Despite these reservations, EN has become the standard of care, with a number of guidelines recommending EN over TPN in all critically ill patients with an intact gastrointestinal tract who require nutritional support (Heyland, *et al.* 2003).

5.3.2 TIMING OF NUTRIENT DELIVERY IN CRITICAL ILLNESS

The optimal time to start nutritional support in critical illness is unknown. However, it is recognised that patients should not be deprived of nutrients for more than 5 days as earlier studies demonstrated a higher mortality in surgical patients who had nutrition deprived for longer than this duration (Thomas, *et al.* 1979; Thomas and Robert 1979; Mullen, *et al.* 1980). Nutrient deprivation for durations as short as 24 hours may lead to intestinal mucosal atrophy and malabsorption in animals (DeWitt and Kudsk 1999; Alpers 2002). These abnormalities can be reversed or prevented by early introduction of luminal nutrients (Tremel, *et al.* 1994; Hernandez, *et al.* 1999; Alpers 2002). In a more recent randomised controlled study, patients with nutrient-deprivation for a mean duration of 4 days had a significant reduction in villous height and crypt ratio and a increased gut permeability assessed by lactulose-mannitol test (Hernandez, *et al.* 1999), compared those who received enteral feed within 24 hours of admission.

Until recently, the concept of early aggressive feeding was not universally accepted by many critical care staff (Marik and Zaloga 2001). Despite recognising the importance of early feeding, a number of nutritional surveys in intensive care units have reported that less than 50% of eligible patients received enteral nutrition within 48h of admission (McClave, *et al.* 1999; Montejo 1999; Heyland, *et al.* 2003), placing these patients at risk of intestinal mucosal atrophy, increase gut permeability and malnutrition (Alpers 2002; Stollman and Metz 2005). As the integrity of the gastrointestinal tract is thought to be important for the prevention of bacterial translocation and subsequent infective complications (DeWitt and Kudsk 1999;

Alpers 2002), these findings suggest that delayed enteral nutrition may increase the risk of sepsis.

A number of randomised controlled trials have examined the impact of early enteral nutrition on outcomes in critically ill patients (Moore and Moore 1991; Eyer, *et al.* 1993; Chuntrasakul, *et al.* 1996; Singh, *et al.* 1998; Kompan, *et al.* 1999; Minard, *et al.* 2000; Artinian, *et al.* 2006). These have produced conflicting results possibly due to a lack of adequate statistical power (Marik and Zaloga 2001). Meta-analyses using these data have also given an inconclusive answer with a trend toward a reduction in infective complication and mortality, and no difference in length of stay (Heyland, *et al.* 2003). Most recently, Artinian et al (2006) conducted a large study that included 4049 medical critically ill patients. This study showed that early EN was associated with a 20% reduction in ICU mortality and a 25% reduction in hospital mortality. The benefit to mortality was most pronounced amongst patients with the highest APACHE II scores (Artinian, *et al.* 2006), although a higher incidence of ventilated associated pneumonia was reported in patients who had received early feeding. The reason for this finding is unclear but may relate to the more prolonged exposure to nasogastric feeds, a known risk factor for gastro-esophageal reflux and aspiration (Montejo 1999; Mentec, *et al.* 2001).

5.4 CURRENT EVIDENCE BASED RECOMMENDATIONS

Based on current evidence, a number of international working committees have published guidelines for nutritional support in critically ill patients (Edes 1991; Jolliet, *et al.* 1999;

Riley 2002; Heyland, *et al.* 2003; Doig and Simpson 2005). Of these, the Canadian Clinical Practice guideline is best known and has been most widely adopted (Heyland, *et al.* 2003). Although there are minor variations amongst these guidelines, common themes include (Heyland, *et al.* 2003):

- Nutritional support, either in the form of TPN or EN, should be considered in all patients who are admitted to critical care.
- EN is the preferred modality of nutritional support in critically ill patients, particularly in those with intact gastrointestinal tract.
- In patients whom EN is indicated, it should be commenced within 24-48 hours of admission.

5.5 FACTORS IMPEDING ADEQUATE DELIVERY OF ENTERAL NUTRITION

There is a marked discrepancy in clinical practice between the ideal and the actual number of calories delivered to the patient, even when nutritional support is part of standard care for critically ill patients (Martin, *et al.* 2004). A number of earlier surveys of feeding practice have shown that the number of calories actually delivered to patients did not meet nutritional targets, especially during the first 3 days of admission with only 50% to 68% of daily requirements being delivered (Adam and Batson 1997; McClave, *et al.* 1999; De Beaux, *et al.* 2001; De Jonghe, *et al.* 2001; Krishnan, *et al.* 2003). The reasons for the discrepancies

between the ideal and actual caloric delivery have been extensively studied to determine factors that may be amenable to correction.

5.5.1 UNDER-PRESCRIPTION OF NUTRIENTS

It has been reported that the intensivists frequently under-estimate the daily caloric requirements of their patients. Thus, compared to recommendations of 25-35 cal/kg/day determined by a dietitian, the number of calories actually prescribed by the duty intensivist may be as low as 65.6% of the goal requirements (McClave, *et al.* 1999). This inadequate prescription is further compromised if only 50% to 78% of the prescribed target is actually delivered (Adam and Batson 1997; McClave, *et al.* 1999; De Beaux, *et al.* 2001; De Jonghe, *et al.* 2001; Krishnan, *et al.* 2003). Recent data have demonstrated that patients who were cared for by a registered dietitian had significantly more calories and protein, a shorter length of stay, a higher serum albumin and a greater weight gain (Braga, *et al.* 2006). These findings, therefore, suggest a potential role of a dedicated registered dietitian in the assessment and provision of nutritional needs to these patients.

5.5.2 DISTURBED UPPER GASTROINTESTINAL MOTILITY

The most common factor restricting the delivery of enteral nutrition in critically ill patients is the presence of impaired gastric motility that leads to slow gastric emptying and interruptions to feeds in up to 73% of patients. This is usually manifest as high GRV, but can also present with regurgitation, vomiting or even pulmonary aspiration. As discussed in Chapter 4, although the relationship between GRV and gastric emptying or aspiration is not ideal

(McClave, *et al.* 2005), the majority of intensive care units base the decision to hold or stop feeds on an arbitrarily determined volume of gastric residues, ranging from 75 mL to 500 mL (McClave, *et al.* 1999; Montejo 1999; Chapman, *et al.* 2000; MacLaren, *et al.* 2000; MacLaren, *et al.* 2001; Mentec, *et al.* 2001; Berne, *et al.* 2002; Reignier, *et al.* 2002). It has been further suggested that the use of low cut-off volumes leads to unnecessary cessation of feeds and expose patients to risk of malnutrition (McClave, *et al.* 1999; McClave, *et al.* 2005).

5.5.3 MEDICAL INTERVENTIONS

Critically ill patients frequently undergo diagnostic and therapeutic interventions which require fasting and consequent interruption to feeding. Thus, it is not surprising that surgical, endoscopic or imaging procedures account for 25-35% of disruption of enteral feeds (Adam and Batson 1997; McClave, *et al.* 1999; De Beaux, *et al.* 2001). Whilst it is acceptable to temporarily cease feed for surgical and endoscopic procedures, it may be unnecessary to stop feed for routine imaging investigations as these activities are frequent and unlikely to expose the patients to a minimal risk of aspiration.

5.5.4 NURSING CARE ACTIVITIES

In addition to medical interventions, basic nursing care activities such as bed baths or dressing changes also lead to temporary cessation of enteral feeds. In some cases, this may result in up to 20% reduction in enteral feed (Adam and Batson 1997; McClave, *et al.* 1999; De Beaux, *et al.* 2001).

5.6 OPTIMIZATION OF NUTRITIONAL SUPPORT IN CRITICAL ILLNESS

In order to deliver the required nutritional target, a number of strategies are necessary. These include increasing the awareness of intensive care clinicians on the benefits of enteral nutrition, implementing feeding protocols and prompt treatment of feed intolerance.

5.6.1 TEAM APPROACH

Optimal delivery of nutrition to critically ill patients is best achieved with team approach, including a dedicated dietitian to assess and determine the daily nutritional requirement (Braga, *et al.* 2006) and avoid under-prescription of caloric requirements. Nursing staff can reduce interruptions of feeds from basic nursing care activities and routine imaging procedures. Furthermore, cessation of enteral feeds for minor medical interventions such as imaging procedures is usually unnecessary and should be avoided.

5.6.2 IMPACT OF FEEDING PROTOCOLS

Feeding protocols or flow charts would be expected to increase both staff awareness and improve the consistency of delivery of nutritional support in the critical care setting. Such protocols can also be used to reduce unnecessary interruption or cessation of feeds. The outcomes of critically ill patients before and after the implementation of an evidence-based nutritional protocol have been evaluated (Adam and Batson 1997; Barr, *et al.* 2004). Introduction of such a protocol was associated with an increased likelihood that patients

would receive enteral nutrition and a shortened duration of mechanical ventilation. More importantly, the risk of death was 56% lower in patients who received enteral nutrition (Barr, *et al.* 2004). However, there have been no randomised trials that directly evaluate the impact of feeding protocols on outcomes in these patients. The implementation of a feeding protocol that involves mandatory prokinetic therapy for a specified GRV reduced the number of patients with high GRVs, with a trend towards shorter time to reach goal feeding rate (Pinilla, *et al.* 2001). Thus, although current evidence supports the implementation of an evidence-based nutritional protocol, this has not been conclusively demonstrated.

5.6.3 MANAGEMENT OF GASTRIC DYSMOTILITY AND FEED INTOLERANCE

Despite the above measures, it is essential to recognise and institute treatment of gastric dysmotility and feed intolerance as early as possible in order to prevent the related morbidities. Current evidence suggests that prokinetic therapy should be the first line therapy in the treatment of feed intolerance (Booth, *et al.* 2002; Doherty and Winter 2003; Heyland, *et al.* 2003). However, the choice of prokinetic agents, optimal regimen and duration of treatment require further study (Chapter 4).

The benefits of post-pyloric feeding in patients with no evidence of impaired gastric emptying are uncertain and post pyloric feeding is not currently recommended (Marik and Zaloga 2001; Heyland, *et al.* 2002; Ho, *et al.* 2006). Although direct small intestinal feeding has been recommended for patients with feed intolerance refractory to prokinetic therapy (Davies and Bellomo 2004), data that support this practice are lacking.

5.6.4 PARENTERAL NUTRITION

Nutritional support via the parenteral route is recommended in critically ill patients at risk of malnutrition in instances where enteral nutrition cannot be initiated within 48 hours of admission. In surgical patients who have undergone laparotomy for either gastrointestinal cancer resection (Kudsk, *et al.* 1992) or multiple trauma injury (Driscoll and Blackburn 1990; Kudsk, *et al.* 1992; Buzby 1993; Jeejeebhoy 2001), early initiation of PN has been associated with a small reduction in mortality (Doig and Simpson 2005). In a recent meta-analysis, the survival benefits from early initiation of parenteral nutrition were even greater in patients with medical illness or closed head injury, where an overall reduction in mortality of 23% was seen, compared to those who received delayed enteral feeding (Doig and Simpson 2005).

Despite these benefits, the use of parenteral nutrition in clinical practice is not routine. This reflects concerns about complications associated with this approach, including sepsis and metabolic disturbances. A number of measures have been implemented over the years to minimize the risk of septic complications related to parenteral nutrition in critically ill patients. First, meticulous care of the intravenous access lines, the use of antibiotic impregnated central lines and early recognition of line sepsis are essential to reduce the risk of parenteral nutrition associated sepsis (Stratton and Smith 2006) and are universally adopted by all intensive care units. Second, hyperglycemia during the provision of parenteral nutrition is associated with an increased risk of cardiac complications, infection, systemic sepsis, renal failure (Cheung, *et al.* 2005) and is an independent risk factor for death (Umpierrez, *et al.* 2002; Vanhorebeek, *et al.* 2005). Maintenance of euglycemia via intensive insulin therapy, therefore, has been shown to reduce mortality in critically ill patients (Van

den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003; Krinsley 2004). Furthermore, caloric requirement should be assessed carefully to avoid over-feeding as it can lead to hyperglycemia (Driscoll and Blackburn 1990; Van den Berghe, *et al.* 2003) and fatty infiltration of the liver (Benotti and Bistrian 1987; Klein, *et al.* 1998). Third, it is important to recognise that prolonged use of parenteral nutrition, particularly with formulations rich in oxidisable lipids, may promote organ injury such as acute respiratory distress syndrome (Battistella, *et al.* 1997; Suchner, *et al.* 2001). Lipids are oxidant prone and can promote oxidant-induced cell injury (Carpentier, *et al.* 1979; Carpentier, *et al.* 1997). Thus, the use of parenteral nutrition formulations with minimal oxidisable lipids is advisable in critically ill patients who require prolonged PN support (Carpentier, *et al.* 1979; Carpentier, *et al.* 1997).

The role of supplementary parenteral nutrition to enteral nutrition during critical illness has also been evaluated. Perhaps surprisingly, in critically ill patients with an intact gastrointestinal tract, supplementation of enteral nutrition by parenteral nutrition to achieve 100% of the goal caloric requirement is associated with a trend toward an increased mortality, compared to enteral nutrition alone (Heyland, *et al.* 2003; Doig and Simpson 2005); and therefore, is not recommended. Currently, there are no data regarding the role of parenteral nutrition, as either the primary or supplementary source of nutritional support, in patients who have feed intolerance and are refractory to prokinetic therapy. Despite this lack of evidence, TPN has been recommended as an equally effective and safe alternative for these patients (Jeejeebhoy 2001).

Overall, the data support the use of parenteral nutrition in critically ill patients who are at risk of malnutrition and in whom enteral nutrition cannot be initiated within 48 hours of admission due to gastrointestinal dysfunction. Meticulous line care and aggressive management of hyperglycemia are necessary at all time during the provision of TPN. Finally, there does not appear to be a role for combined parenteral nutrition and enteral nutrition in critically ill patients.

5.7 CONCLUSIONS

Nutritional support during critical illness improves overall patient outcomes and survival. For patients with an intact gastrointestinal tract, the enteral route is preferred to parenteral nutrition because of advantages in cost, morbidity, and ease of administration. Strategies such as the implementation of an evidence-based nutritional protocol may optimize the delivery of nutritional requirement. The treatment of feed intolerance caused by gastric dysmotility is initially with prokinetic therapy, although the optimal treatment approach with these drugs is unknown. There are limited data to support the benefits of post-pyloric feeding and TPN as first line therapies in feed intolerant patients. However, these therapies are frequently used in patients who are refractory to prokinetic therapy.

SECTION 2:

COMMON METHODOLOGIES

CHAPTER 6: PATIENTS AND COMMON TECHNIQUES USED IN THIS THESIS

6.1 INTRODUCTION

This chapter focuses on description of the methods common to studies performed in this thesis, to allow accurate interpretation of these studies and their results. In healthy volunteers and critically ill patients, proximal gastric motor activity was evaluated using a gastric barostat and distal gastric motility was assessed by combined antro-pyloro-duodenal perfusion-based manometry. Gastric emptying and intra-gastric meal distribution were assessed with radionuclide imaging. In some studies, gastric emptying was also measured using the ^{13}C-octanoic acid breath test. These techniques are well accepted approaches to assess gastric motor function in the non-critically ill population. Where a new technique has been established, this is specified and described in detail in the relevant chapter.

6.2 SUBJECTS

6.2.1 HEALTHY VOLUNTEERS.

Healthy subjects were recruited primarily by the placement of advertisements and information sheets on notice boards located within the hospital. Prior to enrolment, subjects were screened to exclude previous or current gastrointestinal illness, diabetes mellitus, liver disease, renal failure and or the use of medications that could affect gastrointestinal function. Subjects with a history of abdominal surgery (except for appendicectomy) and a history of structural abnormalities of the nose or pharynx were excluded. In all female subjects, the presence of pregnancy or possible pregnancy was specifically sought by direct questioning

and urinary pregnancy test. Subjects who potentially be pregnant or had a positive test were excluded. All subjects were non-smokers.

6.2.2 CRITICALLY ILL PATIENTS.

Critically ill patients were recruited from a 24-bed, mixed medical and surgical tertiary level Intensive Care Unit at the Royal Adelaide Hospital, from January 2004 to February 2007. To be eligible for enrolment, patients needed to be (i) over 17 years of age, (ii) mechanically ventilated, and (iii) able to receive enteral nutrition via a naso-gastric or oro-gastric feeding tube.

For all studies in this thesis, the exclusion criteria were a history of (i) suspected bowel obstruction or perforation, (ii) major abdominal surgery within 6 weeks, (iii) prior oesophagectomy, partial or total gastrectomy or significant bowel resection, (iv) coagulopathy manifest by an INR > 1.5 and a platelet count < 80,000 per mL, or (v) administration of opioid analgesia or prokinetic therapy within 24 hours prior to the study, except in studies that examined the impact of sedation (Chapter 10) and prokinetic (Chapter 11) therapies on gastric motor function.

Given the survival benefit of tight blood glucose concentration control in this population, all patients were managed according to a standardized insulin protocol, adopted from Kingsley et al (2004), that aimed to maintain the blood glucose concentration between 5.0-7.9 mmol/L. The presence of pregnancy or possible pregnancy was specifically sought by direct questioning of next of kin and was an exclusion criterion.

6.2.3 COMMON LIMITATIONS IN STUDYING CRITICALLY ILL PATIENTS.

Due to the difficulty in recruiting critically ill patients for research study, there are several limitations in the interpretation of the results derived from the current thesis. In studies (Chapter 7 and 8) that compare data between critically ill patients and healthy volunteers, the potential limitation of most concern was the absence of factors such as mechanical ventilation, sedatives and inotropes in healthy subjects, which have been shown or have been proposed to disturb gastric motor function. However, these factors define critically ill patients and, thereby, reflect the "true" state of gastric motility during critical illness. Another limitation is the age difference as, in general, the critically ill patients were approximately 20 years older than healthy subjects. Current data suggest that healthy aging is associated with a very small but measurable slowing of gastric emptying (Hutson, *et al.* 1989; Kao, *et al.* 1998). Even with comparison between critically ill groups, the heterogeneity in admission diagnosis, mode of ventilation and sedation, and medications within the study population often limit the interpretation of the data. In order to minimize this limitation, comparative groups in the majority of studies in the current thesis (except for studies in Chapter 7 and 8) were relatively well-matched for these factors.

Another potential limitation is the sub-optimal posture during the assessment gastric motility and emptying by barostat technique and gastric scintigraphy. Although barostat and scintigraphic studies are best performed in the upright sitting position (Azpiroz and Malagelada 1985; Azpiroz 1997; Camilleri, *et al.* 1998), this is not possible in critically ill patients. Hebbard et al (1995) recommended that if upright posture is not possible, then the same posture should be controlled between the studied groups. For this reason, both barostat and gastric scintigraphy assessments in the current thesis were performed at 30 degree

recumbent position in both patients and healthy subjects. The normal reference range for gastric emptying in supine position, as median (IQR), has been established "in-house" in a group of 22 healthy volunteers (Ritz, *et al.* 2001).

6.3 ETHICS APPROVAL AND CONSENT

All protocols were approved by the Royal Adelaide Hospital Research Ethics Committee prior to the recruitment of subjects. For studies that involved an investigational therapeutic drug, the protocols were also approved by the Royal Adelaide Hospital Investigational Drug Sub-Committee.

In healthy subjects, signed, informed consent was obtained from each subject prior to participation in each study. All subjects understood they were free to discontinue studies at any time. All subjects were offered an honorarium for their participation.

As critically ill patients were unable to give consent, signed informed consent was obtained from the subject's next of kin or from the guardianship board if the subject did not have a next of kin. This is permitted according to the South Australian state law. In all cases, the next of kin and/or the whole family were informed about the nature of the study together with the anticipated risk and benefit prior to decision making. All next of kin of studied subjects were given a written information sheet about the study and understood that they were free to withdraw consent or discontinue studies at any time, and that there is no direct benefit to the patient.

6.4 STUDY ENVIRONMENT

All studies in healthy subjects were conducted in the clinical research study rooms in the Department of Gastroenterology of the Royal Adelaide Hospital. Studies performed in critically ill patients were conducted in the patient's room within the Intensive Care Unit. Both medical and nursing staffs responsible for the care of the participating patients were informed about the study in advance. On the study day, equipment was brought to the patient's room and arranged so as not to interfere with patient care. In order to minimise the risk of reflux and aspiration, all patients were studied in the 30 degree head-up, supine position. The next of kins of participating patients were allowed to visit during the conduct of the study.

6.5 DRUG PREPARATION AND ADMINISTRATION

The studies described in Chapter 11 involved the use of prokinetic agents, metoclopramide and erythromycin, for the management of feed intolerance. In these studies, the medications were prepared, blinded and randomised by a single pharmacist in the Pharmacy Department of the Royal Adelaide Hospital, South Australia. Both active prokinetic agents and placebo treatment were prepared in a 10-mL syringe, sealed in a black plastic bag with label clearly documented the study number, date and time to be given. In all studies, placebo was 0.9% saline. Prepared treatment medication was then stored in the fridge located in the drug room of the Intensive Care Unit. The code for blinding and randomization was not broken until the completion of the study.

All study drugs were administered by trained nursing staff in the Intensive Care Unit. Two months prior to the commencement of the studies, nursing staff were invited to a number of educational sessions concern the nature of these studies, including special emphasis on drug administration. At enrolment, both verbal and written instructions were repeated to the nursing staff responsible for the participating patients. The assigned study drugs were clearly documented in both the patient's case notes and critical care chart. All drugs were administered as a slow intravenous bolus over 10 minutes.

6.6 PROTOCOL FOR ENTERAL FEEDING IN CRITICALLY ILL PATIENTS

In addition to the initial medical evaluation on admission to the Intensive Care Unit of the Royal Adelaide Hospital, all patients were assessed for any potential contraindications of enteral nutrition. In the absence of any contraindication, enteral feeding was prescribed by the attending intensive care physician with a view to provide early establishment and maintenance of enteral feeding in a protocol-driven fashion. Gluten- and lactose-free Nutrison Standard® (Nutricia N.V., Zoetermeer, The Netherlands; per 100 mL contains 100 kcal, 4 g protein, 12.3 g carbohydrate, and 35% of fat) is the standard enteral feed preparation provided by the Unit, unless patients have severe liver or renal failure. The daily caloric requirement of each patient was determined by the Unit dietitian, based on the patient's estimated body mass index (BMI). Feeds were delivered at a constant rate using a Compat® Enteral Feeding pump (Novartis Medical Nutrition, Fremont, MI, USA).

According to the 'feeding-protocol' adopted at the Intensive Care Unit of the Royal Adelaide Hospital, naso-gastric feeding is commenced at 40 mL/h in all patients (Figure. 6.1). After 6 hours of naso-gastric feeds, manual gastric aspiration, using a 60 mL syringe, is performed to assess GRV. Thereafter, this practice of GRV monitoring is continued 6 hourly until enteral feeding is ceased. A GRV of less than 250 mL is returned to the patient and the feeding rate increased by 20 mL/hr until the prescribed daily requirement rate is reached. Patients who continue to have gastric aspirate of less than 250 mL are defined as 'feed-tolerant'.

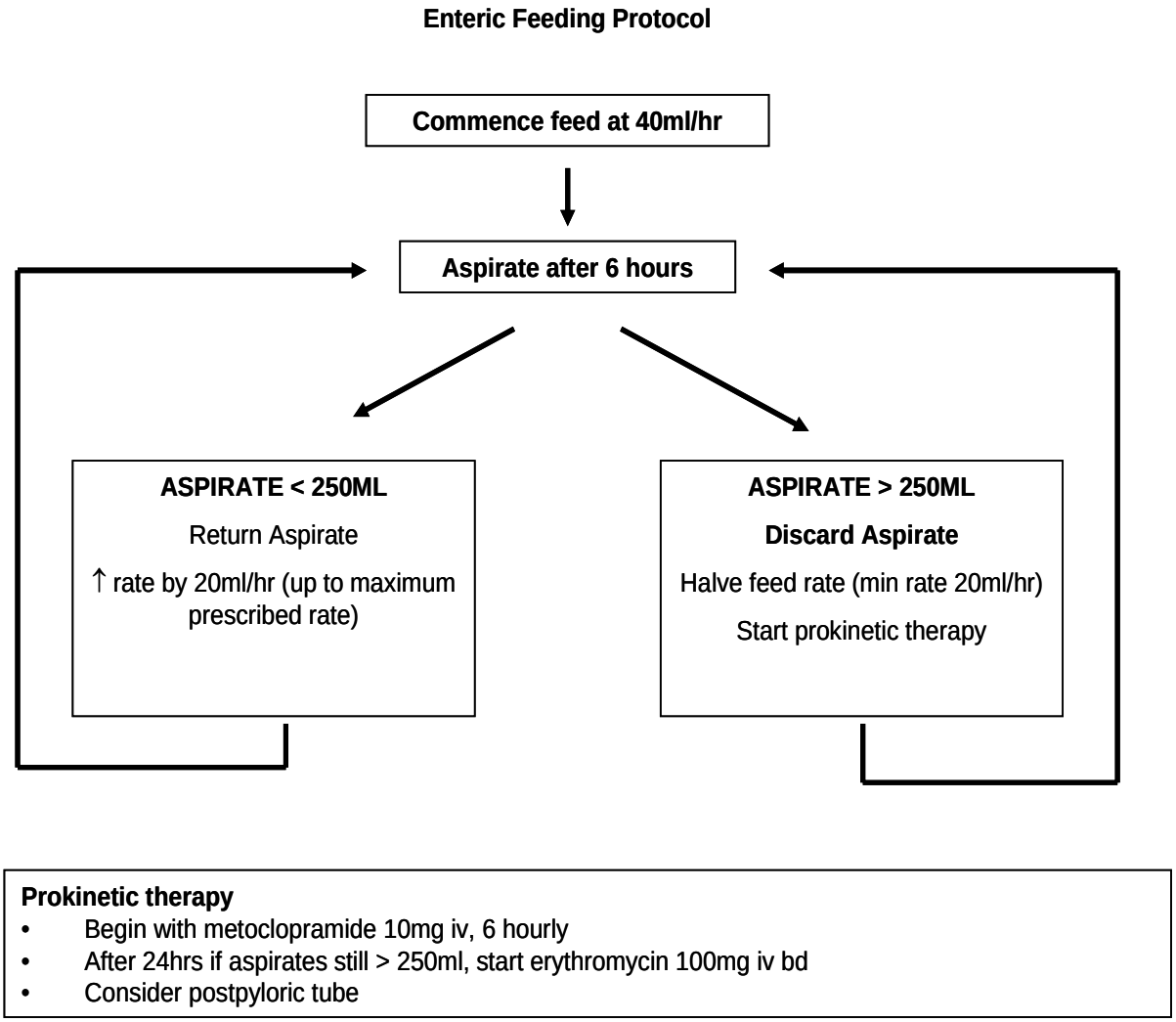


Figure 6.1 Enteral feeding protocol adopted at the Intensive Care Unit of the Royal Adelaide Hospital.

If a gastric aspirate is ≥ 250 mL in volume, the aspirate is discarded and the feeding rate reduced by half to a minimum rate of 20 mL/h. These patients are labelled as 'feed-intolerant', an indication that treatment with prokinetic therapy, either intravenous 10 mg QID metoclopramide or 200 mg BD erythromycin, is required. Traditionally, the choice of the initial prokinetic agent is dependent on the preference of the caring physician. If the GRV continues to be greater than 250 mL despite these measures, treatment with combined erythromycin and metoclopramide therapy or insertion of a post-pyloric feeding tube is performed.

6.7 TECHNIQUES USED TO ASSESS GASTRIC MOTOR ACTIVITY AND EMPTYING

6.7.1 GASTRIC BAROSTAT

6.7.1.1 Background.

The gastric barostat was originally developed by Azpiroz and Malagelada as an direct technique to assess motor and sensory function of the proximal stomach (Azpiroz and Malagelada 1984, 1985; Azpiroz 1994, 1997), and has been generally accepted as the gold standard for examining proximal gastric motility (De Schepper, *et al.* 2004). It involves the introduction of a polyethylene bag or balloon, with a maximum volume of 1.2 litres, into the gastric fundus and simultaneously measures intragastric pressure as well as volume (Azpiroz and Malagelada 1984, 1985; Azpiroz 1994, 1997). The bag is connected to a barostat device

via a polyvinyl tube with two lumens, one to inject or withdraw air and one for monitoring the pressure within the bag. The barostat can be programmed to maintain either (i) a constant intra-gastric pressure by varying intra-bag volume (*iso-baric* volume study), or (ii) a fixed intra-bag volume at which variations in intra-bag pressures are recorded (*iso-volumetric* pressure study). Initially, the minimum distending pressure (MDP), a pressure at which the balloon is in apposition with the gastric wall, is determined by distending the bag to a volume of 30 mL or until respiratory variation is noted (Azpiroz and Malagelada 1984, 1985; Azpiroz 1994, 1997). By maintaining an arbitrary intra-bag pressure of 1 or 2 mmHg above the MDP, the iso-baric volume fluctuations of the balloon indirectly reflect the volume fluctuation of the proximal stomach and thus changes in gastric tone. Gastric compliance can be examined by measuring the changes in intra-bag pressure after a set of fixed volume distension (Azpiroz and Malagelada 1984, 1985; Azpiroz 1994, 1997).

Although the technique has been used extensively and validated by the demonstration of the effects of disease, there is a problem with reproducibility (Sarnelli, *et al.* 2001; De Schepper, *et al.* 2004). On two occasions, separated by 7 days, a mean intra-individual difference of approximately 100 mL in post prandial relaxation has been reported in both healthy subjects and patients with dyspepsia (Sarnelli, *et al.* 2001). While this intra-individual variability may be acceptable in healthy subjects (given post-prandial relaxation varies from 400 to 600 mL), it may be considerable in dyspeptic patients as the median post-prandial relaxation in these patients is relatively small (~140 to 200 mL) (Mearin and Malagelada 1993; Sarnelli, *et al.* 2001). Another disadvantage of this technique is the impact of the balloon on the fundo-antral reflex, the intra-gastric distribution of the meal and possible gastric emptying. The

direct stimulus imposed by the balloon on the stomach wall has been reported to exaggerate antral relaxation, and induce a more distal distribution of meal and a slightly more accelerated gastric emptying (Ropert, *et al.* 1993; Mundt, *et al.* 2002). Furthermore, the technique is invasive, uncomfortable or stressful for many subjects, and thus may influence measurements of tone and sensation. Recently, concurrent assessment of gastric motility by barostat and MRI suggested that barostat technique may overestimate fundal relaxation (de Zwart, *et al.* 2007). Due to these disadvantages and special expertise required, the clinical application of gastric barostat has been limited to a few academic, tertiary centers. This technique, however, is used extensively in research settings to evaluate various aspects of gastric physiology in health and in patients with dyspepsia and diabetes mellitus, as well as assess the pharmacological effects of various therapies for dyspepsia and slow gastric emptying.

6.7.1.2 Equipment.

In the current thesis, the equipment and techniques used to examine proximal gastric motility were identical in all studies (Chapter 7 and Chapter 10). The electronic gastric barostat used (Distender Series II; G&J Electronics, Ontario, Canada) was based on that developed by Azpiroz and Malagelada (1984), which consisted of a bellows mechanism that introduced and withdrew air from a thin flaccid-walled bag positioned in the proximal stomach. The bellows was connected to the bag by a 110 cm-long polyvinyl chloride catheter that contained: (i) a 3 mm channel through which air was introduced or withdrawn, and (ii) a 0.97 mm air-filled channel that was used to monitor intra-bag pressure. When inflated, the barostat bag was approximately spherical in shape and had a capacity of 1200 mL. The barostat pumping unit had a maximum displacement of 800 mL and over the range of volumes used the compliance

of the barostat bag was greater than 4000 mL/mmHg. The air was introduced or withdrawn at a rate of 33 mL per sec when the pressure in the intragastric bag differed from the set pressure by greater than 0.4 mmHg.

Data from the barostat, sampled at 1 Hz, were recorded on a Powermac 7100 computer (Apple Computer, Cupertino, CA), using custom-written data-acquisition software (Labview: National Instruments, Austin, TX). This software was also used to program the barostat to perform distensions in stepwise increments (Hebbard, *et al.* 1996). The measured intra-bag volume was corrected for the effects of air compression.

6.7.1.3 Data analysis.

Changes in proximal gastric volume were assessed by changes in volume in the polyethylene bag. Data stored onto the Powermac 7100 computer (Apple Computer, Cupertino, CA) were subsequently imported into a display and analysis program (Acqknowledge, Biopac System, Goleta, CA) for manual analysis.

Intra-bag volumes were determined at 2 minute intervals and mean baseline volumes were measured over 10 minutes before each infusion. Changes in intra-bag volume during nutrient infusions were calculated as the difference between the actual bag volume and the mean baseline volume immediately before infusion. The serial changes in bag volume during the infusions were plotted and compared. Proximal gastric relaxation was indirectly inferred from changes in intra-bag volume (Azpiroz 1997).

Assessment of fundic slow volume waves was also performed. These were defined as changes in proximal gastric volume of greater than 30 mL that reverted in less than 2 minutes to a volume within 50% of the previous level (Azpiroz and Malagelada 1984). The number and amplitude (volume) of fundic slow waves (per 10 minute) was determined during fasting and in response to small intestinal nutrients.

6.7.2 ANTRO-PYLORO-DUODENAL MANOMETRY.

6.7.2.1 Background.

Manometry is an indirect but accurate method to assess gastric wall motion that results in lumen-occlusive contractions. The system normally consists of a manometric tube assembly, either perfused or incorporating micro-transducers, and a recorder. The most important feature of this system is that each component has a much faster response rate than the maximal rise rate of the manometric event, so that the motor activity can be examined continuously on second-by-second basis (Dodds 1976; Dodds, *et al.* 1976; Dodds, *et al.* 1978; Phillips and Camilleri 1992; Quigley, *et al.* 1992; Mearin and Malagelada 1993; Verhagen, *et al.* 1999). Furthermore, with the ability to measure pressure waves concurrently at multiple sites within a region, manometry allows the determination of the direction of wave propagation as well as the assessment of the pressure wave organisation between these regions (Quigley, *et al.* 1992; Mearin and Malagelada 1993; Byrne and Quigley 1997; Gu, *et al.* 1998). However, the disadvantages of manometry are the inability to detect non-lumen-occlusive contractions and measure gastric emptying or intra-luminal flow (Quigley, *et al.* 1992; Mearin and Malagelada 1993; Byrne and Quigley 1997; Gu, *et al.* 1998).

In this thesis, antro-pyloro-duodenal (APD) motility was assessed by the most commonly used system, perfusion manometry with a sleeve sensor (Dent 1976; Dent, *et al.* 1977; Dent and Holloway 1996). This system allows gastric, pyloric and duodenal pressures to be recorded for long periods during both in the fasting and post-prandial states (Dent 1976; Dent, *et al.* 1977; Phillips and Camilleri 1992; Quigley, *et al.* 1992; Dent and Holloway 1996; Byrne and Quigley 1997). The array of side-holes, which are the focal pressure sensors, allows accurate assessment of lumen-occlusive contractions as well as the organisation of antro-duodenal motor activity (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Houghton, *et al.* 1988; Phillips and Camilleri 1992; Byrne and Quigley 1997). Due to the short length of the pyloric sphincter and its mobility during both fasting and post-prandial states (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Houghton, *et al.* 1988), side-hole manometry is not suitable to evaluate motor activity of the pylorus. The use of manometric assembly with a single or a chain of side-holes at the pylorus fails to provide a reliable and continuous record of pyloric motor activity (Fisher and Cohen 1973; White, *et al.* 1981, 1983), even with continuous monitoring of trans-mucosal potential difference (TMPD, see below). These weaknesses can be overcome by a sleeve sensor (Dent 1976; Dent, *et al.* 1977), which is more tolerant to axial mobility and able to record pressures along its length throughout the observation period. In combination with side-hole manometry in the antro-duodenal region, an accurately positioned sleeve sensor across the pylorus by continuous TMPD monitoring provides the most effective method of prolonged monitoring motor activity of the antro-pyloro-duodenum (Heddle, *et al.* 1988; Fone, *et al.* 1990; Fraser, *et al.* 1993; Heddle, *et al.* 1993; Fraser, *et al.* 1994; Chapman, *et al.* 2005).

There are, however, several limitations of the sleeve sensor related to its physical properties. First, the compliance of the sleeve membrane limits the pressure rise rate in the distal portion of the sensor and potentially leads to an under-recording of pyloric motility, particularly phasic pressures (Heddle, *et al.* 1988; Sivri and Mittal 1991). Second, sleeve pressure can be artificially elevated by distortion of the sleeve membrane, either by mucosal folds or angulation of the catheter in the proximal duodenum (Houghton, *et al.* 1988). This limitation can be minimised by shortening the sleeve length and ensuring that the catheter distal to the sleeve is as flexible as possible. Third, it is not possible to differentiate localised from non-localised pyloric pressure waves when sleeve sensor is used in isolation as it records the maximal pressure exerted at any point along its length (Sivri and Mittal 1991). This problem can be overcome by concurrent use of side-hole manometry in the antrum and duodenum (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Tougas, *et al.* 1992).

6.7.2.2 Trans-mucosal potential difference (TMPD) measurements.

In order to assess pyloric motility accurately, the correct position of the sleeve sensor across the pylorus needs to be monitored and maintained continuously. Without the need of radiology, sleeve sensor position can be monitored accurately by measuring TMPD, which is the electrical potential difference between the mucosal and serosal aspects of the gastrointestinal tract (Read and Fordtran 1979). The difference in mucosal potential between the stomach and duodenum gives rise to a gradient in TMPD (Andersson and Grossman 1965; Read and Fordtran 1979). The correct position of the sleeve was defined as when antral potential was more negative than -20 mV, duodenal potential was more positive than -15 mV and the potential difference between the two was greater than 15 mV (Andersson and Grossman 1965; Fisher and Cohen 1973; Heddle, *et al.* 1988; Houghton, *et al.* 1988; Fone, *et*

al. 1989; Fone, *et al.* 1990; Heddle, *et al.* 1993). This knowledge has been used in many previous human studies to determine to position of the pylorus, without exposing subjects to radiation (Andersson and Grossman 1965; Fisher and Cohen 1973; Heddle, *et al.* 1988; Houghton, *et al.* 1988; Fone, *et al.* 1989; Fone, *et al.* 1990; Heddle, *et al.* 1993). In the current thesis, TMPD values were displayed continuously throughout studies that examined antro-pyloro-duodenal motility. The position of the catheter was adjusted as necessary to maintain the position of the sleeve sensor across the pylorus.

6.7.2.3 Equipment.

The motor activity of the APD region in Chapter 7 was assessed using a multi-channel perfusion manometric assembly (Dentsleeve, Adelaide, South Australia) that incorporated a sleeve sensor for recording pyloric activity, a technique which has been used previously by many investigators (Heddle, *et al.* 1988; Fone, *et al.* 1990; Fone, *et al.* 1990; Fraser, *et al.* 1993; Fraser, *et al.* 1994; Chapman, *et al.* 2005). The assembly consisted of a 100 cm long silicon rubber catheter with an outer diameter 3.5 mm that incorporated 15 pressure-recording channels (side-holes spaced 1.5 cm apart) with a 4 cm-sleeve sensor and a duodenal feeding channel (Figure 6.2). The assembly was positioned so that 5 side-holes were located in the gastric antrum, the sleeve sensor straddled the gastroduodenal junction and 7 side-holes were located in the proximal duodenum. The infusion port, located at the catheter tip, enabled the delivery of enteral feed into the duodenum, 9cm distal to the pylorus.

All manometric lumina were perfused with degassed, distilled water at 0.04 mL per minute, except the two channels on either side of the sleeve (channel 7 & 11) which were perfused with 0.9% saline for monitoring of TMPD. Pressures were measured by external transducers

(Abbott Critical Care, Illinois) and recorded at 10Hz on a Power Macintosh G3 computer using previously validated purpose written software (HAD, G Hebbard, Melbourne, Australia) and Labview as a base program.

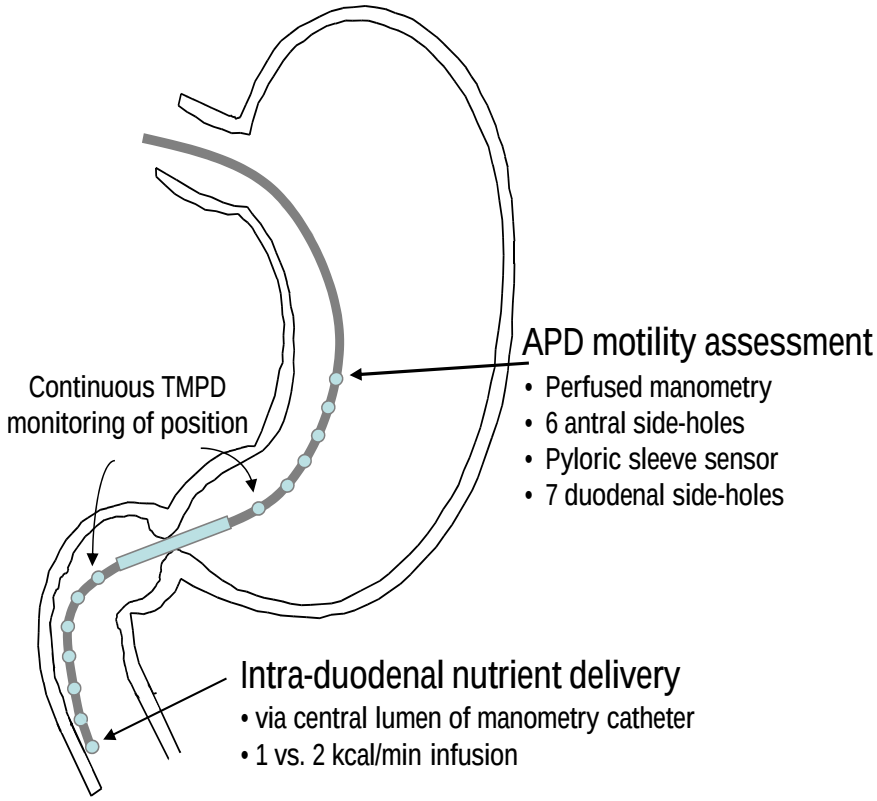


Figure 6.2 Outline of the recording technique and position of antro-pyloro-duodenal manometric assessment in both healthy and critically ill subjects. In both groups, intra-duodenal nutrients were delivered by a central lumen of the APD catheter.

6.7.2.3 Data analysis.

Manometric data were converted into Acqknowledge 3.2.7 (Biopac System Inc, Santa Barbara, Ca, USA) for storage and analysis. Recordings were analysed manually to determine the frequency, origin and characteristics of APD pressure wave activity. Pressure

waves were only included in the analysis when the assembly was positioned correctly according to established TMPD criteria (Heddle, *et al.* 1988; Fone, *et al.* 1990; Fone, *et al.* 1990; Fraser, *et al.* 1993; Fraser, *et al.* 1994; Chapman, *et al.* 2005). A pressure wave in the antrum and pylorus was defined as a pressure rise ≥ 10mmHg from baseline and lasting between 6.1 and 20 seconds (Heddle, *et al.* 1988; Fone, *et al.* 1990; Fone, *et al.* 1990; Fraser, *et al.* 1993; Fraser, *et al.* 1994; Chapman, *et al.* 2005). A duodenal pressure wave was defined as a pressure rise ≥ 6mmHg from baseline and lasting between 0.8 and 7 seconds (Heddle, *et al.* 1988; Fone, *et al.* 1990; Fone, *et al.* 1990; Fraser, *et al.* 1993; Fraser, *et al.* 1994; Chapman, *et al.* 2005).

Pressure waves in adjacent channels were regarded as temporally related if their onsets were within 5 seconds (in the antrum) or 3 seconds (in the duodenum) of each other (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Heddle, *et al.* 1993; Chapman, *et al.* 2005). A propagated pressure wave sequence was defined as 3 or more temporally related pressure waves (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Heddle, *et al.* 1993; Chapman, *et al.* 2005). The total number of waves (propagated and non-propagated) were quantified within the antrum (6 cm proximal to the pylorus) and duodenum (3 cm distal to the pylorus). Propagated sequences were grouped according to whether they were antral, duodenal, or propagated from the antrum to duodenum. All propagated antral waves (PAWs) were assigned a direction (antegrade, retrograde or mixed) and length (based on side-hole spacings) of propagation (Heddle, *et al.* 1988; Houghton, *et al.* 1988; Heddle, *et al.* 1993; Chapman, *et al.* 2005). For all identified PAWs, the presence of an associated pyloric wave was determined.

6.7.3 GASTRIC SCINTIGRAPHY.

6.7.3.1 Background.

In humans, gastric scintigraphy shows not only the time course of gastric emptying of liquids and/or solids, but also allows the intragastric distribution of meal components to be followed (Camilleri, *et al.* 1985; Collins, *et al.* 1988; Malbert, *et al.* 1997; Camilleri, *et al.* 1998; Maurer and Parkman 2006; Troncon, *et al.* 2006). It is currently regarded as the clinical gold standard in the evaluation of gastric emptying (Horowitz and Dent 1991; Camilleri, *et al.* 1998; Maurer and Parkman 2006). Furthermore, with recent technical advances, it is possible to visualize gastric contractions together with emptying (Fried 1994). The procedure is non-invasive and entails a relatively low exposure to ionizing radiation.

The gastric scintigraphic studies that were performed in the current thesis are different from those of routine clinical scintigraphy for several reasons. First, nutrient containing liquids rather than solid meal was measured because only liquid nutrients can be administered to the critically ill patients. The "4-hour" scanning time was adopted because gastric emptying in critically ill can be severely delayed and this scanning time has been demonstrated to differentiate delayed from normal gastric emptying (Thomforde, *et al.* 1995; Camilleri, *et al.* 1998). Second, all scintigraphic studies in this thesis (including those of healthy subjects) were performed in supine position with 30 degree head elevation, rather than the sitting position. Furthermore, in order to minimize unnecessary movement of critically ill patients for research purposes, a mobile single headed gamma camera was used. Due to the lack of published normal values on the rate of gastric emptying of the specific nutrient-liquid meal, a set of normal values has been established 'in-house' from a group of 22 healthy volunteers (personal communication with M Chapman).

As with solid emptying, there are several pitfalls that need to be considered during the measurement of gastric emptying of a liquid meal. First, correction must be made for movement, radionuclide decay and attenuation of gamma rays due to intra-gastric redistribution of the test meal (Collins, *et al.* 1984). Second, the 'diluting effect' of gastric secretion is not quantified in the analysis (Schwizer, *et al.* 1994; Camilleri, *et al.* 1998). Third, the results can be influenced by the position of the gamma camera, with an anteriorly placed gamma camera underestimating and a posteriorly positioned detector overestimating the rate of gastric emptying (Heading, *et al.* 1976). This problem can be corrected by using a dual headed camera, obtaining lateral image of the stomach or by rotating the subjects to obtain both anterior and posterior images (Collins, *et al.* 1984). Fourth, there is a considerable intra-individual coefficient of variation of almost 15% in gastric emptying measurements of healthy subjects, which is an important factor that needs to consider in the establishment of normal data (Degen and Phillips 1996).

6.7.3.2 Equipment.

A mobile single-head gamma camera (GE Starcam 3200iXTA mobile camera; General Electric, Milwaukee, WI) fitted with a high energy 400keV collimator was used to assess gastric emptying and intra-gastric meal distribution in studies detailed in Chapter 9. All scintigraphic studies in patients were performed at their bedside within the intensive care unit. Scintigraphic counts were recorded at a frame rate of 1 per 3 minute, for a total duration of 240 minutes. The lay-out of the study is illustrated in Figure 6.3.

All patients were studied supine at 30º head elevation with the camera orientated in the left anterior oblique position in order to maximize visualisation of both proximal and distal stomach. Via the pre-existing naso-gastric feeding tube, a standard test meal consisting of 100 mL of Ensure® (Abbott Laboratories, Ohio, USA; composition: 13% protein, 64% carbohydrate, 21% fat; energy content: 1 kcal/mL) labelled with 20 MBq 99mTechnetium-V-thiocyanate was infused slowly over 5 minutes in all patients. The time that delivery of the meal into the stomach was completed was defined as t = 0 minute.

6.7.3.3 Data analysis.

Gastric emptying was determined by a previously validated technique (Collins, *et al.* 1983; Collins, *et al.* 1988). The isotopic count within the defined gastric regions of interest was measured and used to derive gastric emptying curves, which expressed the percentage of meal remaining in the stomach over time. Scintigraphic images were acquired for 240 minutes (3-minute frames). The amounts of the meal remaining in the total, proximal and distal stomach at 0, 5, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes were calculated. The data were corrected for subject movement, radionuclide decay and γ-ray attenuation (Collins, *et al.* 1984).

The regional distribution of meal within the stomach was also determined by constructing proximal and distal regions of interest (ROI) (Collins, *et al.* 1988). The proximal ROI was defined as the proximal reservoir area that filled shortly after the completion of the delivery of liquid meal. The remaining distal portion of the total gastric ROI was labelled as the 'distal gastric ROI'.

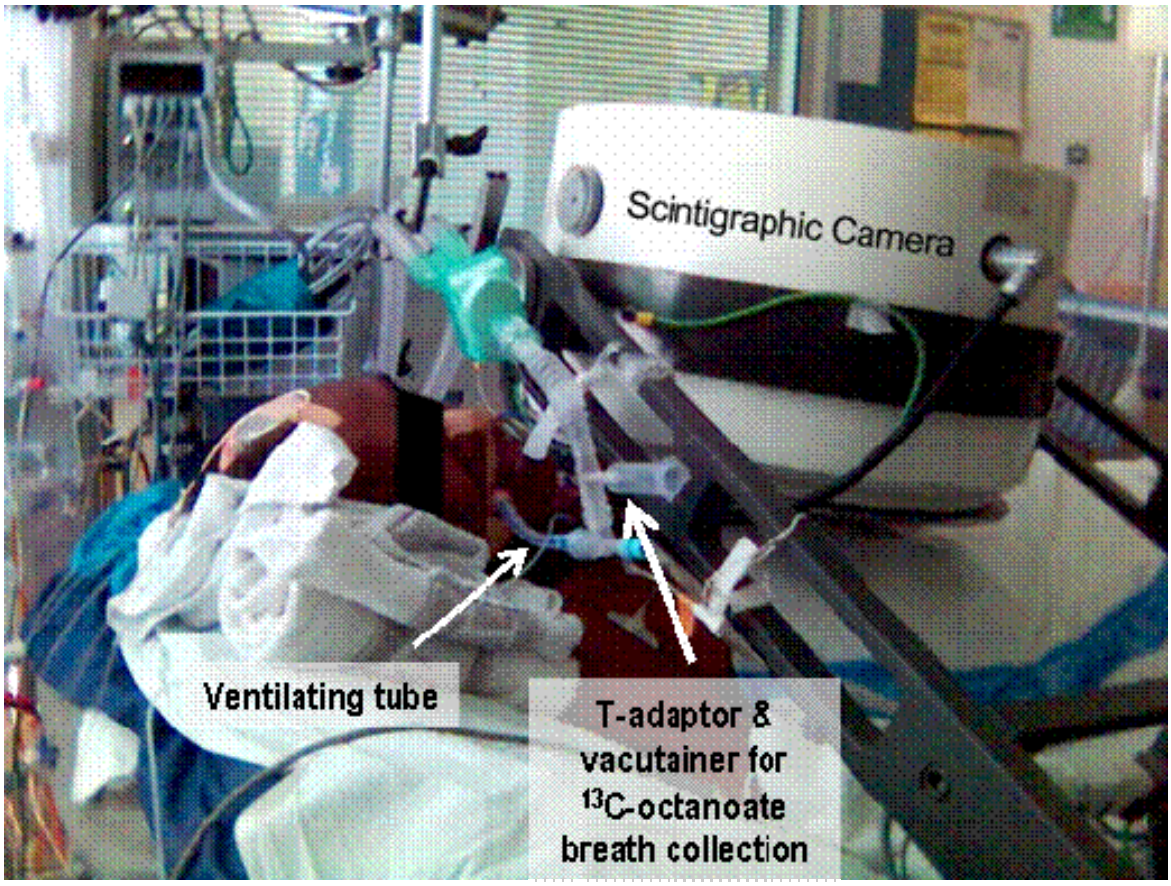


Figure 6.3 A photograph of a mobile scintigraphic camera used to assess gastric emptying in a critically ill patient. Gastric emptying of this patient was also assessed by ^{13}C-octanoate breath test. The photograph demonstrated the position of the T-adaptor and vacutainer within the closed ventilating system, used to collect end-expiratory breath for measurement of ^{13}C-octanoate.

From the emptying curves, the gastric half emptying time (t1/2) was calculated as the time taken for 50% of the meal to empty. However, determination of gastric t1/2 was not possible in approximately one third of critically ill patients because the emptying did not reach 50% at 240 minute. Due to the inherent weaknesses of extrapolating gastric t1/2 from a computer generated best-fitted emptying curve, t1/2 variable was not reported in the current thesis. Consequently, the definition of "delayed" gastric emptying was based only on gastric retention data at 240 minute, which has been reported to have a higher predictive value for

identifying stasis in non-critically ill patients (Camilleri, *et al.* 1998; Kim, *et al.* 2000). In the current thesis, delayed gastric emptying based on scintigraphic assessment was defined by > 10% meal retention at 240 minute (Nguyen, *et al.* 2006).

6.7.4 ^{13}C-OCTANOATE BREATH TESTS

6.7.4.1 Background.

The ^{13}C-octanoate breath test is an indirect technique to measure gastric emptying. The test is based on the assumption that the absorption of ^{13}C-octanoate is dependent on the rate of gastric emptying. Once absorbed into the circulation, ^{13}C is released from the lung, particularly at the end-expiratory phase of respiration. This non-invasive technique has been validated against gastric scintigraphy, using both solid and liquid meals, in healthy subjects and non-critically ill patients (Ghoos, *et al.* 1993; Choi, *et al.* 1997; Maes, *et al.* 1998; Cappello, *et al.* 2000; Hellmig, *et al.* 2006; Punkkinen, *et al.* 2006). Ghoos et al. (1993) have reported an excellent correlation between the gastric emptying variables, half-emptying time and lag phase, determined by the breath test and by scintigraphy. Furthermore, this test has shown only a modest degree of intra-individual reproducibility with a mean coefficient of variance of 12% (Choi, *et al.* 1997). The test, however, may not be accurate in patients with pancreatic, hepatic or pulmonary failure and with visceral hemodynamic changes such as occur during physical exercise or in intensive care (Kim, *et al.* 2000), because ^{13}C-labeled substrate needs to be metabolized by the liver after its absorption from the duodenum and then requires the lung to excrete the substrate as breath ^{13}CO2.

Recently, this technique has been used increasingly for research purposes in critically ill

patients because of its simplicity, non-invasiveness and avoidance of exposure to radiation. Whilst critically ill patients with significant liver failure were excluded from the studies due to the above reasons, patients with respiratory failure and hemodynamic instability could not be excluded as these conditions are almost universally present in every critically ill patient. Despite these weaknesses, preliminary data from the author suggest that breath test has a sensitivity of 71% and a specificity of 100% in detecting delayed gastric emptying with a modest correlation between gastric t1/2 determined by breath test and scintigraphy (Nguyen, *et al.* 2006).

6.7.4.2 Protocol.

Gastric emptying in several studies, detailed in Chapters 8, 9 and 10, was measured by ^{13}C-octanoate breath test, and the technique was adapted from Ghoos and colleagues (Ghoos, *et al.* 1993). After verifying the correct position of the nasogastric tube (12-Fr Flexiflo [Ross Laboratories, Columbus, OH] or 14-Fr Levin tube [Pharma-Plast, Lynge, Denmark]) by air insufflation and measurement of the gastric fluid pH, all gastric contents were aspirated and discarded. In both patients and healthy subjects, 100µl ^{13}C octanoate (100mg/mL; Cambridge Isotope Laboratories, Andover, MA) was added to 100 mL Ensure® (Abbott Australia, Kurnell, Australia), a liquid meal that contains 106 kcal/100mL. The labelled Ensure was shaken for 1 minute to distribute the marker in the meal before it was infused into the stomach over 5 minutes. Breath samples were taken before meal instillation, every 5 minutes for 1 hour and every 15 minutes for a further 3 hours after the meal. In healthy subjects, end-expiratory breath samples were collected by asking them to fully expire into sample tubes, through a straw. In patients, end-expiratory breath samples were collected

from the ventilation tube using a T-adapter (Datex-Engstrom, Helsinki, Finland) and holder for vacutainer (Blood needle holder, Reko, Lisarow, Australia), containing a needle (VenoJect®, Terumo Corporation, Tokyo, Japan) (Figure 6.3). Previous data suggested that equilibration of CO_2 concentration between the ventilation tube and evacuated 10-mL tubes (Exetainer®, Buckinghamshire, England) took a fraction of a second and is a reliable technique of breath sampling (Ritz, *et al.* 2001). To avoid sampling other than end-expiratory air, samples were timed to the end-expiratory phase by observation of the patients and the time-flow curve on the ventilation monitor.

6.7.4.3 Data analysis.

In the studies described in this thesis, the concentration of CO_2 and the percentage of $^{13}CO_2$ were measured in each sample using an isotope ratio mass spectrometer (Europa Scientific, ABCA model 20\20, Crewe, United Kingdom). Samples containing < 1% CO_2 were regarded as being non-end-expiratory and were excluded from further analysis.

The optimal method for the analysis of $^{13}CO_2$ breath test remains controversial, as the values for gastric emptying using exponential models of $^{13}CO_2$ breath excretion have been different from those using scintigraphy (Choi, *et al.* 1997; Maes, *et al.* 1998; Cappello, *et al.* 2000; Kim, *et al.* 2000; Mansi, *et al.* 2004; Hauser, *et al.* 2006). The $^{13}CO_2$ breath concentration over time was plotted and the resultant curves used to calculate two important variables of gastric emptying using non-linear regression formulae: $y = at^b e^{-et}$; where y is the percentage of $^{13}CO_2$ excretion in breath per hour, t is time in hours and a, b and c are regression estimated constants (Ghoos, *et al.* 1993; Maes, *et al.* 1994; Maes, *et al.* 1998). The first and

more reliable measurement of gastric emptying is gastric emptying coefficient (GEC = ln(y)), which is a global index for the gastric emptying rate as it represents both the rate of appearance and disappearance of the label in breath (Ghoos, *et al.* 1993; Maes, *et al.* 1994; Maes, *et al.* 1998). The second variable is gastric half emptying time (t50), which is derived from the $^{13}CO_2$ excretion curve by calculating the area under the curve (AUC), as described previously by Raychaudhuri et al (1998). As the determination of this variable involves estimation and extrapolation of data, it is not as reliable as GEC. For this reason, the definition of "delayed" gastric emptying by $^{13}CO_2$ breath test is based only on GEC. As reported previously (Ritz, *et al.* 2001), the normal range of GEC is between 3.2 and 3.8 and delayed gastric emptying was defined as a GEC of less than 3.2.

6.7.5 GASTRIC RESIDUAL VOLUME.

6.7.5.1 Background.

Monitoring of gastric residual volume is the most widely adopted clinical technique to assess gastric emptying indirectly and the patient's ability to tolerate enteral feeding. The rationale underlying this practice is based on the belief that the stomach is a container of finite size and can be over-filled if input exceeds output over time. It is assumed, therefore, that the presence of "high" GRVs indirectly indicates slow gastric emptying (McClave, *et al.* 1992; McClave and Snider 2002; Heyland, *et al.* 2003) and predisposes the patients to intolerance of nasogastric feeds and the risk of pulmonary aspiration (McClave, *et al.* 2002; McClave and Snider 2002; Metheny, *et al.* 2004).

As described in Chapter 4, the technique has not been critically validated, particularly against the gold-standard scintigraphy and hence, there are controversies surrounding the validity of the technique as a marker of gastric emptying. Using paracetamol absorption test, there was a weak but significant correlation between GRVs and the rate of gastric emptying (Tarling, *et al.* 1997), and emptying may be normal in patients with relatively high gastric residual volumes (Cohen, *et al.* 2000). Consequently, a wide range of arbitrary cut-off volumes, ranging from 75 mL to 500 mL, has been proposed as an indirect marker of delayed gastric emptying and pulmonary aspiration (McClave, *et al.* 1992; McClave and Snider 2002; McClave, *et al.* 2005). Of these, the cut-off value for GRV of 250 mL has been adopted widely in a number of clinical trials as a marker of delayed gastric and feed intolerance (Chapman, *et al.* 2000; Yavagal, *et al.* 2000; Mentec, *et al.* 2001; Berne, *et al.* 2002).

6.7.5.2 Protocol.

The intensive care unit of the Royal Adelaide Hospital adopts the practice of monitoring GRV as part of the feeding protocol, aiming to identify patients who are at risk of delayed gastric emptying and thus, at risk of aspiration. Manual aspiration of the gastric contents using a 60 mL syringe is performed before and 6-hourly after the commencement of naso-gastric (NG) feeding. All gastric aspirate volumes obtained are recorded on the nursing chart. If the initial 6 hourly gastric residue is less than 250mL, the feeding rate is increased by 20 mL/h every 6 hours up to the patient's predicted requirement rate (60-100mL/hr) that is determined independently by a dietitian, based on the patient's body mass index and Harris-Bennedict formula (Boullata, *et al.* 2007). In patients who are feed-tolerant (i.e. gastric aspirates continuously less than 250mL), the assigned therapy is continued for 7 days or until

discharge. At all time-points, successful feeding is defined as a gastric volume < 250mL with a feeding rate ≥ 40 mL/h. Intolerance of enteral feeding is defined as 6-hrly GRV > 250 mL while on continuous naso-gastric feed at a rate of at least 40 mL/h.

6.8 ASSAYS OF GUT HORMONES

Gut hormone levels, particularly of plasma CCK and PYY, were evaluated in several studies described in Chapters 8 and 10. The method involved in the measurement of plasma CCK and PYY was identical amongst the studies. In all patients, blood samples were collected into ice-chilled EDTA-treated tubes containing 400-kIU aprotinin (Trasylol; Bayer Australia Ltd, Pymble, Australia) per millilitre blood. The samples were then centrifuged at 4^{o}C within 30 minutes of collection, and stored at -70^{o}C for subsequent analysis. Both CCK and PYY assays were performed by an experienced laboratory technician from the Department of Medicine.

6.8.1 CHOLECYSTOKININ ASSAY

Plasma CCK concentrations were measured by radioimmunoassay using previously described method (Santangelo, *et al.* 1998). Samples were extracted in 66% ethanol, dried down and resuspended in assay buffer (50 mM phosphate, 10 mM EDTA, 2 g /L gelatin, pH 7.4). Standards were prepared using synthetic sulphated CCK-8 (Sigma Chemical, St Louis, MO, USA). Antibody (C2581, Lot 105H4852, Sigma Chemical) was added at a working dilution

of 1/17,500 and sulphated CCK-8 125I-Labelled with Bolton and Hunter reagent (74 TBq/mmol, Amersham International, Amersham, Bucks, UK) was used as a tracer. Incubation was for 7 days at 4°C. The antibody bound fraction was separated by the addition of dextran-coated charcoal containing gelatin (0.015 g gelatin, 0.09g dextran, 0.15 g charcoal in 30 mL assay buffer) and the radioactivity determined in the supernatants following centrifugation. Intra-assay CV was 9% and inter-assay CV was 15%. Sensitivity was 1 pmol/L (Santangelo, *et al.* 1998).

6.8.2 PEPTIDE YY ASSAY

Plasma PYY concentrations were measured by radioimmunoassay using an antiserum raised in rabbits against human PYY (1-36) (Sigma-Aldrich, St. Louis, MO) (Pilichiewicz, *et al.* 2006). This anti-serum shows less than 0.001% cross-reactivity with human pancreatic polypeptide and sulphated CCK-8 and 0.0025% cross-reactivity with human neuropeptide Y. Tracer (Prosearch International, Malvern, Vic, Australia) was prepared by radio-labelling synthetic human PYY (1–36) (Auspep; Parkville, VIC, Australia) using the lactoperoxidase method. Monoiodo-tyrosine-PYY was separated from free iodine-125, diiodo-PYY, and unlabeled PYY by reverse-phase HPLC (Phenomenex Jupiter C4 300A 5u column cat. no. 00B-4167-EO 250 _ 4.6 mm). Standards (1.6–50 fmol/tube) or samples (200 µl plasma) were incubated in assay buffer (0.05 M phosphate containing 0.5% BSA and 0.02% azide (pH 7.4)) with 100 µl antiserum at a final dilution of 1:10,000 for 20–24 h at 4°C, 100 µl iodinated PYY (10,000 cpm) was then added, and the incubation continued for another 20–24 h. Separation of the antibody bound tracer from free tracer was achieved by the addition of 200 µl dextran-coated charcoal containing gelatin (0.015 g gelatin, 0.09 g dextran, 0.15 g

charcoal/30 mL assay buffer), was incubated at 4°C for 20 minutes, and then was centrifuged at 4°C for 25 minutes. Radioactivity of the bound fraction was determined by counting the supernatants in a gamma counter. The intra- and inter- assay coefficients of variation were 12.3% and 16.6%, respectively (Pilichiewicz, *et al.* 2006). The minimum detectable concentration was 4 pmol/L.

6.9 MEDICAL RECORDS AUDIT

Studies in Chapter 9 and Chapter 10 of this thesis involved a retrospective review of data. Although this approach has the potential for selection bias, it is frequently impractical to perform such studies prospectively as a much longer period would be necessary. Furthermore, data derived from retrospective studies are useful in stimulating further prospective studies.

In all cases, the required information was carefully reviewed and documented from both case notes and critical care observation charts. The following information and measured outcomes were recorded: age, sex, medications including sedatives, inotropes and prokinetics, admission diagnosis, duration of ICU stay, duration of feeding, co-morbidities with particularly attention to the history of diabetes mellitus gastrointestinal illness and surgery, admission APACHE II score, feed rate achieved, gastric residual volume, the presence of feed intolerance, and blood glucose concentrations with insulin requirement on admission and during feeds.

6.10 STATISTICAL ANALYSIS

All data presented in this thesis are expressed as mean ± SEM, unless stated otherwise. Categorical data were compared using Fisher's exact test or Chi-square test with Yate's correction. For independent measurements, data were compared with unpaired Student's t-test (parametric data) or Mann-Whitney U test (non-parametric data). For comparison which involved a number of measures performed over time, a two-way repeated measures analysis of variance (ANOVA) with post-hoc comparisons was used to analyse the data. Correlations were performed with Pearson's correlation coefficient. For analyses in which there were a number of inter-related factors, comparisons were performed using linear and hierarchical regression models. In Chapter 11, the differences in the success of feeding between the treatment groups over time were assessed using Kaplan Meier survival curves with a log-rank test. Risk factors for poor response to prokinetic therapy were assessed by the Cox proportional hazards model. In all studies, two-tailed tests of significance were used and a P-value of less than 0.05 was considered significant in all analyses.

All statistical analyses of the current thesis were advised and confirmed by an independent statistician from the Department of Public Healthy, University of Adelaide. Furthermore, complicated analyses such as hierarchical regression models, Kaplan Meier survival curves and Cox proportional hazards model were performed by the statistician.

SECTION 3:

RESULTS

CHAPTER 7: FURTHER CHARACTERIZATION OF GASTRIC MOTOR DISTURBANCES IN CRITICALLY ILL PATIENTS

7.1 INTRODUCTION

Whilst impaired gastric motor function is common and adversely impacts the outcome of the critically ill patients, current understanding on the nature of the gastric dysmotility remains limited (Chapter 4). Impaired gastric emptying in critical illness has been attributed to distal gastric 'pump failure' (Fennerty 2002), principally because only the motor activity of the antro-pyloro-duodenal region has been evaluated in detail (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Dive, *et al.* 2000; Chapman, *et al.* 2005). Enteral nutrition is delivered to the stomach of critically ill patients in liquid form. Despite the importance of proximal stomach in liquid gastric emptying in humans (Kelly 1980), there have been no studies on proximal gastric motor activity in these patients.

In addition, although the integration between the proximal and distal gastric motor activity is thought to be important in the distribution of intra-gastric meal and therefore, gastric emptying, in both animals (Cannon 1898; Heddle, *et al.* 1993) and humans (Piessevaux, *et al.* 2001; Nguyen, *et al.* 2007), the relationship between the proximal and distal gastric motor activity has also not been evaluated in these patients. This may be important as retention of meal in the proximal stomach has been reported to be significantly greater in critically ill patients with delayed gastric emptying compared to those with normal emptying (Nguyen, *et al.* 2006).

The work described in this chapter examines and characterizes the motor activity in the proximal stomach and the motor integration between the proximal and distal stomach in critically ill patients.

7.2 PROXIMAL GASTRIC MOTOR FUNCTION DURING FASTING AND NUTRIENT STIMULATION

7.2.1 INTRODUCTION

Data from both animal and human studies indicate that the proximal stomach plays an important role in the regulation of liquid gastric emptying (Chapter 2), by generating a gastro-duodenal pressure gradient that propels liquids into the duodenum (Indireshkumar, *et al.* 2000). In dogs, a linear relationship exists between intra-gastric pressure and the rate of gastric emptying of liquids (Horowitz, *et al.* 1994; Indireshkumar, *et al.* 2000). Resection of the fundus increases intra-gastric pressure after a meal and resulting in a rapid gastric emptying (Wilbur, *et al.* 1974) (Chapter 3). In humans, selective vagotomy which denervate the gastric fundus and body impairs gastric accommodation, increases intra-gastric pressure and accelerates gastric emptying (Kelly 1980; Moragas, *et al.* 1993; Azpiroz 1994).

In view of the importance of the proximal stomach in the regulation of liquid gastric emptying and the lack of proximal gastric motility data in critically ill patients, the current study was designed to assess proximal gastric motor activity during fasting and in response to small intestinal nutrient in these patients. In addition, given the recent findings suggested that duodenal nutrient inhibitory feedback on the antro-pyloro-duodenal motility is enhanced (Chapman, *et al.* 2005), it was hypothesized that nutrient feedback to the proximal stomach would also be increased and be associated with more profound proximal gastric relaxation. In order to minimize the variation in nutrient stimulation due to erratic gastric emptying of critically ill patients, nutrient loads were infused directly into the duodenum in order to provide a constant nutrient delivery at physiological levels to the small intestinal receptors.

7.2.2 METHODS

7.2.2.1 Subjects.

Studies were performed in 13 medical, mechanically ventilated critically ill patients (49.3 ± 4.7 yr; 11M), who were admitted to the intensive care unit at the Royal Adelaide Hospital between January and September 2004. All patients were on a standardized insulin protocol, able to receive enteral nutrition, and had no known history of diabetes mellitus (Chapter 6). Data from critically ill patients were compared with those from 12 healthy volunteers (27.7 ± 2.9 yr; 8M). The demographic characteristics of the subjects are summarized in Table 7.2.1.

Table 7.2.1 Demographic characteristics of critically ill patients and healthy volunteers

	Critically ill patients (n=13)	**Healthy subjects (n=12)**
Age(yr)	49.3 ± 4.7 *	27.7 ± 2.9
Sex (M:F)	11:2	8:4
BMI (kg/m^2)	29.7 ± 1.7	24.1 ± 1.0
APACHE II score		
On admission	24.1 ± 1.3	Not applicable
Study day	24.7 ± 1.8	
Days in ICU prior to study	5.0 ± 0.2 days	Not applicable
Diagnosis (n)	Head injury (2), Motor vehicle accident (2), Cardiac arrest and failure(3), Acute pancreatitis (2), Subdural hemorrhage(1), Uro-sepsis (1), Exacerbation of COAD (1), Exacerbation of asthma (1)	Not applicable

* P<0.01, vs. healthy subjects. COAD - chronic obstructed airway disease

7.2.2.2 Study Protocol.

Proximal gastric motility in this study was assessed using a barostat (Chapter 6). In both patients and healthy subjects, the study was performed after at least 6 hours fasting and in a 30 degree recumbent position. Whilst the techniques of placing barostat assembly and post-pyloric feeding tube were different between critically ill patients and healthy subjects, the final position of the assemblies was similar between the groups, as outlined in Figure 7.2.1.

In all critically ill patients, placement of both barostat catheter and post-pyloric feeding tube were performed with endoscopic assistance, at the bedside in the intensive care unit without additional sedation to that required for ventilation. To standardise the sedative regime in patients, propofol alone was used, and opioids, benzodiazepines or prokinetic agents were not administered for 24 hours prior to and during the study. A 114 cm naso-duodenal feeding tube (12 French, Flexiflo, Abbott, Ireland) was initially inserted into the duodenum over a guidewire (THSF-35-260, Cook, Australia) and the barostat catheter was then guided into the stomach by the endoscope, through the mouth. The barostat balloon was inflated with 400 ml of air and was gently retracted into the fundus under direct vision. Gastric contents (air and fluid) were aspirated completely prior to withdrawal of the endoscope. Correct placement of the naso-duodenal feeding tube was confirmed at the time of placement by measurement of the antro-duodenal TMPD gradient (Chapter 6), and subsequently by radiography.

In contrast, the barostat catheter and infusion tube were swallowed and allowed to pass into correct position spontaneously without the need of endoscopy in the healthy subjects. After insertion of the barostat catheter to a depth of 55cm, the balloon was inflated with 400 ml of

air and the catheter was pulled back until resistance was felt. Duodenal nutrient infusion was achieved by inserting a manometric catheter (Dentsleeve, Adelaide, Australia), with a central feeding lumen and lead-weighted tip, into the duodenum. The correct positioning of the infusion catheter was determined by continuous measurement of antroduodenal TMPD gradient (Chapter 6). Radiological confirmation was not performed.

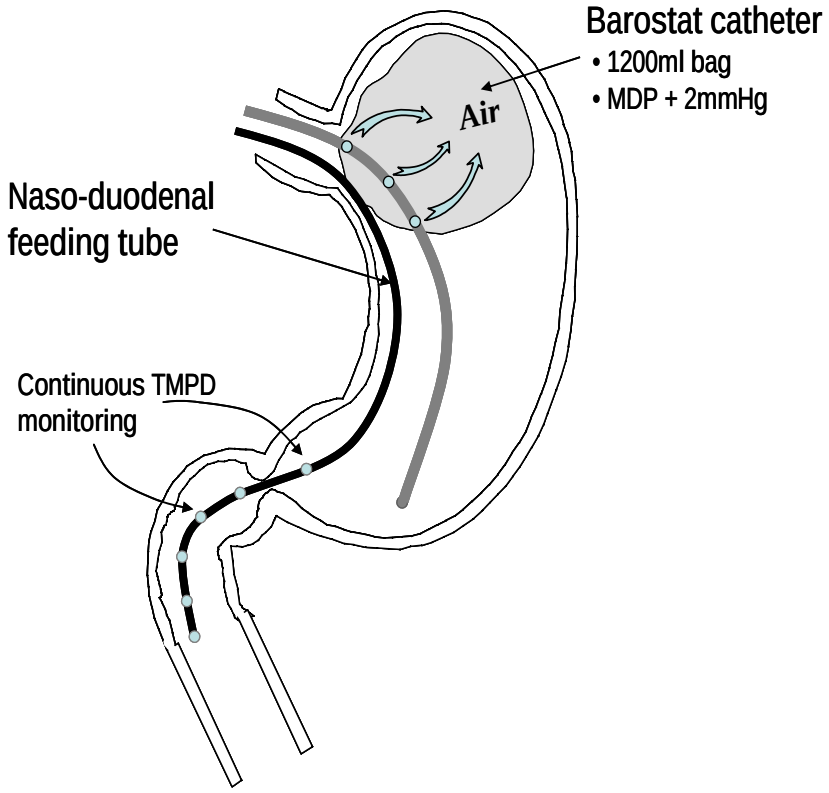


Figure 7.2.1 Outline of techniques and position of the barostat recording assembly and the naso-duodenal feeding tube in healthy and critically ill subjects.

After confirming that the catheters were positioned correctly, air in the barostat balloon was aspirated and the catheter was connected to the barostat. The minimum distending pressure (MDP), defined as the first pressure level that provided an intragastric bag volume of more than 30ml, was determined (Azpiroz and Malagelada 1985). The baseline pressure for the

study was then set at MDP + 2 mmHg (Azpiroz and Malagelada 1985) and an *isobaric* study was performed continuously over 3.5 hours. All studies began with a 15 minute baseline recording, during which normal saline (0.9% NaCl) was infused into the duodenum at a rate of 4 mL/min. Each subject then received a 60 minute duodenal infusion of 2 kcal/min of Ensure® (Chapter 6). In order to examine proximal gastric motor recovery, barostat measurements were continued for 2 hours after the nutrient infusion had ceased. Blood glucose concentrations were also measured at baseline and every 20 minutes during nutrient infusion, using a portable glucometer (Precision Plus, Abbott Laboratories, Bedford, USA).

7.2.2.3 Data analysis

The data were stored and manually analysed using custom-written program in Acqknowledge (Acqknowledge, Biopac System, CA). The method of data analysis on the proximal gastric motility, including proximal gastric volume and fundic waves, is outlined in Chapter 6.

7.2.2.4 Statistical analysis

The differences in demographic characteristics, baseline volumes, MDPs and fundic volume waves between the healthy subjects and critically ill patients were compared using Student's unpaired t-test. A repeated measures mixed-model analysis of variance (ANOVA) was used to compare: (i) the proximal gastric bag volume response between the groups, with time and treatment as the factors; (ii) the blood glucose responses between the groups, with time and treatment as the factors. Student's unpaired t-test was used to compare the maximum changes in proximal gastric volume between the 2 groups. As data were non-parametric, the time required for proximal stomach to return to baseline level after nutrient stimulation was expressed as median and inter-quartile range (IQR), and the differences between the groups were compared using Mann-Whitney test.

7.2.3 RESULTS

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

7.2.3.1 Baseline measurements

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

7.2.3.2 Proximal gastric volume response to small intestinal nutrients

In the healthy subjects, there was a "biphasic" proximal gastric volume response to small intestinal nutrients, with the first relaxation occurring within the first 15 minutes of the infusion (Figure 7.2.2A). Proximal gastric volumes reduced by 57 ± 4% (mean volume reduction = 184 ± 24 mL) after 30 minutes of nutrient infusion, and thereafter increased to a second smaller peak at 50 minutes of the infusion. In critically ill patients, the increase in proximal gastric volume in response to small intestinal nutrients was initially slower and smaller than healthy subjects (change in volume at 10^{th} minute: 45 ± 26 mL vs. 196 ± 29 mL; P<0.001; Figure 7.2.2B). Proximal gastric volume did not peak until 40 minutes after the start of the infusion, but eventually reached similar level to that seen in healthy subjects. The maximal increase in proximal gastric volume did not differ between the 2 groups (patients: 199 ± 35 mL vs. controls: 233 ± 76 mL; Figure 7.2.2B).

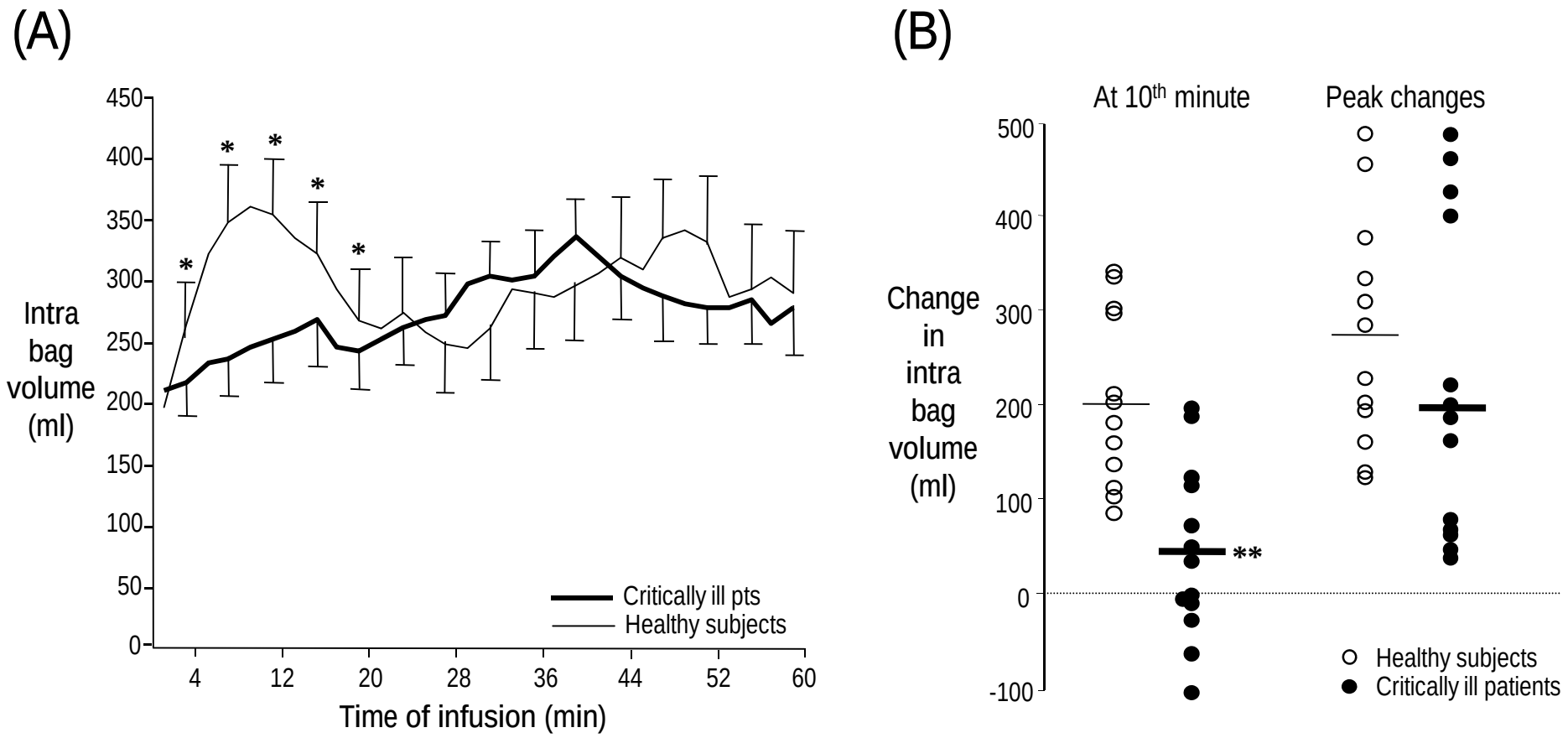


Figure 7.2.2 (A) Changes in proximal intra-bag volume during 2 kcal/min infusions, in healthy (dotted line; n=12) and critically ill subjects (solid line; n=13). * P<0.05, vs. healthy subjects. (B) Changes in proximal intra-bag volume from baseline, at 10th minute and at peak level during nutrient infusion, in healthy (white dot; n=12) and critically ill subjects (black dot; n=13). ** P<0.001, vs. healthy subjects.

7.2.3.3 Proximal gastric motor recovery after nutrient stimulation

In healthy subjects, proximal gastric volumes returned to baseline within 30 minutes of cessation of small intestinal nutrient infusion (median = 18 minutes; IQR: 0-24 minutes). In patients, the median time required for the proximal stomach to return to baseline was significantly longer than that in healthy subjects (median = 106 minutes; IQR: 47-120 minutes; P<0.001) (Figure 7.2.3), and in only 2 of the 13 patients had proximal gastric volume returned to baseline within 30 minutes of cessation of the infusion. In 6 of 13 patients, proximal gastric volume had not returned to baseline by 2 hours after nutrient infusion had finished.

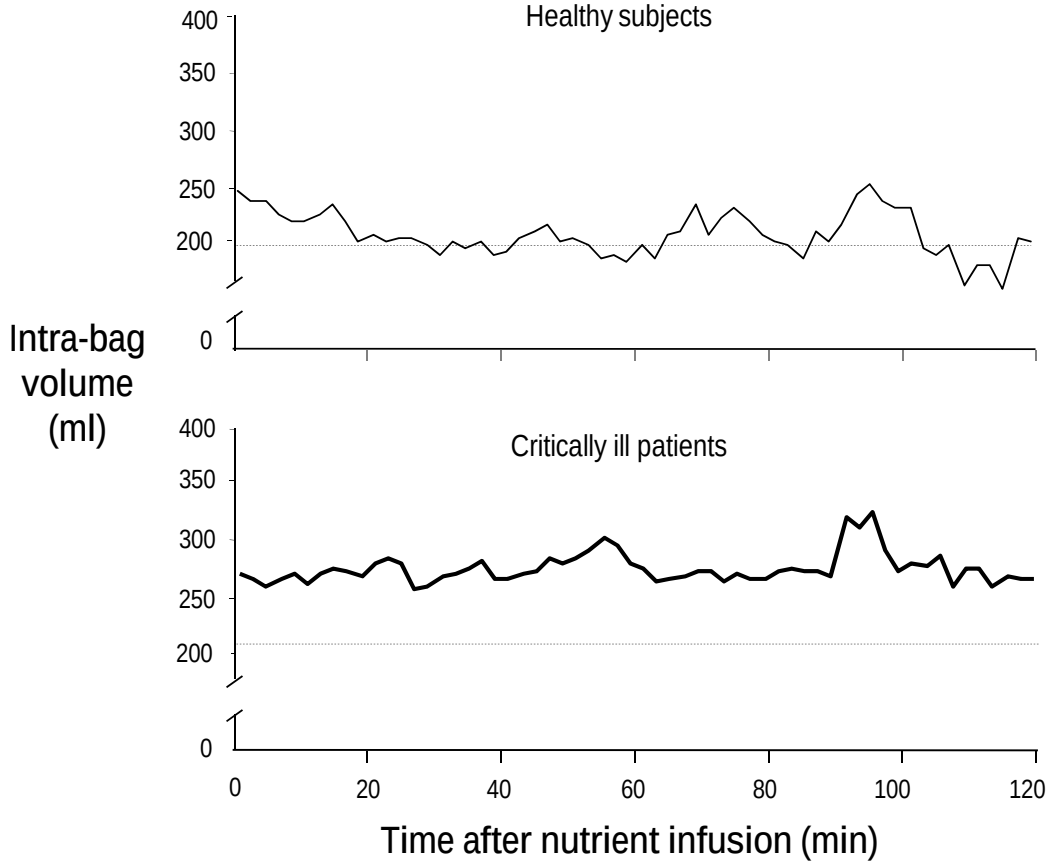


Figure 7.2.3 Time course for the proximal gastric volume to return to baseline levels (…) after nutrient stimulation, in healthy (—) and critically ill subjects (▬).

7.2.3.4 Fundic volume waves during fasting and in responses to duodenal nutrients

The frequency of fundic volume waves in critically ill patients was lower than in healthy subjects, during both fasting and throughout nutrient infusion ($P<0.005$; Figure 7.2.4). In addition, the volume of fundic waves was smaller in the patients than in the healthy subjects (44 ± 3 mL vs. 87 ± 8 mL; $P<0.001$).

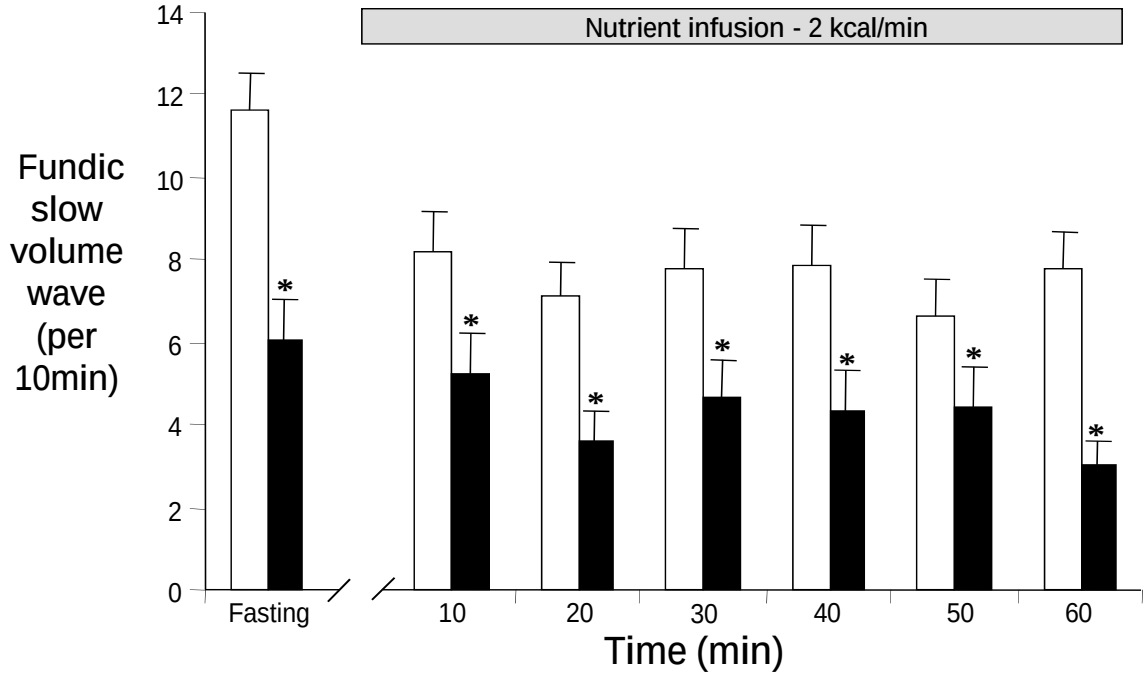


Figure 7.2.4 Fundic slow volume wave (per 10 minute) during 2kcal/min nutrient infusions, in healthy (□) and critically ill subjects (■). * $P<0.05$, vs. healthy subjects.

7.2.3.5 Blood glucose concentration

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

7.2.4 DISCUSSION

The current study is the first to examine proximal gastric motor activity in the critically ill patients. The data demonstrate that, in critically ill patients: (i) proximal gastric relaxation is delayed although the magnitude of the response is normal, (ii) fundic volume slow wave activity is reduced and (iii) the recovery of proximal gastric volumes to pre-stimulation levels is delayed. Whilst the significances of these findings remain unclear, similar abnormalities in proximal gastric motility have been reported in patients with gastroparesis secondary to diabetes mellitus (Hebbard, *et al.* 1996; Undeland, *et al.* 1997; Samsom, *et al.* 1998; Undeland, *et al.* 1998). These findings provide a possible mechanism for the delay in liquid gastric emptying in critically ill patients. It is conceivable that the marked reduction in fundic volume waves and possibly, the failure of the proximal stomach to return to baseline volume after nutrient stimulation may impair the redistribution of meal from the proximal stomach distally for peristaltic pump and thereby, contribute to slow gastric emptying (Kelly 1980; Ricci and McCallum 1988; Collins, *et al.* 1991; Ropert, *et al.* 1993). This concept is supported by findings that increased fundic wave activity is associated with accelerated gastric emptying of liquid (Frank, *et al.* 1995).

The mechanisms that underlie the changes in proximal gastric motility in critical illness are unknown. The initial delay in proximal gastric relaxation could relate to physical restriction from a combination of positive mechanical ventilation and high intra-abdominal pressure as reflected by higher MDP (Malbrain 2004; Malbrain, *et al.* 2005). However the eventual relaxation to normal values suggests this is unlikely to be the cause. Impaired gastric accommodation has been described in diabetes mellitus with autonomic neuropathy (Hould, *et al.* 1994; Kellow, *et al.* 1999; Paterson, *et al.* 2000). Autonomic dysfunction has also been

reported in critically ill patients (Schmidt, *et al.* 2001; Schmidt, *et al.* 2005), and could cause both delayed gastric relaxation and potentially prolong recovery via impairment of different components of the autonomic nervous system. In light of recent reports of interactions between inflammatory mediators, neurotransmitters and intrinsic neural pathways (Kellow, *et al.* 1999; Emch, *et al.* 2000), it is also possible that high circulating cytokine levels in critical illness could impair neural relaxation pathways (Emch, *et al.* 2000, 2002). Opioids and sedative drugs have been reported to alter gastric emptying and proximal gastric motility (Mittal, *et al.* 1986; Heyland, *et al.* 1996; McArthur, *et al.* 1999). While propofol inhibits gastric emptying in animals (Inada, *et al.* 2004), its effects in humans are less clear (Hammas, *et al.* 1998; Chassard, *et al.* 2002; Memis, *et al.* 2006). A small study of healthy humans reported that the combination of propofol and morphine cause a reduced proximal gastric volume compared to morphine alone, but this had no effect on gastric emptying (Hammas, *et al.* 2001). Whilst these findings suggest propofol may reduce proximal gastric relaxation, a proper randomised controlled study examining the impact of propofol alone on gastric motility is warranted.

In view of recent data that suggest delayed gastric emptying is associated with excessive proximal retention of the meal in the proximal stomach (Nguyen, *et al.* 2007), the subsequent prolonged recovery of proximal stomach to baseline after nutrient stimulation may be pathogenetic significance. The mechanisms underlying this abnormality are not known but likely to involve multiple pathways. In particular, those proposed mechanisms that responsible for the initial impaired proximal relaxation are unlikely to regulate the subsequent prolonged relaxation. Although hyperglycemia increases proximal gastric relaxation in both healthy and diabetic subjects (MacGregor, *et al.* 1976; Hebbard, *et al.* 1996; Hebbard, *et al.* 1996; Kong and Horowitz 1999), the elevation of blood glucose levels in the patients was

minor compared to healthy humans and did not exceed the normal post-prandial 'physiological' range. Thus, it seems unlikely to significantly contribute to the prolonged relaxation. Gastric relaxation due to opiate drugs such as morphine (Mittal, *et al.* 1986) also appears unlikely to explain the findings as patients had not received opioid for at least 24 hours. The neurotransmitter nitric oxide may have an important role in mediating proximal gastric relaxation (Desai, *et al.* 1991; Desai, *et al.* 1994). Nitric oxide synthesis is increased in critically ill patients (Wong, *et al.* 1996; Argaman, *et al.* 2003) and could contribute to prolonged proximal gastric relaxation.

The biphasic pattern of proximal gastric relaxation in the healthy subjects in response to small intestinal nutrients is intriguing. This was a consistent observation in all 12 healthy subjects. Physiologically, it is possible that the reduction in proximal gastric volumes from 20 to 35 minute of nutrient infusion reflects proximal gastric contractions to redistribute feed to the distal stomach. This pattern of proximal gastric response, however, has not been reported in barostat studies during intra-gastric (Ropert, *et al.* 1993; Frank, *et al.* 1995) or intra-duodenal (Barbera, *et al.* 2000) nutrient delivery. In the study by Barbara et al (2000), the biphasic pattern of proximal gastric volume was not observed, but the recording of intra-gastric volume was performed for only 30 minutes of duodenal nutrient infusion and thus, may have been too short to detect the second peak. Thus, although the reasons for differences in the proximal gastric response reported to date remain unclear, they may relate to the site of nutrient administration, duration of infusion and even temporal stimulation of different nutrient receptors at different intestinal site relating to the transit of nutrients.

There were a number of methodological factors that may have potentially influenced the interpretation of the current study. Intra-gastric delivery of nutrient was avoided for several

reasons. Most importantly, the variable gastric emptying rate in this group of patients (Heyland, *et al.* 1996; Mentec, *et al.* 2001; Mutlu, *et al.* 2001) would lead to an unpredictable degree of feedback response. Thus, a constant delivery of 2-3kcal/min of nutrient to the small intestine was used to test the feedback response in a standardized fashion (Lin, *et al.* 1989; Mearadji, *et al.* 1999). The effects of performing endoscopy on gastric motility are unknown but are unlikely to be important in the context of nasogastric tube intubation. To minimise the impact of this, the procedure was performed with a narrow diameter endoscope (6 mm) with minimal air inflation and gastric contents were aspirated from the stomach prior to the start of the study. Although information regarding proximal gastric compliance would be of major interest, its determination was prevented by concerns that positive intra-bag pressures in mechanically ventilated patients would interfere with patient ventilation due to the splinting of the diaphragm. The issues related to performing barostat studies in supine position and the older age in critically ill patients have been discussed in Chapter 6. In order to minimize the effects of posture on bag volume (Hebbard, *et al.* 1995), barostat studies were performed in supine position in both healthy subjects and critically ill patients. Similarly, although the controls were 20 years younger than the patients, it is unlikely that this difference would substantially affect the findings as healthy aging does not affect on proximal gastric motor responses to meal (Rayner, *et al.* 2000).

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

7.3 INTEGRATION OF MOTOR ACTIVITY BETWEEN THE PROXIMAL AND DISTAL STOMACH

7.3.1 INTRODUCTION

A functional integration between proximal and distal gastric motility has been observed in both animals (Cannon 1898; Heddle, *et al.* 1993) and humans (Piessevaux, *et al.* 2001; Nguyen, *et al.* 2007), during fasting and nutrient stimulation. At fluoroscopy, the proximal-distal gastric integration appears to distribute ingesta between the two regions and optimize gastric emptying in animals (Cannon 1898). The concept that disruption to gastric regional integration results in a maldistribution of meal and slows gastric emptying has been supported by recent data in patients with functional dyspepsia (Caldarella, *et al.* 2003). In these patients, the 'tonic' interaction between the proximal and distal stomach was impaired, as reflected by the impaired antro-fundic reflex during balloon distension of the antrum (Caldarella, *et al.* 2003), and was associated with abnormal meal distribution. It has been suggested that the disruption in the 'tonic' integration between the gastric regions may represent an important element in the pathophysiology of symptoms in patients with functional dyspepsia (Caldarella, *et al.* 2003; Boeckxstaens and Tytgat 2004).

In addition to the motor abnormalities reported in the proximal (Chapter 7.2) and distal stomach (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005) of the critically ill patients, it was hypothesized that a disruption of proximal-distal gastric motor integration may also be present and contribute to the slow gastric emptying in these patients.

This hypothesis could explain the major retention of the meal in the proximal stomach of these patients, particularly those with delayed gastric emptying (Nguyen, *et al.* 2006). The aims of this study were, therefore, to investigate the (i) presence and (ii) characteristics of the functional integration between proximal and distal gastric motility in critical illness.

7.3.2 METHODS

7.3.2.1 Subjects

Studies were performed in 10 mechanically ventilated critically ill patients (54.4 ± 4.5 yr; 7M), who were admitted to the intensive care unit at the Royal Adelaide Hospital between September 2004 and July 2005. All patients were on standardized insulin protocol, able to receive enteral nutrition, had no known history of diabetes mellitus and shared the common exclusion criteria described in Chapter 6. Data were compared with those from 10 healthy volunteers (27.1 ± 2.5 yr; 5M). The differences in demographic characteristics between the groups are outlined in Table 7.3.1.

7.3.2.2 Study Protocol.

All subjects underwent concurrent assessment of proximal gastric and antro-pyloro-duodenal motilities after at least a 6-hour fast and in a 30 degree recumbent position. In the healthy subjects, the manometric assembly (Dentsleeve, Adelaide, Australia) was initially introduced into the stomach via an anaesthetised nostril. The subject was then placed in the right lateral position to facilitate passage of the catheter tip across the pylorus and its progression into the duodenum by peristalsis. Once the manometric assembly was positioned correctly according

to antro-duodenal TMPD criteria (Chapter 6), the barostat catheter were swallowed and allowed to pass into correct position spontaneously. After insertion of the barostat catheter to a depth of 55cm, the balloon was inflated with 400 mL of air and the catheter was pulled back until resistance was felt (Azpiroz and Malagelada 1984, 1985). Final position of the measuring devices is outlined in Figure 7.3.1.

Table 7.3.1 Demographic characteristics of critically ill patients and healthy volunteers

	Critically ill patients (n=10)	**Healthy subjects (n=10)**
Age (yr)	54.4 ± 4.5 *	27.1 ± 2.5
Sex (M:F)	7:3	5:5
BMI (kg/m^2)	26.2 ± 2.3	23.8 ± 1.5
APACHE II score		
On admission	25.1 ± 1.7	N/A
Study day	25.3 ± 1.8	N/A
Days in ICU prior to study	7.3 ± 0.9	N/A
Admission diagnosis (n)	Sepsis (5) Head injury (3) Motor vehicle accident (1) Ruptured coronary artery (1)	N/A
Inotropes (A/NA†)	6	NA

* P<0.05, vs. healthy subjects † Adrenaline or nor-adrenaline

In the critically ill patients, both the barostat assembly and the APD manometric catheter (Chapter 6) were positioned with endoscopic assistance at the bedside in the intensive care unit, without sedation additional to that required for ventilation. Sedation with propofol alone

was used in all patients. First, the tip of the APD manometric catheter (Dentsleeve, Adelaide, Australia) was guided into the duodenum by snaring the tip of the catheter, and the catheter was positioned so that the sleeve traversed the pylorus (Figure 7.3.1). After correct placement of the APD manometric catheter, the barostat catheter was guided endoscopically into the stomach, through the mouth. Under direct vision, the barostat balloon was inflated with 400 mL of air and was gently retracted into the fundus without much retraction of the APD manometric catheter. Gastric contents (air and fluid) were aspirated completely prior to withdrawal of the endoscope. The correct position of the APD manometric catheter was checked by radiography prior to the start of the study and monitored by continuous measurement of the TMPD gradient (Chapter 6).

After determination of minimum distending pressure (MDP), concurrent barostat recording at MDP + 2 mmHg, and APD manometry were performed. All studies commenced with a 30 minute baseline recording during Phase 2 of the MMC (baseline 1), during which normal saline (0.9%) was infused into the duodenum at a rate of 4 mL/min. In random order, each subject then received two 60 minute duodenal infusions of Ensure® at 1 or 2 kcal/min. Ensure® was diluted 1:4 with normal saline (0.9%) for the 1 kcal/min infusion and 1:2 for the 2 kcal/min infusion, and infused at a rate of 4 mL/min. The nutrient infusions were separated by a 2 hour "washout period" consisting of 1.5 hour of no infusion, followed by 30 minutes of intraduodenal infusion of saline (baseline 2).

Blood glucose concentrations were measured using a portable glucometer (Precision Plus, Abbott Laboratories, Bedford, USA) immediately before and every 20 minutes during, each nutrient infusion.

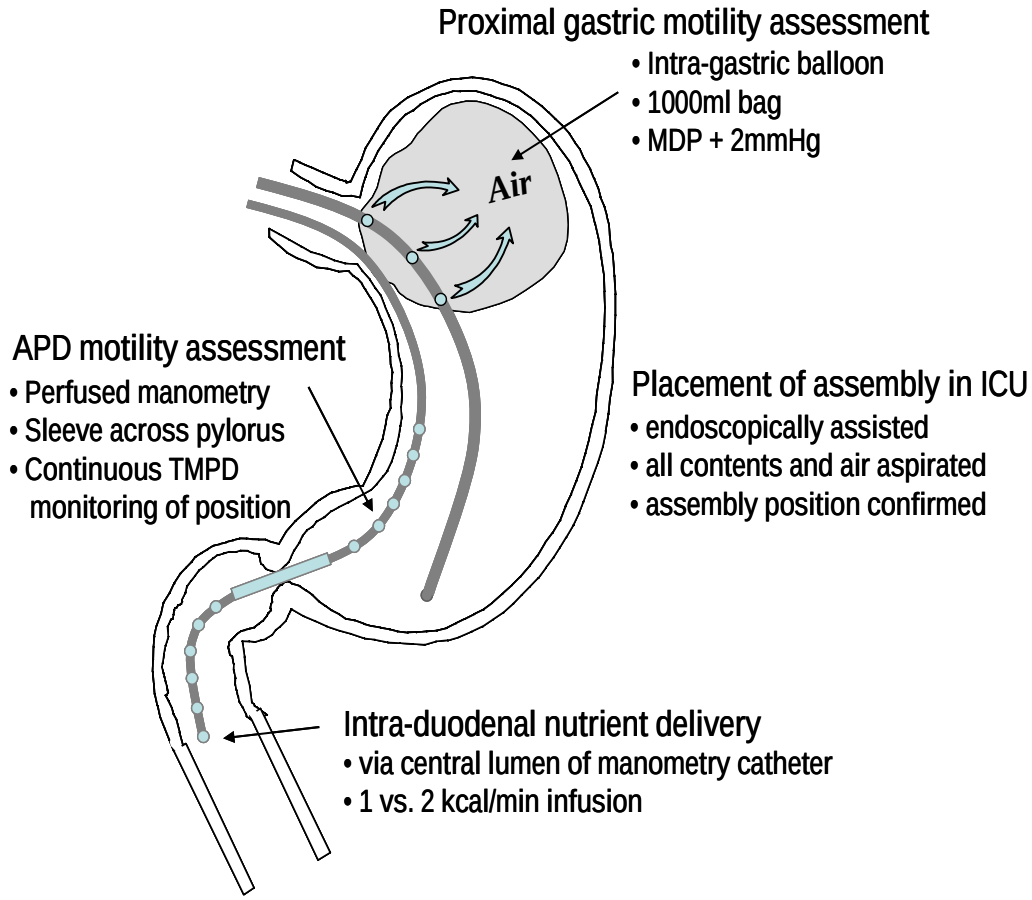


Figure 7.3.1 Outline of study techniques and position of the monitoring assemblies.

7.3.2.3 Data Analysis

The methods used to analyse the motility of (i) the proximal stomach and (ii) antro-pyloro-duodenum have been outlined in Chapter 6. To determine the relationship between proximal and distal gastric motility, the barostat and manometric recordings were combined for analysis. After correction for the different acquisition rates, the data were imported into AcqKnowledge 3.2.7 for manual analysis. Correct alignment of the two recordings was achieved using time markers and cough events (Chapter 6).

The functional association between proximal and distal gastric motor activity was examined by assessing the temporal relationship between the propagated antral waves and fundic waves (FW). A PAW was considered to be associated with a FW if its onset, measured at the most proximal antral site (A1 or A2), occurred within a time window of 10 seconds before and after the occurrence of the FW (Heddle, *et al.* 1993). The definitions of fundic wave, antral waves (propagated and isolated) and functional association between the gastric regions are outlined schematically in Figure 7.3.2, and are best demonstrated in the healthy volunteers (Figure 7.3.2A). The degree of association between gastric regions in the current study was reported as the proportion of FWs followed by a PAW (Heddle, *et al.* 1993; Nguyen, *et al.* 2007), over the study period.

7.3.2.4 Statistical analysis

The differences in demographic characteristics, baseline volumes, MDPs, fundic volume waves, and antro-pyloric waves between the healthy subjects and critically ill patients were compared using Student's unpaired t-test. A repeated measures mixed-model analysis of variance (ANOVA) was used to compare: (i) the proximal intra-bag volume response, (ii) fundic waves, (iii) antral waves and (iv) the blood glucose responses, with time and treatment as the factors. Student's unpaired t-test was used to compare the difference in the relationship of fundic waves and antral wave between the groups. The time required for proximal stomach to return to baseline level after nutrient stimulation was expressed as median and interquartile range (IQR). The differences between the times required for proximal stomach to return to baseline level were compared using Mann-Whitney test.

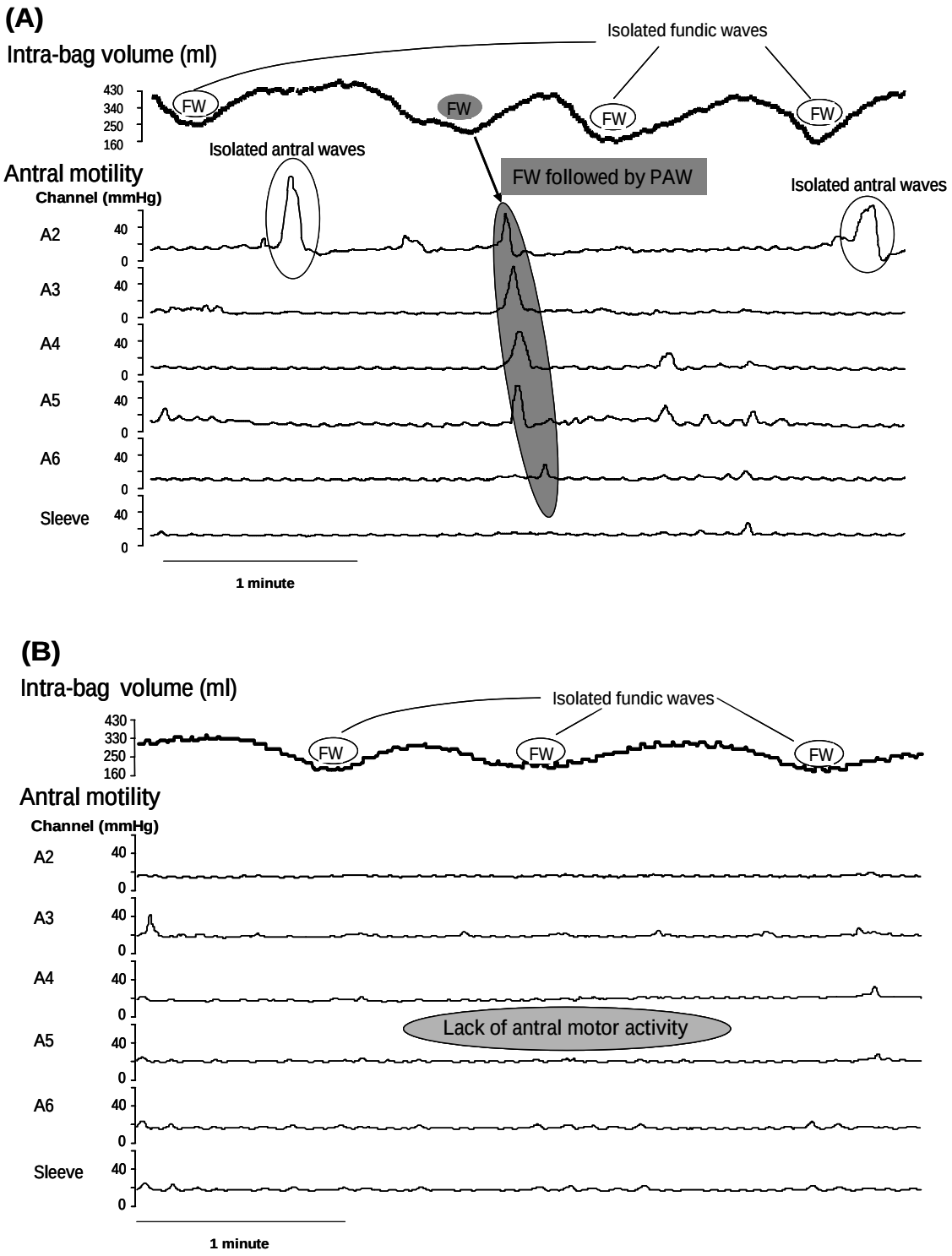


Figure 7.3.2 Example of a combined recording from the proximal and distal stomach in (A) healthy subjects and (B) critically ill patients, with demonstration of definitions: (i) fundic waves (FW), (ii) propagated antral waves (PAW), (iii) isolated antral waves and (iv) associated fundic-propagated antral waves.

7.3.3 RESULTS

7.3.3.1 Proximal gastric motility

The mean MDP in patients was significantly higher than in healthy subjects (12.1 ± 1.0 mmHg vs. 7.7 ± 0.8 mmHg, P=0.003). However, the baseline proximal gastric volume was similar between the two groups (patients: 260 ± 55 mL vs. healthy volunteers: 234 ± 29 mL; P=0.70).

In healthy subjects, there was a dose-dependent increase in proximal gastric volume within 10 minutes of duodenal nutrient stimulation (Figure 7.3.3). In patients, there was no difference in the proximal gastric response between the 1 kcal/min and 2 kcal/min infusions. Compared to healthy volunteers, the proximal gastric volume response in the critically ill patients was similar during 1 kcal/min infusion but was significantly lesser during 2 kcal/min infusion. The difference in proximal gastric relaxation was most pronounced within the first 10 minutes of nutrient infusion. In patients, the proximal gastric volume did not peak until 40 minutes after the start of the infusion.

In patients, the frequency of FW was significantly lower than that of healthy subjects, at both baseline (7.3 ± 1.9 waves/10 min vs. 15.4 ± 1.9 waves/10 min; P<0.05) and during nutrient infusions (Figure 7.3.4). During duodenal nutrient stimulation, the FW frequency was reduced in a dose-dependent fashion in healthy subjects, but not in critically ill patients (Figure 7.3.4). Compared to healthy volunteers (97 ± 8 mL), the volume amplitude of FWs was also reduced in patients (47 ± 5 mL; P<0.01).

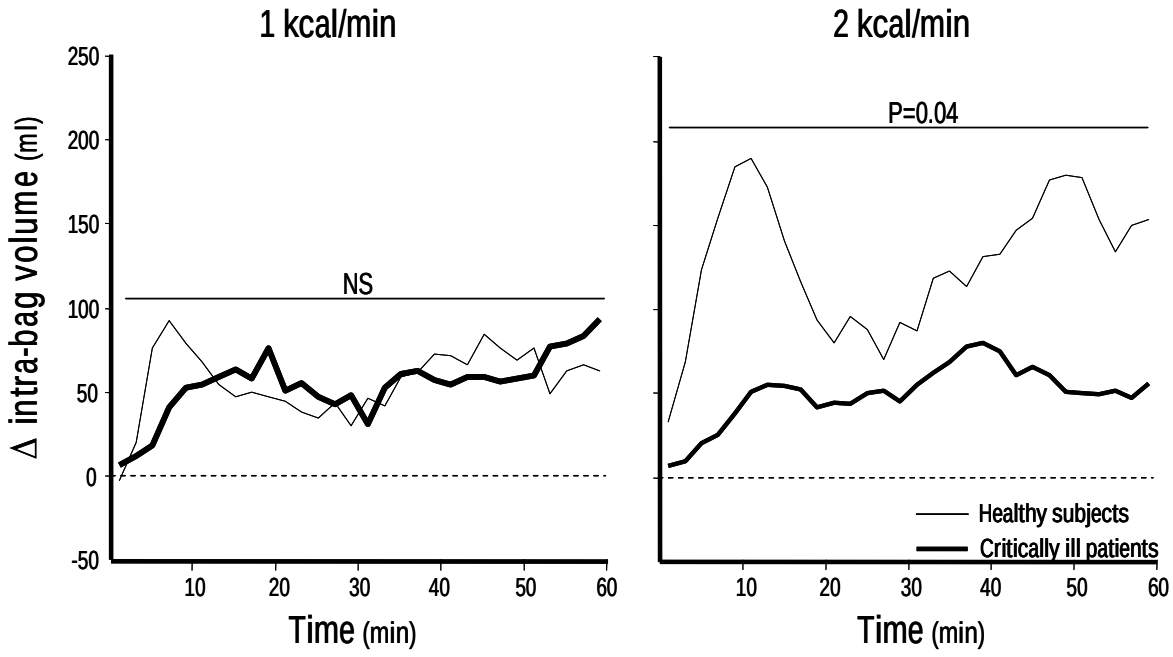


Figure 7.3.3 Changes in proximal intra-bag volume during 1 kcal/min and 2 kcal/min infusions in healthy subjects (—) and critically ill patients (**—**).

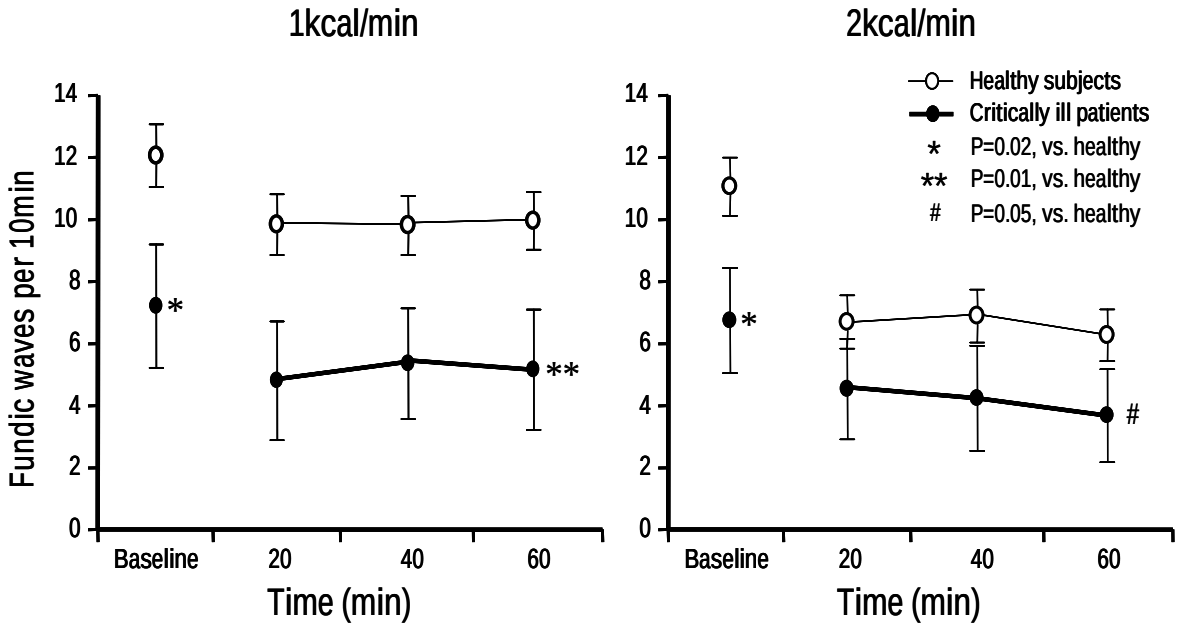


Figure 7.3.4 The mean frequency of fundic slow volume waves (per 10 minute), during fasting and duodenal nutrient stimulation in healthy subjects (○) and critically ill patients (●).

7.3.3.2 Antro-pyloro-duodenal motility.

At baseline, the frequency of both total and propagated antral waves was lower in patients, than in healthy subjects (Figure 7.3.5). There was no difference in the proportion of PAWs associated with a pyloric contraction between the two groups (54% vs. 52%; patients vs. healthy subjects, respectively).

During duodenal nutrient stimulation, there was a dose-dependent reduction in the frequency of both total and propagated antral waves in both critically ill and healthy subjects (Figure 7.3.5). In patients, the frequencies of total and propagated antral waves were lower during the 1 and 2 kcal/min infusions, when compared to healthy subjects. Furthermore, the magnitude of reduction in antral wave frequency was greater in the patients (50 ± 10% vs. 22 ± 6%; P=0.03). PAWs in patients were more likely to be retrograde (24 ± 9% vs. 3 ± 1%; P=0.03), propagated over a shorter distance (5.4 ± 0.4 cm vs. 7.0 ± 0.4 cm; P=0.02) and rarely propagated into the duodenum, compared to healthy subjects.

In healthy subjects, the proportion of PAWs that were associated with a pyloric contraction was similar between the 1 and 2 kcal/min infusions (56% vs. 53%; respectively). In patients, there was a dose-dependent increase in the proportion of PAWs associated with a pyloric contraction during nutrient stimulation (76% vs. 100%, $P<0.05$; 1 vs. 2 kcal/min; respectively), and the proportion was significantly higher than in healthy subjects (1 kcal/min: $P<0.05$; 2 kcal/min: $P<0.001$).

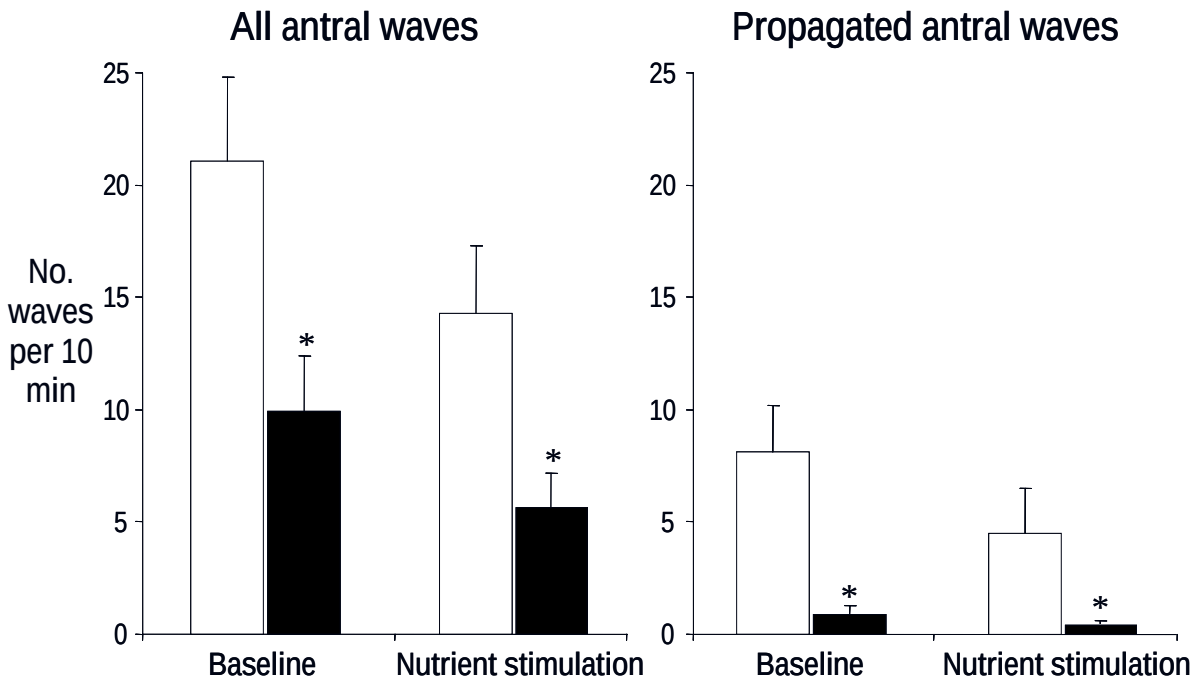


Figure 7.3.5 Antral wave activity and propagation characteristics (per 10 minute) during fasting and small intestinal nutrient stimulation in healthy subjects (□) and critically ill patients (■).
* P<0.001, vs. healthy subjects.

7.3.3.3 Relationship between proximal and distal stomach in humans.

In both critically ill and healthy subjects, all PAWs began either simultaneously with, or after the onset of the associated FW. At baseline, the proportion of FWs followed by a PAW was significantly smaller in patients (11 ± 4%) than in healthy subjects (34 ± 6%; P=0.02) (Figure 7.3.6). Duodenal nutrient stimulation did not affect the proportion of FWs followed by a PAW in either healthy subjects (1 kcal/min: 33 ± 7%, P=0.89; and 2 kcal/min: 21 ± 8%, P=0.43) or critically ill patients (1 kcal/min: 10 ± 4%, P=0.91; and 2 kcal/min: 5 ± 1%, P=0.49). In patients, the proportion of FWs followed by a distally PAW remained less than in healthy subjects, during both the 1 kcal/min and 2 kcal/min infusions.

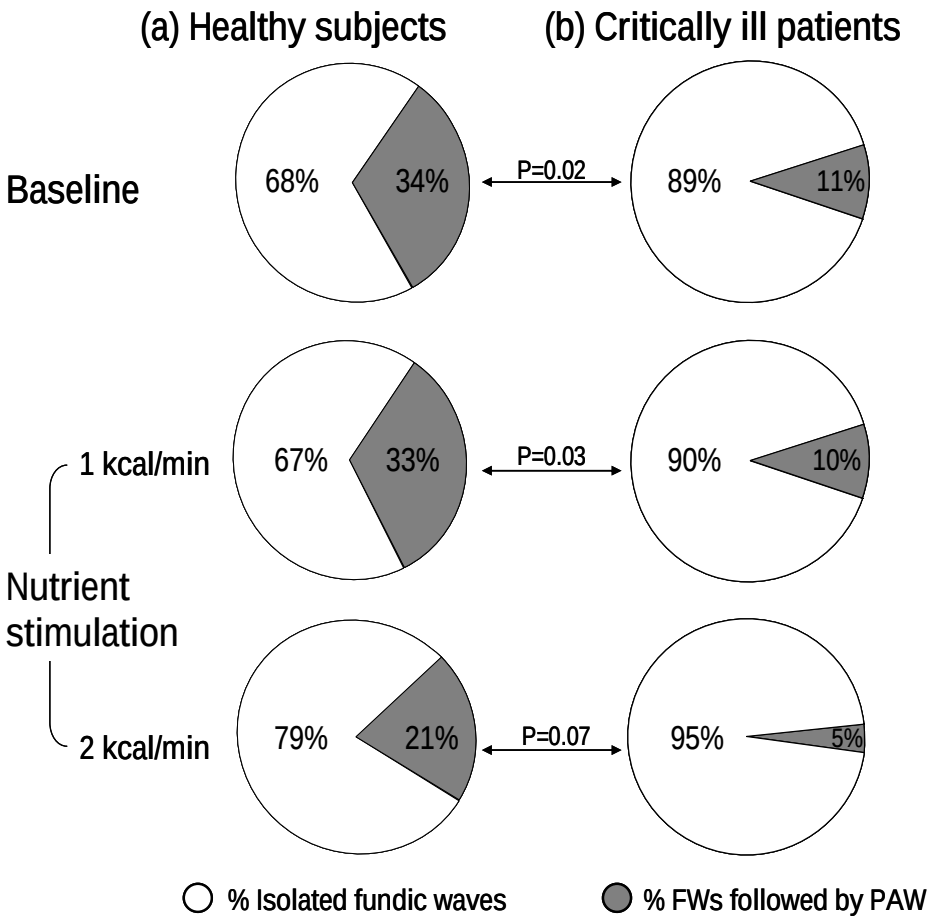


Figure 7.3.6 Relationship between fundic volume waves and propagated antral waves, during fasting and small intestinal nutrient stimulation, in healthy subjects and critically ill patients.

7.3.3.4 Blood glucose response.

At baseline, the blood glucose concentration was higher in patients (7.6 ± 0.5 mmol/L) than in healthy subjects (5.3 ± 0.2 mmol/L, P=0.02; Figure 7.3.7). In both groups, blood glucose concentrations were increased during duodenal nutrient stimulation (both 1 and 2 kcal/min), and were higher in critically ill patients (P<0.01).

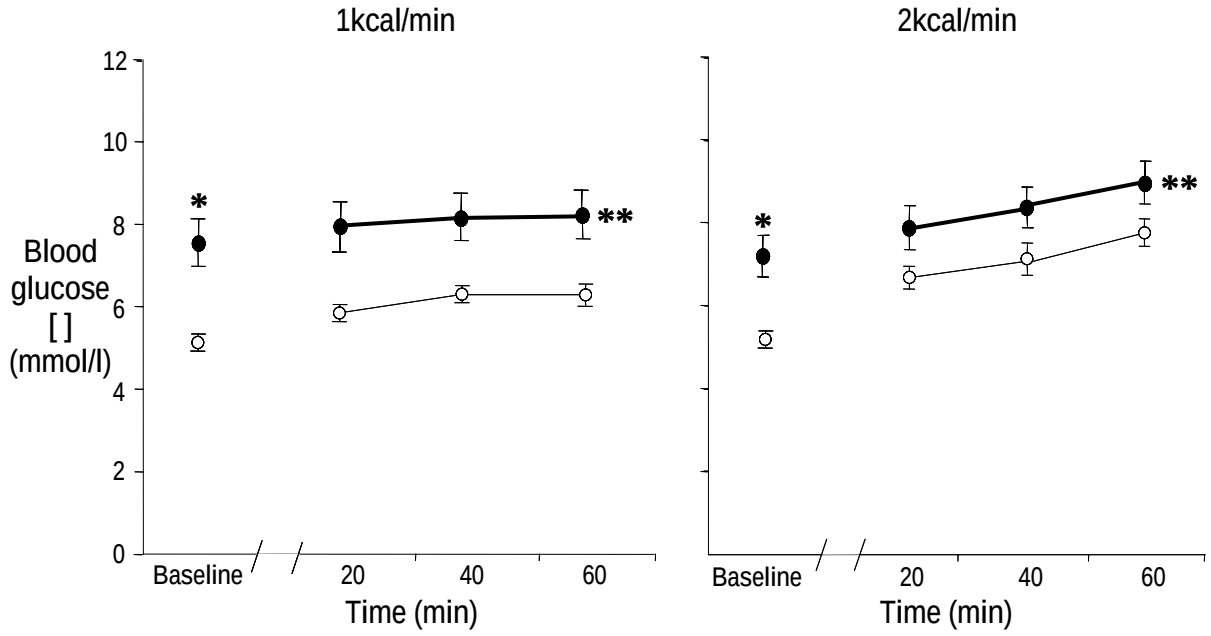


Figure 7.3.7 Blood glucose concentrations during fasting and nutrient stimulation in healthy subjects (○) and critically ill patients (●). * P=0.02, vs. healthy subjects. ** P<0.01, vs. healthy subjects.

7.3.4 DISCUSSION

In addition to confirming previous data described in Chapter 7.2 and previous reports (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005) on distal gastric dysmotility in critically ill patients, the current study demonstrates that the motor association between the two gastric regions is disturbed with a marked reduction in propagated antral waves, which were more likely to be retrograde. As suggested by data in animal models (Cannon 1898; Heddle, *et al.* 1993) and patients with functional dyspepsia (Caldarella, *et al.* 2003), such disruption of the proximal-distal gastric integration during critical illness could result in a greater retention of enteral feed in the proximal stomach (Nguyen, *et al.* 2006), and may contribute to the high frequency of delayed gastric emptying in these patients (Heyland,

et al. 1996; Ritz, *et al.* 2001). Furthermore, upon arrival into the gastric antrum, ingesta may not be cleared effectively due to motor disturbances in the antro-pyloro-duodenum (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005).

In addition to a quantitative reduction in antral wave activity, the current study has shown that the characteristics of propagated antral waves are markedly abnormal in critical illness. Not only did PAWs constitute a very small proportion of all antral waves in these patients, but also when present these were propagated over a shorter distance, were more likely to be retrograde and rarely extended to the duodenum. These findings are consistent with previous studies (Dive, *et al.* 1994; Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005), confirming that the majority of antral waves in critically ill patients are isolated contractions. These patterns have previously been shown to influence the mechanics of antral emptying (White, *et al.* 1981; King, *et al.* 1985; Savoye-Collet, *et al.* 2003). Whilst intermittent, isolated antral waves are primarily responsible for the mixing and triturate of solid food (White, *et al.* 1981), PAWs clear the content into the duodenum in the presence of an open pylorus (White, *et al.* 1981; King, *et al.* 1985; Savoye-Collet, *et al.* 2003). Thus, in critically ill patients, even when gastric contents reach the antrum, their clearance into the duodenum is likely to be impaired due to a lack of PAWs, as well as the recently reported hyperactivity of the pylorus (Chapman, *et al.* 2005).

In light of current opinion that the proximal stomach is a major determinant of liquid gastric emptying (Kelly 1980; Collins, *et al.* 1991), a contribution of proximal gastric dysmotility to delayed gastric emptying in critical illness is likely to be important. Naso-gastric feeding with

liquid nutrients is the most common method of nutritional support for critically ill patients (Heyland, *et al.* 2003). Abnormal proximal gastric accommodation, characterized by both delayed and excessive relaxation, suggests that the reduction in fundic wave frequency and amplitude and the delayed recovery of the fundus to pre-stimulation volume may play a major role in delayed gastric emptying in these patients (Chapter 7.2). As fundic waves are believed to re-distribute ingesta into the antrum (Cannon 1898; Kelly 1980; Azpiroz and Malagelada 1984, 1985), reduced activity would limit the transfer of gastric content distally, and thus, contribute further to excessive proximal gastric retention by failing to perform the antro-pyloro-duodenal mechanics that result in gastric emptying.

The exact mechanisms responsible for the functional integration between the proximal and distal stomach, and its disruption in critical illness, are unknown. In dogs, both *in vitro* and *in vivo* experiments have demonstrated the intrinsic intramural innervation exists between the fundus and antrum (Holle, *et al.* 1994; Hennig, *et al.* 1997). Extrinsic vagal pathways, particularly the cholinergic innervation, also appear to play a role in the mediation of the fundo-antral reflex (Rao, *et al.* 2002; Rao, *et al.* 2005). As pacemaker cells are absent in the proximal stomach (Kelly and Code 1971; Kelly and La Force 1972; Szurszewski 1994), the regulatory input for this regional integration is most likely to be central and mediated via the vagal and/or intrinsic intramural neural circuitry (Dalton, *et al.* 1992) (Chapter 3). In critical illness, many factors such as vagal dysfunction (Schmidt, *et al.* 2001; Schmidt, *et al.* 2005), use of opiates (Mittal, *et al.* 1986; Yuan, *et al.* 1998) or catecholamines (Mentec, *et al.* 2001) and inflammatory cytokine production (Lodato, *et al.* 1999; Emch, *et al.* 2000) may also contribute to this disruption, by impairing the function of extrinsic vagal nerves or even more

centrally. In the current study, inotropic use and cytokine related to sepsis may contribute to the observed dysmotilities as these factors were present in up to 50% of patients. Although hyperglycemia interferes with gastric motor function in both healthy and diabetic subjects (MacGregor, *et al.* 1976; Fraser, *et al.* 1990; Fraser, *et al.* 1991; Hebbard, *et al.* 1996), the elevation of blood glucose levels in the patients was minor and seems unlikely to significantly contribute to the disturbed motility observed in the current study. While propofol slows gastric emptying in animals (Inada, *et al.* 2004), its inhibitory effects on gastric emptying are not observed in humans (Hammas, *et al.* 1998; Hammas, *et al.* 2001; Chassard, *et al.* 2002; Memis, *et al.* 2006). The impact of propofol on results of the current study is unknown as the data on the gastric motility effects of propofol in critical illness are lacking.

In addition to the common limitations outlined in Chapter 6, the current study had a number of other potential limitations. When combined with ultra-sound, manometry fails to detect up to 25% of antral contractions that are not luminally occlusive (Savoye-Collet, *et al.* 2003). The impact of these missed contractions on the results is, however, likely to be minimal as the limitation would have been consistent for both groups, and the function of the non-luminal occlusive contractions remains unclear (Savoye-Collet, *et al.* 2003). Intra-duodenal rather than intra-gastric nutrient administration was used in the current study to ensure reliable assessment of the entero-gastric feedback response to various nutrient loads (Mearadji, *et al.* 1999) and avoided the interference of the barostat balloon to meal distribution (Mearadji, *et al.* 1999; Savoye-Collet, *et al.* 2003). The sample size of the current study was relatively small, but the study is technically very challenging and statistical differences have been demonstrated previously by studies with equal sample size (Houghton, *et al.* 1988; Heddle, *et*

al. 1993; Dive, *et al.* 1994; Holle, *et al.* 1994). The relationship between fundic wave and pyloric activity was not examined because it did not exist in dogs (Heddle, *et al.* 1993), and pyloric activity has previously been reported in critical illness (Chapman, *et al.* 2005).

In conclusion, in critical illness, not only are there motor disturbances in the proximal and distal stomach, but the association between these regions is diminished, which may further impair intra-gastric meal distribution. The impact of this disruption on gastric emptying in critically ill patients requires further study.

7.4 SUMMARY AND CONCLUSIONS

The findings in the current chapter have significantly enhanced our understanding on the gastric dysmotility of critical illness, and clearly demonstrated that the motor activity is impaired in multiple regions of the stomach in these patients. In addition to motor disturbances in the proximal and distal stomach, the motor integration between these regions is also diminished or disrupted.

Whilst it is not possible to quantify the contribution of impaired motility of each gastric region to the overall gastric emptying, the data on the intra-gastric distribution of meal in these patients (Nguyen, *et al.* 2006) suggest that the disruption of the gastric integration and prolonged gastric relaxation in response to duodenal nutrient stimulation play a significant role in the pathogenesis of slow gastric emptying during critical illness, especially as liquid formulae. As motor integration between proximal and distal stomach assists the transfer of meal from proximal stomach distally for further emptying (Cannon 1898; Kelly 1980; Heddle, *et al.* 1993), the disruption of this integration is likely to explain for the observed relationship between excessive proximal gastric retention and delayed gastric emptying in critically ill patients (Nguyen, *et al.* 2006).

The clinical implications from improving the understanding of the nature of disturbed gastric motility in critically ill patients are profound. Although antro-pyloro-duodenal motility is significantly impaired in these patients, therapies that correct only the motor function of this region are unlikely to substantially improve gastric emptying as the majority of the meal

retains in the proximal stomach and fails to re-distribute distally for emptying. Therapeutically, an effective therapy needs not only to correct the dysmotility in each gastric region but also to improve the motor integration between the proximal and distal stomach. Furthermore, as excessive proximal retention of meal is an important risk factor for gastro-oesophageal reflux (Tefera, *et al.* 2001; Tefera, *et al.* 2002), therapy that induces fundal contractions and improves intra-gastric distribution of meal is also likely to minimize the incidence of gastro-oesophageal reflux as well as increase the rate of gastric emptying in these patients. It would seem appropriate, therefore, to investigate the effects of current gastrokinetic agents on these parameters.

CHAPTER 8: RELATIONSHIP BETWEEN HUMORAL RESPONSES TO NUTRIENTS, GASTRIC EMPTYING AND FEED INTOLERANCE IN CRITICALLY ILL PATIENTS

8.1 INTRODUCTION

"Entero-gastric" feedback is a major factor regulating gastric emptying (Lin, *et al.* 1989; Spiller 1990) and is mediated by both neural and humoral mechanisms (Chapter 3). Two of the best characterised humoral mediators of this feedback response are CCK and PYY, both of which play an important role in the regulation of gastric emptying, appetite and energy homeostasis (Chapter 3).

A number of findings indicate that entero-gastric hormones may be important in the pathogenesis of disordered gastrointestinal motility during critical illness. For instance, it has been recently reported that antro-pyloro-duodenal motor response to intestinal nutrients is heightened in critically ill patients (Chapman, *et al.* 2005). Similarly, the work performed in this thesis has shown that the recovery of proximal gastric volumes after duodenal nutrient stimulation is also delayed (Chapter 7). In addition, recent data also suggest that plasma levels of PYY and ghrelin, gut hormones that are known to modulate nutrient feedback, are disturbed during critical illness (Nematy, *et al.* 2005) and 'early' PYY release in response to an intra-gastric meal is enhanced in patients with cardiac cachexia related to primary pulmonary hypertension (Le Roux, *et al.* 2005)(Chapter 4). Although there are no data regarding the plasma CCK and PYY response to small intestinal nutrients or its relationship to gastric emptying during critical illness, available evidence suggests that a possible relationship between enterogastric hormones and gastric emptying in these patients. It is hypothesised that the CCK and PYY response to intestinal nutrients is increased during critical illness, and that

there is a relationship between plasma concentration of these hormones and the rate of gastric emptying.

The work described in this chapter, therefore, aimed to examine (i) the responses of plasma CCK and PYY to intestinal nutrients and its relationship to feed intolerance; and (ii) the relationship between plasma concentrations of these hormones and the rate of gastric emptying in critically ill patients.

8.2 PLASMA CONCENTRATIONS OF CCK AND PYY DURING FASTING AND IN RESPONSE TO DUODENAL NUTRIENT STIMULATION IN CRITICALLY ILL PATIENTS

8.2.1 INTRODUCTION

As plasma CCK and PYY are the major humoral mediators of the entero-gastric feedback reflex, which is abnormally heightened in critically ill patients, it was hypothesized that plasma CCK and PYY concentrations would be elevated during critical illness, particularly in patients intolerant of gastric feeding. The aims of this study were, therefore, to determine the CCK and PYY response to small intestinal nutrient infusion in critically ill patients, and their relationship to feed intolerance.

8.2.2 METHODS

8.2.2.1 Subjects

Studies were performed in 31 unselected mechanically ventilated, critically ill patients (49 ± 3 yr, 23M, BMI: 30.5 ± 1.5 kg/m^2), who were admitted to the intensive care unit at the Royal Adelaide Hospital, from March 2004 to September 2005. All patients were sedated with propofol, able to receive enteral nutrition and had common exclusion criteria described in Chapter 6. Over the same time period, 28 age and gender-matched healthy subjects (44 ± 2 yr, 21M, BMI 25.5 ± 1.0 kg/m^2) were also studied.

8.2.2.2 Study protocol

Both critically ill patients and healthy subjects were studied in the morning, after a minimum of 8 hours fasting. All patients received propofol for sedation in the 24 hours prior to and during the study. Analgesia with intermittent boluses of fentanyl was given to patients where pain relief was required, for example those with multi-trauma, burns or pancreatitis. A 12F x 114 cm naso-duodenal feeding tube (Flexiflo, Abbott, Ireland) was inserted into the distal duodenum via an endoscopically placed guide-wire (THSF-35-260, Cook, Australia). Correct placement of the naso-duodenal feeding tube was confirmed by an abdominal X-ray and was monitored continuously by measurement of the duodenal TMPD (Chapter 6).

In healthy volunteers, a silicone rubber catheter (Dentsleeve, Adelaide, Australia) with a central feeding lumen, instead of a Flexiflo feeding tube, was used to deliver nutrients into the duodenum. The catheter was inserted into the stomach via an anaesthetised nostril and allowed to migrate into the duodenum by peristalsis, without the assistance of either sedation or endoscopy. Passage of the assembly beyond the pylorus was facilitated by small weights located at the catheter tip. Post-pyloric positioning of the assembly was determined by continuous measurement of the antro-duodenal TMPD gradient (Chapter 6). Radiological confirmation was not performed.

After catheter placement, the study began with an infusion of normal saline (0.9 %) at a rate of 4 mL/min for 15 minutes (baseline 1). Each subject then received two 60 minute duodenal infusions of Ensure® (Chapter 6; composition: 13% protein, 64% carbohydrate, 21% fat; energy content = 1 kcal per millilitre) at 1 kcal/min and 2 kcal/min, in a randomised, single

blind fashion. Prior to the study, the order of infusions was determined by blind selection from a concealed box. Ensure® was diluted with normal saline (0.9%) to 1:4 for the 1 kcal/min infusion and to 1:2 for the 2 kcal/min infusion; the resulting solutions were infused at a rate of 4 mL/min. The nutrient infusions were separated by a 2 hour "washout" period, which consisted of 1.5 hour of no infusion followed by 30 minutes of intra-duodenal infusion of normal saline at a rate of 4 mL/min (Figure 8.2.1).

Blood samples were collected at baseline and at 20, 40 and 60 minute during the nutrient infusions for the measurement of plasma concentrations of CCK and PYY, as described in Chapter 6. As plasma CCK clearance is dependent on renal function, the creatinine clearance was calculated in patients using the Cockroft - Gault equation. Renal function was considered to be impaired if the creatinine clearance was less than 65mL/hr (Lameire and Hoste 2004).

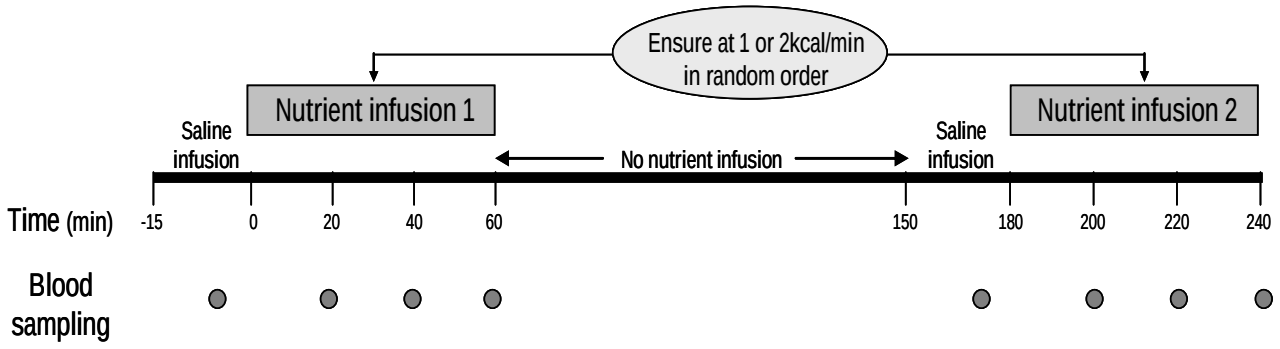


Figure 8.2.1 Outline of study protocol**.** Closed circles indicate time of blood sampling for plasma hormonal measurement.

8.2.2.3 Statistical analysis

The demographic characteristics of critically ill patients and healthy subjects were compared using Student's unpaired t-test. A two-way repeated measures analysis of variance (ANOVA) with post-hoc comparisons was used to evaluate: (i) the effects of the two nutrient infusions on plasma CCK and PYY in each group; (ii) potential differences in CCK and PYY responses to small intestinal nutrients between the groups; (iii) potential differences in CCK and PYY responses to nutrients between patients who were tolerating feed and those who were not; (iv) the effect of renal function on the CCK/PYY responses to nutrients.

8.2.3 RESULTS

Demographic details of the critically ill patients are shown in Table 8.2.1. The body mass index (BMI) of the patients was significantly higher than that of the healthy subjects (30.5 ± 1.5 kg/m^2 vs. 25.5 ± 1.0 kg/m^2; P=0.03). Twenty three (39%) patients had received enteral nutritional support prior to the study and of these, 9 (39%) patients were feed intolerant. The duration of feeding was similar between feed-tolerant and feed-intolerant patients (3.2 ± 0.7 days vs. 3.9 ± 1.0 days, respectively). The medications administered during the study included inotropic support with either adrenaline or noradrenalin (n=12), and acid suppression therapy (n=23). Seven of the 10 patients with renal impairment required haemodialysis. These patients were significantly older and had higher APACHE II scores than those with normal renal function. Whilst samples were available for CCK assays from all patients, only 19 enterally fed patients had sufficient volume for PYY assays (Table 8.2.1).

Table 8.2.1 Demographic data and admission characteristics of critically ill patients

Pt	Age (yr)	Gender	BMI (kg/m^2)	Days in ICU	Admission APACHE II	Prior nutritional support	Feed Tolerance	Renal function	Inotrope support	Acid suppression therapy	IV propofol (mg/24h)	Admission Diagnosis	Assay available
1	36	M	27	3	26	Yes	No	Normal	No	Yes	1200	Head injury	CCK/PYY
2	59	M	31	3	23	Yes	Yes	Normal	No	Yes	2400	Meningitis	CCK/PYY
3	17	M	20	10	18	Yes	No	Normal	No	Yes	6000	Head injury	CCK/PYY
4	66	F	33	5	26	Yes	No	Impaired	No	No	1200	Pancreatitis	CCK/PYY
5	23	M	25	5	21	Yes	No	Normal	Nor A	Yes	720	Multi-trauma	CCK/PYY
6	29	M	19	13	30	Yes	Yes	Normal	Nor A	Yes	4800	Sepsis	CCK/PYY
7	57	F	35	7	37	Yes	No	Impaired	A	Yes	1200	Sepsis	CCK/PYY
8	23	M	26	10	25	Yes	Yes	Normal	No	No	1680	Burns injury	CCK/PYY
9	72	F	29	6	21	Yes	Yes	Impaired	Nor A	Yes	1200	Sepsis	CCK/PYY
10	53	M	29	3	27	Yes	No	Impaired	Nor A	Yes	4800	Severe pneumonia	CCK/PYY
11	41	M	41	9	18	Yes	Yes	Normal	No	Yes	1200	Severe pneumonia	CCK/PYY
12	74	M	35	5	27	Yes	Yes	Impaired	A	Yes	1440	Cardiac failure	CCK/PYY
13	27	M	26	2	26	Yes	No	Normal	Nor A	Yes	480	Pancreatitis	CCK/PYY
14	47	M	27	8	19	Yes	Yes	Normal	No	Yes	6000	Multi-trauma	CCK/PYY
15	66	F	34	4	28	Yes	No	Impaired	Nor A	No	1200	Cardiac failure	CCK/PYY
16	55	M	29	9	30	Yes	Yes	Normal	No	Yes	480	SDH	CCK/PYY
17	36	M	27	11	29	Yes	No	Normal	No	Yes	960	Multi-trauma	CCK/PYY
18	55	F	21	7	22	Yes	Yes	Normal	No	Yes	3120	Multi-trauma	CCK/PYY
19	59	M	20	6	29	Yes	Yes	Normal	Nor A	No	720	Sepsis	CCK/PYY
20	59	M	35	3	29	Yes	Yes	Normal	No	No	1200	SAH	CCK
21	65	F	23	22	24	Yes	Yes	Normal	No	Yes	980	Severe pneumonia	CCK
22	43	F	34	6	27	Yes	Yes	Impaired	No	No	2400	Sepsis	CCK
23	49	M	27	5	21	No	NA	Normal	No	Yes	1800	Sepsis	CCK
24	29	M	20	7	22	No	NA	Impaired	Nor A	Yes	620	Cardiac failure	CCK
25	25	M	23	3	21	No	NA	Normal	No	Yes	3000	Head injury	CCK
26	47	M	27	5	32	No	NA	Impaired	No	Yes	2800	Sepsis	CCK
27	76	M	24	4	21	No	NA	Normal	Nor A	Yes	2400	Severe pneumonia	CCK
28	70	F	39	2	29	No	NA	Normal	Nor A	No	980	Sepsis	CCK
29	36	M	27	4	29	No	NA	Normal	No	Yes	1200	Multi-trauma	CCK
30	74	M	31	4	24	No	NA	Impaired	No	Yes	2800	Severe pneumonia	CCK
31	59	M	29	3	22	No	NA	Normal	No	No	1650	Multi-trauma	CCK

A/ Nor A – adrenaline or noradrenalin; SDH – subdural haemorrhage; SAH – subarachnoid haemorrhage; M – male; F - female

8.2.3.1 Effects of critical illness on plasma CCK and PYY concentrations during fasting

Fasting plasma CCK and PYY concentrations were significantly higher in the critically ill patients than in the healthy subjects (Figure 8.2.2). However, amongst both healthy subjects and critically ill patients, baseline CCK and PYY concentrations prior to the 1 kcal/min and 2 kcal/min infusions were similar within the group (Figure 8.2.2).

In patients, there was a negative correlation between fasting PYY but not CCK concentrations and body weight ($r= -0.52$; $P=0.05$). A positive correlation was seen between PYY and with the length of stay in ICU ($r= 0.47$; $P<0.05$). Neither inotropic support nor acid-suppression therapy had any effect on fasting plasma CCK concentrations. However, there was a trend for patients who received inotropic support to have higher fasting plasma PYY concentrations than those without inotropic support (31.2 ± 5.8 pmol/L vs. 23.5 ± 6.0 pmol/L; $P=0.125$). Plasma CCK and PYY concentrations were similar between patients with and without sepsis. There was no correlation between fasting plasma CCK and PYY and age, gender or APACHE II score.

8.2.3.2 Effects of critical illness on plasma CCK and PYY concentrations during duodenal nutrient stimulation

In healthy subjects, there was a dose-dependent increase in plasma CCK and PYY concentrations in response to the different nutrient loads (Figure 8.2.2). The increase was seen by 20 minute of duodenal nutrient infusion and plateaued thereafter. In patients,

however, the dose-dependent increase in plasma hormonal concentrations was only observed with CCK (P<0.01) but not PYY (Figure 8.2.2 & Table 8.2.2).

The plasma CCK and PYY concentrations in critically ill patients were significantly higher than those of healthy subjects, during both 1 kcal/min and 2 kcal/min infusions (Figure 8.2.2). During 1 kcal/min infusion, the magnitude of elevation in both plasma CCK and PYY concentrations in patients was greater than that of healthy subjects. However, during 2 kcal/min infusions, the magnitude of elevation in plasma CCK, but not PYY, was greater in patients than healthy subjects (Table 8.2.2).

Table 8.2.2 The integrated increase (AUC) in plasma CCK and PYY, during 1 kcal/min and 2 kcal/min nutrients infusions, in healthy subjects and critically ill patients.

	Integrated increase in CCK AUC $_{(0\text{-}60min)}$ (pmol/L.min)		**Integrated increase in PYY** AUC $_{(0\text{-}60min)}$ (pmol/L.min)	
	1 kcal/min	2 kcal/min	1 kcal/min	2 kcal/min
Healthy subjects	69 ± 15	129 ± 18 *	186 ± 58	412 ± 78 *
Critically ill patients	172 ± 17 *	259 ± 34 **	441 ± 153 *	684 ± 258

* P<0.01, vs. 1 kcal/min healthy subjects; ** P<0.01, vs. 1 kcal/min patients

In patients, there was no relationship between changes in plasma CCK and PYY concentrations during nutrient stimulation and APACHE II score, presence of sepsis, and use of either inotropic or acid-suppression therapies. However, there was a positive correlation between the magnitude of the plasma PYY elevation and the fasting concentration (r= 0.76, P<0.0001), body weight (r= 0.45, P<0.05) and length of ICU stay (r= 0.6, P<0.05).

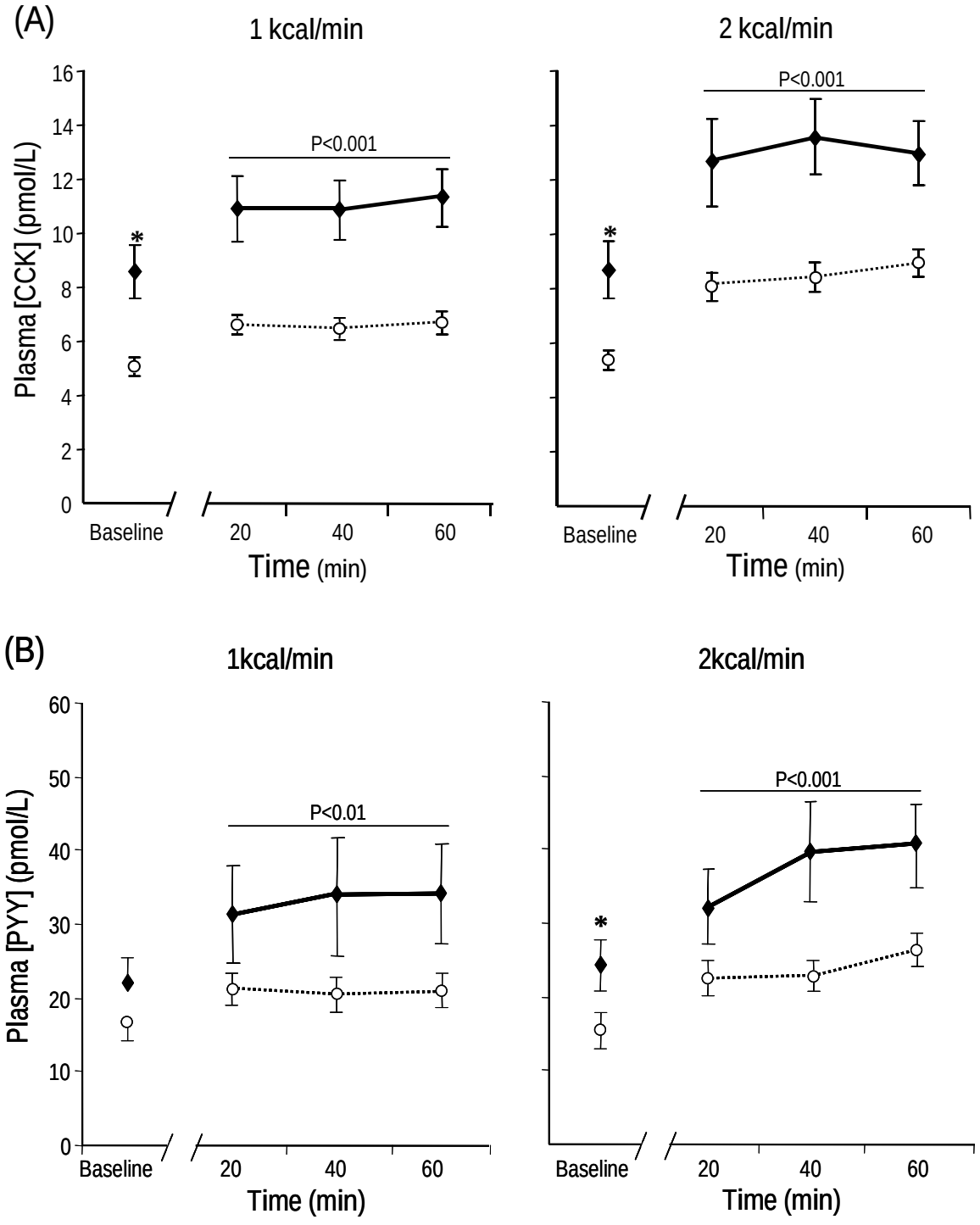


Figure 8.2.2 Plasma CKK (A) and PYY (B) concentrations during fasting and duodenal nutrient infusion at 1 kcal/min and 2 kcal/min in healthy subjects (○) and critically ill patients (♦). * P<0.05, vs. healthy subjects.

8.2.3.3 Relationship between plasma PYY and CCK during critical illness

In patients, there was a strong positive correlation between integrated plasma PYY and CCK concentrations during both fasting (r= 0.52, P<0.05; Figure 8.2.3a) and nutrient stimulation (r= 0.98, P<0.0001; Figure 8.2.3b). In healthy subjects, there was a positive correlation between plasma PYY and CCK concentrations during nutrient stimulation (r= 0.43; P<0.05), but not during fasting (r = 0.29; P=0.27).

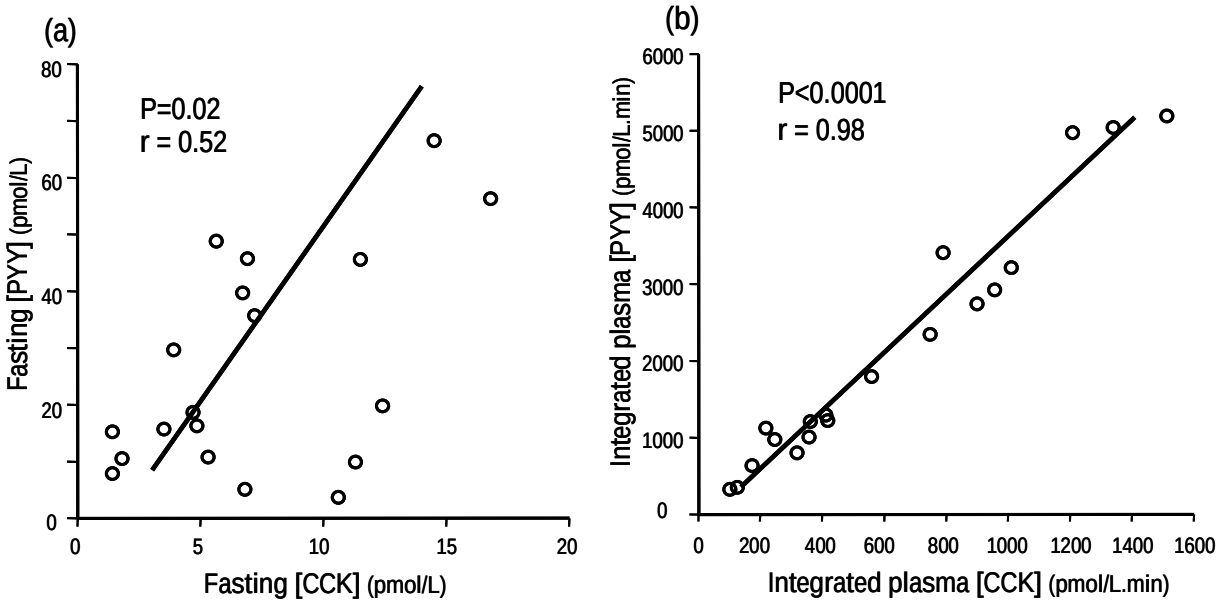


Figure 8.2.3 Relationship between plasma PYY and CCK concentrations in critically ill patients during fasting and duodenal nutrient-stimulation (expressed as integrated plasma levels ($AUC_{(0\text{-}180min)}$, pmol/L.min)).

8.2.3.4 Effects of feed tolerance on plasma CCK and PYY concentrations

Baseline plasma CCK and PYY concentrations were higher in critically ill patients who were intolerant of gastric feeding, when compared to patients who were feed tolerant (P<0.01; Figure 8.2.4). In feed-intolerant patients, the increases in plasma CCK and PYY in response to both nutrient infusions were approximately 1.5 to 2-fold higher than those of feed-tolerant patients. There were no differences in either the baseline or nutrient-stimulated plasma CCK concentrations between patients who tolerated gastric feeding and healthy subjects (Figure 8.2.4).

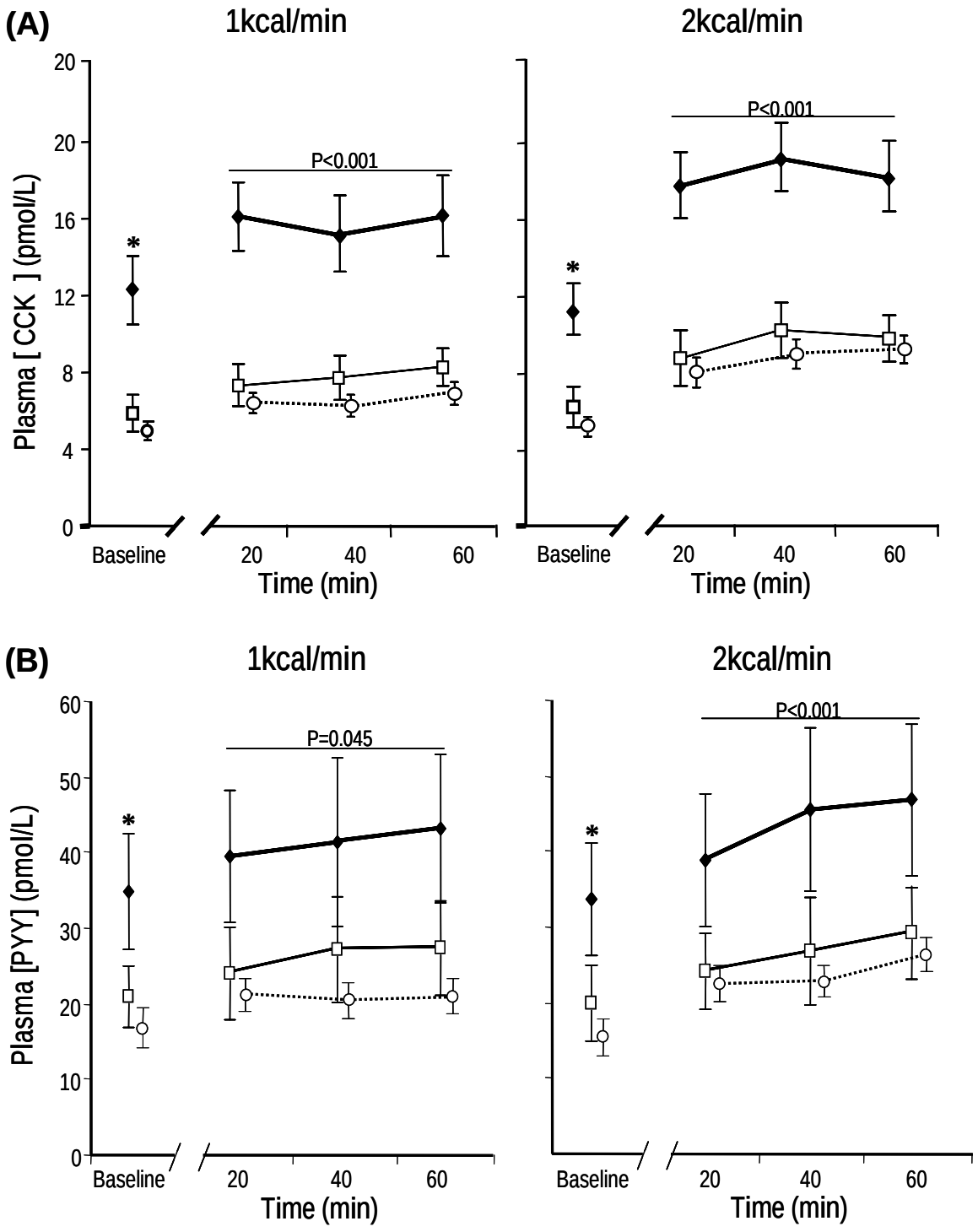


Figure 8.2.4 Plasma CCK (A) and PYY (B) concentrations at baseline and during intra-duodenal nutrient infusion in feed-intolerant (♦) and feed-tolerant (□) critically ill patients, and healthy subjects (○). * P<0.01 vs. feed tolerance and healthy subjects.

8.2.3.5 Effect of impaired renal function on plasma CCK and PYY concentrations

Plasma CCK concentrations at baseline and during the 1 kcal/min infusion, but not 2 kcal/min, were higher in patients with impaired renal function compared with those with normal renal function (baseline: 11.7 ± 2.0 pmol/L vs. 6.7 ± 1.0 pmol/L, P=0.056; nutrient-stimulated: P<0.05). After exclusion of patients with renal impairment, plasma CCK concentrations were still higher in critically ill patients than in healthy subjects (P<0.001; Figure 8.2.5). In contrast, there were no differences in either fasting or nutrient stimulated plasma PYY level between patients with impaired and normal renal function.

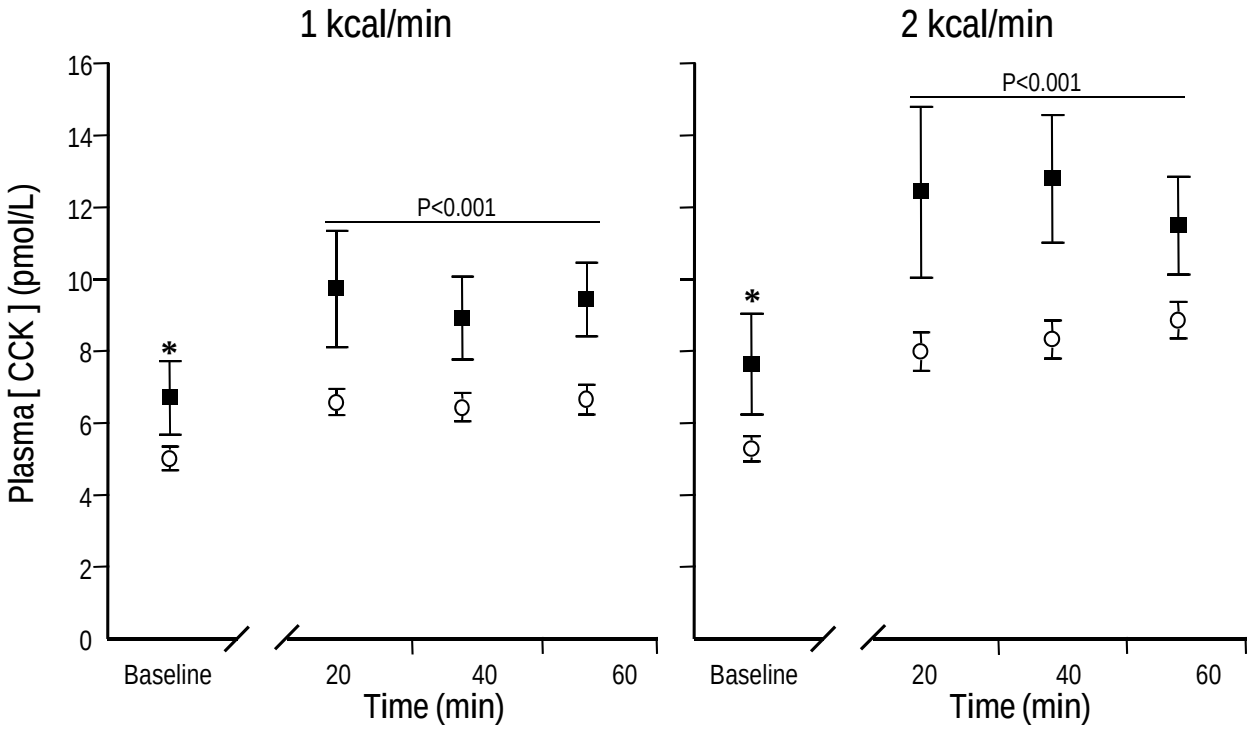


Figure 8.2.5 Plasma cholecystokinin concentrations during nutrient infusions in critically ill patients with normal renal function (■) and healthy subjects (○). * P<0.001 vs. healthy subjects.

8.2.3.5 Effects of prior nutritional support on plasma CCK and PYY

There were no differences in either the baseline or nutrient-stimulated plasma CCK concentrations between patients with or without prior nutritional support. In patients without prior feeding, there was a trend for baseline plasma CCK concentrations to be higher than feed-tolerant patients (P=0.09), and lower than feed-intolerant patients (P=0.07).

8.2.4 DISCUSSION

The current study is the first to evaluate plasma CCK and PYY concentrations in critical illness. During both fasting and in response to duodenal nutrient infusion, the major observations are that: (i) plasma CCK and PYY concentrations are significantly higher in critically ill patients than in healthy subjects, and also in feed-intolerant patients compared to those who tolerated gastric feeding; (ii) the release of PYY by duodenal nutrients in the critically ill does not exhibit the same dose-dependency as is evident with CCK release and that of healthy subjects, and (iii) there is a close relationship between nutrient stimulated plasma PYY and CCK concentrations. Although renal impairment was associated with higher baseline plasma CCK concentrations, it did not affect nutrient-stimulated CCK responses in critically ill patients. These findings are consistent with the hypothesis that the heightened enterogastric feedback response is related to an increased release of these gut hormones, and suggests a potential contribution for these entero-gastric hormones to delayed gastric emptying in critical illness.

The elevated CCK and PYY responses to duodenal nutrients in critically ill patients, particularly in those who did not tolerate gastric feeds, provides a potential mechanism for the

disturbances in gastric motility and emptying that occur frequently in critically ill patients (Dive, *et al.* 1994; Heyland, *et al.* 1996; Bosscha, *et al.* 1998; Ritz, *et al.* 2001; Chapman, *et al.* 2005) (Chapter 7). Supporting this speculation is the similarity in CCK and PYY responses between feed tolerant patients and healthy subjects. The motor disturbances reported in both proximal (Chapter 7) and distal (Dive, *et al.* 1994; Bosscha, *et al.* 1998; Chapman, *et al.* 2005) region of the stomach of critically ill patients are similar to the previously reported effects of CCK and PYY infusions on gastric motility in healthy humans (Yamagishi and Debas 1978; Fried, *et al.* 1991; Fraser, *et al.* 1993; Borovicka, *et al.* 1996). The inhibitory effects of these hormones on gastric emptying are complex, which include mediation through the CCK_1-receptors on the sensory fibres of the vagus nerves (Moran and McHugh 1988; Moran, *et al.* 1997) and of PYY via Y2 receptors in the dorsal vagal complex by PYY (Adrian, *et al.* 1985; Chen, *et al.* 1996; Batterham, *et al.* 2006). It is therefore possible that abnormally high plasma concentrations of these entero-gastric hormones during critical illness may contribute to the disturbed gastric motility via these pathways.

The mechanisms responsible for the abnormally high plasma CCK and PYY concentrations during fasting and in response to small intestinal nutrient infusion in critically ill patients are unknown. Recent data suggest that the presence of inflammation may have a role in the regulation of entero-endocrine cells in the small intestine (McDermott, *et al.* 2006). In a mouse model, upper gut inflammation has been reported to increase plasma CCK concentrations and reduce energy intake (McDermott, *et al.* 2006), via an effect on CD_4 T-lymphocytes and the related inflammatory cytokines (IL-3 and IL-4), can up-regulate CCK expressing cells. Systemic inflammation with elevated inflammatory cytokines is common in

critically ill patients (Souba 1994; Jeevanandam, *et al.* 2000; Winkelman 2004) and this could result in increased CCK responses to intestinal nutrients in these patients. As that nutritional deprivation is common in critically ill patients and starvation is associated with both slow gastric emptying and higher basal CCK and PYY concentrations (Harty, *et al.* 1991; Tamai, *et al.* 1993; Corvilain, *et al.* 1995; Benini, *et al.* 2004; Wright, *et al.* 2004), nutritional deprivation may also be relevant. However, there were no differences in plasma CCK concentrations between patients with or without prior nutritional support, suggesting that nutritional deprivation does not contribute significantly to elevated CCK concentrations in the critically ill. Whilst it is possible that slow gastric emptying leads to more prolonged proximal small intestinal nutrient stimulation, and thereby, higher levels of CCK, this is also unlikely as all patients had fasted for at least 8 hours and plasma CCK concentrations had returned to baseline level prior to each infusion. Although a majority of the patients were on acid suppression therapy with the potential for raised serum gastrin levels, any potential assay cross-reactivity between gastrin and CCK is minimal as that the assay cross-reactivity is less than 2% (Santangelo, *et al.* 1998). In addition, there was no difference in plasma CCK concentrations between patients who were given acid suppression and those were not treated with such therapy.

The elevation of plasma PYY concentration within 20 minutes of nutrient stimulation suggests that the elevated PYY concentrations were most probably mediated by factors in the proximal small intestine rather than direct nutrient-stimulation of the distal ileum (Adrian, *et al.* 1985). CCK is likely to be an important 'proximal' mediator given its known stimulatory effect on the release of PYY in the small intestine (Lin, *et al.* 2000) and the positive

correlation between the hormones demonstrated in the current study. It is also possible that direct neural stimulation in the proximal intestine triggers the release of PYY from the distal ileum (Greeley, *et al.* 1989; Fu-Cheng, *et al.* 1997; Lin, *et al.* 2003). In animals, release of PYY in response to intestinal nutrients cannot be abolished by preventing nutrient delivery to the site of PYY-containing cells in the distal ileum but can only by removing these cells completely (ie. ileo-colectomy) (Greeley, *et al.* 1989). These observations indicate the presence of neural linkage between the proximal gut and the distal PYY-secreting cells. These pathways involve sensory vagal fibres with a variety of mediators including nicotinic, beta-adrenergic, opioid and serotonergic and nitric oxide pathways (Greeley, *et al.* 1989; Fu-Cheng, *et al.* 1997; Lin, *et al.* 2003; Lin, *et al.* 2004). It is unclear whether disturbances to neurotransmitters, especially those known to be altered in the critically ill such as nitric oxide (Mutlu, *et al.* 2001), interfere with neural linkages and increase small intestinal 'sensitivity' to nutrients.

As plasma CCK is cleared renally, patients with chronic renal impairment may have elevated plasma CCK (Aguilera, *et al.* 2001; Aguilera, *et al.* 2003; Wright, *et al.* 2004). In the current study, although the plasma CCK concentrations in patients with renal impairment were higher than in patients with normal renal function during the 1kcal/min infusion, this elevation was due mainly to the higher baseline levels, consisted with impaired clearance (Aguilera, *et al.* 2001). The overall plasma CCK response to nutrients in these patients, however, was similar to that observed in those with normal renal function. Thus, acute renal impairment appears unlikely to account for the increased plasma CCK response to nutrients in critical illness.

Common factors in critical illness such as mechanical ventilation, and drugs like sedatives and inotropic therapy may also contribute, at least in part, to the abnormal PYY and CCK responses. Apart from inducing splanchnic hypo perfusion, mechanical ventilation with high end-inspiratory pressure may also increase pulmonary and systemic cytokine release (Mutlu, *et al.* 2001), with a secondary effect on small intestinal entero-endocrine cell function (McDermott, *et al.* 2006). All patients in the current study received propofol for sedation but, to date, there are no data on the effect of propofol on PYY and CCK. There was a trend for plasma PYY concentrations to be higher in patients who received inotropic therapy but it is unclear whether this elevation is a physiological response to shock, or a direct consequence of the inotropic drugs. In animals, PYY infusion causes intestinal vasoconstriction and a rise in systemic arterial blood pressure (Lundberg, *et al.* 1982).

The data in the current study suggest that CCK and PYY have a major role in disturbed gastric motor function during critical illness. However, the existence of a causal relationship between these factors requires studies using specific antagonists. Such agents exist for CCK-A antagonists and may have therapeutic benefits. Assessment of other gut hormones, such as glucagon-like-peptide 1, secretin, gastric inhibitory polypeptide, neurotensin, and motilin may also clarify this further. The normalisation of fasting PYY levels in critically ill patients after discharge (Nematy, *et al.* 2005) suggests that follow-up studies to examine the long-term recovery of the humoral response and entero-gastric feedback may be important. The decrease in plasma ghrelin during critical illness is intriguing but suggests that the elevated PYY and CCK responses may be a specific phenomenon.

In view of the limited choice and relatively poor efficacy of current prokinetic therapy for feed intolerance in critical illness (Jooste, *et al.* 1999; Chapman, *et al.* 2000; MacLaren, *et al.* 2000) (Chapter 11), CCK antagonists may provide alternative therapeutic agents. The currently available CCK-A antagonist, loxiglumide, has been reported to accelerate gastric emptying of lipid-rich liquid meals in healthy subjects (Schwizer, *et al.* 1997) as well as patients with functional dyspepsia and irritable bowel syndrome (Chua, *et al.* 1994; Cremonini, *et al.* 2005). It has, however, not been used in critical illness thus far.

In conclusion, both fasting and duodenal nutrient-stimulated plasma PYY concentrations are elevated in critical illness, particularly in patients who are intolerant of gastric feeding. This elevated response is strongly related to plasma CCK concentrations, suggesting an important role for this hormone in mediating increased PYY release. Together, these findings provide an underlying humoral mechanism for the enhanced entero-gastric reflex and subsequent delayed gastric emptying in critical illness.

8.3 THE RELATIONSHIP BETWEEN GASTRIC EMPTYING, PLASMA CCK AND PYY CONCENTRATIONS IN CRITICAL ILLNESS

8.3.1 INTRODUCTION

The findings in Chapter 8.2 are consistent with the hypothesis that an enhanced entero-gastric feedback inhibition is potentially due to the increased release of gut hormones and may be important in the regulation of gastric emptying in critical illness. The aim of this study was to evaluate the relationship between plasma CCK and PYY concentrations and gastric emptying of a liquid meal in critically ill patients. The following hypotheses were specifically examined: (i) plasma concentrations of CCK and PYY are inversely related to gastric emptying; (ii) slow gastric emptying is associated with elevated plasma concentrations of CCK and PYY; and (iii) gastric emptying is a determinant of postprandial concentrations of CCK and PYY.

8.3.2 METHODS

8.3.2.1 Subjects

Studies were performed in 39 unselected medical critically ill patients (55.8 ± 2.7 yr; 24 M), who were admitted to the intensive care unit at the Royal Adelaide Hospital, between May 2005 to December 2006. All patients were able to receive enteral nutrition and shared the common exclusion criteria outlined in Chapter 6.

8.3.2.2 Study protocol

Critically ill patients were studied in the morning, after a minimum 8 hour fast. All patients were sedated, with either propofol or a combination of morphine and midazolam, during and for a minimum of 24 hours prior to the study. The type of sedation given to the patients was determined by the intensivist in charge of the patient. In all patients, a 14 to 16 FG Levin naso-gastric feeding tube (Pharma-Plast, Lynge, Denmark) was already in situ in the stomach, as part of clinical care, and the correct position of the feeding tube was confirmed radiologically prior to commencing the study.

Gastric emptying of 100 mL liquid nutrient meal (Ensure®; Abbott Australia, Kurnell, Australia; containing 106 kcal with 21% of fat) was measured by the ^{13}C-octanoate breath test (Chapter 6), with the patient in the supine position and the head of the bed elevated to 30°. The start of the study (t = 0 minute) was defined as the time when all of the Ensure meal had been infused into the stomach. Breath was collected for measurement of $^{13}CO_2$ concentration at standardized time points and the resultant curves used to calculate the gastric emptying coefficient (GEC = ln(y)) (Chapter 6), which provides a reliable single global index for the gastric emptying rate as it represents both the rate of appearance and disappearance of the label in breath (Ghoos, *et al.* 1993). In the current study, delayed gastric emptying was defined as a GEC of less than 3.2 (Ritz, *et al.* 2001).

Blood samples (5mL) for the measurement of plasma CCK and PYY concentrations were collected into chilled EDTA tubes, immediately before and at 60 minute and 120 minute after the delivery of the intra-gastric meal. Blood samples were then centrifuged at 4^{o}C within 30

minutes of collection, and stored at -70^{o}C for subsequent analysis. Details of the assays for plasma CCK and PYY are outlined in Chapter 6. Blood samples for the measurement of blood glucose concentrations were also collected at baseline, every 15 minutes for the first hour and every 30 minutes for the subsequent 3 hours.

8.3.2.3 Statistical analysis

Integrated changes in plasma concentrations of CCK and PYY were calculated and expressed as areas under the curve over the 120 minutes ($AUC_{0\text{-}120\ min}$) after the Ensure meal. Differences in demographic characteristics, baseline blood glucose, CCK and PYY concentrations, and $AUC_{0\text{-}120\ min}$ for plasma CCK and PYY between critically ill groups were compared using Student's unpaired t-test and Chi-square test. Changes in plasma concentrations of CCK and PYY over time were determined by one-way repeated measures analysis of variance (ANOVA). Potential differences between patients with normal versus delayed gastric emptying with respect to the plasma CCK, PYY and blood glucose responses to the meal were evaluated using two-way ANOVA with post-hoc analyses. The relationships between gastric emptying with baseline plasma CCK and PYY, changes in plasma CCK and PYY (from baseline to t = 60 minute and t = 120 minute) and demographic factors (age, BMI, APACHE II score, serum creatinine) were assessed using Pearson's correlation.

8.3.3 RESULTS

The duration of ICU stay prior to the study was 4.6 ± 0.3 days. The admission diagnoses included head injury (n=12), multi-trauma (n=11), sepsis (n=10), respiratory failure (n=9),

aortic dissection (n=3), pancreatitis (n=1) and retroperitoneal bleed (n=1). The mean APACHE score was 22.4 ± 0.9 on the study day. Twenty five patients (64%) were sedated with morphine and midazolam and 14 patients (36%) with propofol. Nineteen patients (48%) required inotropic support with either adrenalin or noradrenalin. Acid suppression therapy (ranitidine or pantoprazole) was given to 32 of the 39 (82%) patients. Renal function was normal in the majority of patients (82% (32/39)) at the time of study with a mean serum creatinine of 0.1 ± 0.01 mmol/L. None of the 7 patients with renal impairment (mean serum creatinine = 0.2 ± 0.04 mmol/L) required haemodialysis. Before enrolment into the study, 24 (60%) patients had been given enteral feeds for a mean duration of 3.5 ± 0.4 days. Sixteen (40%) patients had not received nutritional support prior to the study. The mean duration of ICU stay prior to the study did not differ between the two groups (fed: 4.9 ± 0.5 days vs. not fed: 4.2 ± 0.4 days, P=0.78)

8.3.3.1 Gastric emptying

Gastric emptying was delayed in 64% (25/39) of critically ill patients with a mean GEC of 2.8 ± 0.1. The demographic data and characteristics of patients who had normal and delayed gastric emptying are summarised in Table 8.3.1. There was no relationship between GEC and age (P=0.23), gender (P=0.82), BMI (P=0.86), APACHE II score at time of study (P=0.68), type of sedation (P=0.71), use of inotropes (P=0.74) or acid suppression (P=0.59), presence of sepsis (P=0.38) or prior enteral feeding (P=0.97). The mean fasting blood glucose concentration was 7.1 ± 0.2 mmol/L, which increased slightly after the meal to a peak of 8.1 ± 0.3 mmol/L. There were no differences in blood glucose concentrations between patients with delayed and normal GE (P=0.99).

Table 8.3.1 Demographic data and characteristics of critically ill patients, classified according to their rate of gastric emptying (GE).

	Normal GE (n=14)	**Delayed GE (n=25)**	P-value
Gastric Emptying Coefficient	3.3 ± 0.05	2.5 ± 0.1	<0.001
Age (yr)	57.5 ± 3.8	56.3 ± 2.8	0.87
Gender (M:F)	7:7	17:8	0.41
Body mass index (kg/m^2)	28.3 ± 1.3	27.7 ± 1.2	0.78
APACHE II score on study day	22.6 ± 1.1	22.1 ± 1.0	0.86
Serum creatinine (mmol/L)	0.08 ± 0.01	0.11 ± 0.02	0.14
Baseline blood glucose level (mmol/L)	7.1 ± 0.2	7.1 ± 0.2	0.99
Admission diagnosis § (%(n))			
Sepsis	36% (5)	19% (5)	0.28
Respiratory failure	43% (6)	15% (3)	0.13
Multi-trauma	21% (3)	32% (8)	0.48
Head injury †	21% (3)	34% (9)	0.48
Aortic dissection	7% (1)	8% (2)	0.99
Pancreatitis	0% (0)	4% (1)	0.99
Retroperitoneal bleed	7% (1)	0% (0)	0.35
Medication (%(n))			
Morphine ± midazolam	57% (8)	68% (17)	0.44
Propofol	43% (6)	31% (8)	0.44
Inotropes (adrenaline/noradrenalin)	57% (8)	46% (12)	0.51
Plasma CCK concentration (pmol/L)			
Fasting	6.1 ± 0.4	8.5 ± 1.0	0.045
At 60 minute	8.2 ± 0.7	10.1 ± 0.8	0.03
At 120 minute	7.1 ± 0.7	9.8 ± 0.8	0.03
Plasma PYY concentration (pmol/L)			
Fasting	15.6±1.3	22.8 ± 2.2	0.03
At 60 minute	21.0 ± 1.8	25.0 ± 2.2	0.02
At 120 minute	18.9 ± 1.9	24.9 ± 2.0	0.02

§ Patients may have more than 1 admission diagnosis

† Including sub-arachnoid haemorrhage and massive cerebral ischemic event

8.3.3.2 Plasma CCK and PYY concentrations

At baseline, the plasma concentrations of CCK were 7.7 ± 0.9 pmol/L and that of PYY were 20.4 ± 2.0 pmol/L (Figure 8.3.1). There was no relationship between baseline plasma CCK concentrations and age (P=0.25), gender (P=0.82), BMI (P=0.84), APACHE II scores (P=0.40), serum creatinine (P=0.28), the type of sedation, the use of inotropes or acid suppression, the presence of sepsis or prior enteral nutrition. In contrast, baseline plasma PYY concentrations were positively correlated with age (r=0.37, P=0.01) and BMI (r=0.50, P<0.01).

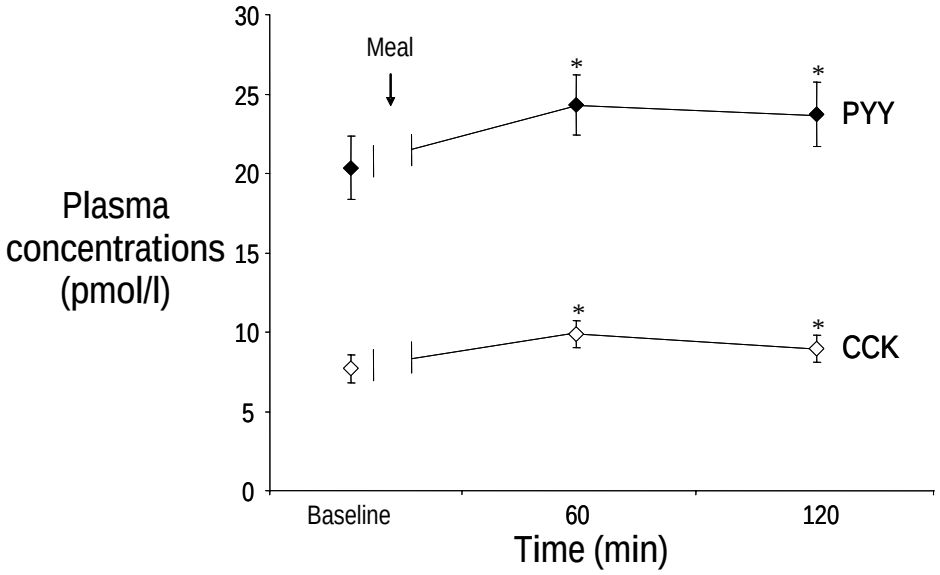


Figure 8.3.1 Plasma CCK and PYY concentrations at baseline and after an intra-gastric meal of 100 mL Ensure (106 kcal with 21% lipid). * P<0.05, vs. baseline concentrations

In response to the gastric meal, there was a small but significant rise in plasma CCK and PYY (P=0.01; Figure 8.3.1). Both plasma CCK and PYY had not returned to baseline at 120 minute, particularly in patients with delayed GE (Table 8.3.1). There was a positive correlation between age and the integrated increase in plasma CCK from baseline to 120

minute (r=0.45; P<0.001), but not with plasma PYY. There was no relationship between integrated plasma CCK or PYY and gender, BMI, APACHE II scores on study day, serum creatinine, the types of sedation, the use of inotropes and acid suppression, and presence of sepsis or prior history of receiving enteral nutrition. Whilst there was no relationship between baseline plasma CCK and PYY (P=0.80), the magnitude of increase in plasma PYY at 60 minute was positively correlated with that of CCK (r=0.33, P=0.03).

8.3.3.3 Relationship between gastric emptying, plasma CCK and PYY concentrations

Baseline plasma CCK (8.5 ± 1.0 pmol/L vs. 6.1 ± 0.4 pmol/L; P=0.045) and PYY (22.8 ± 2.2 pmol/L vs. 15.6 ± 1.3 pmol/L; P=0.03) were higher in patients with delayed GE compared with those with normal GE (Table 8.3.1). The GEC was inversely related to both baseline plasma CCK (r= -0.33, P=0.04) and PYY (r = -0.36, P=0.02) concentrations (Figure 8.3.2).

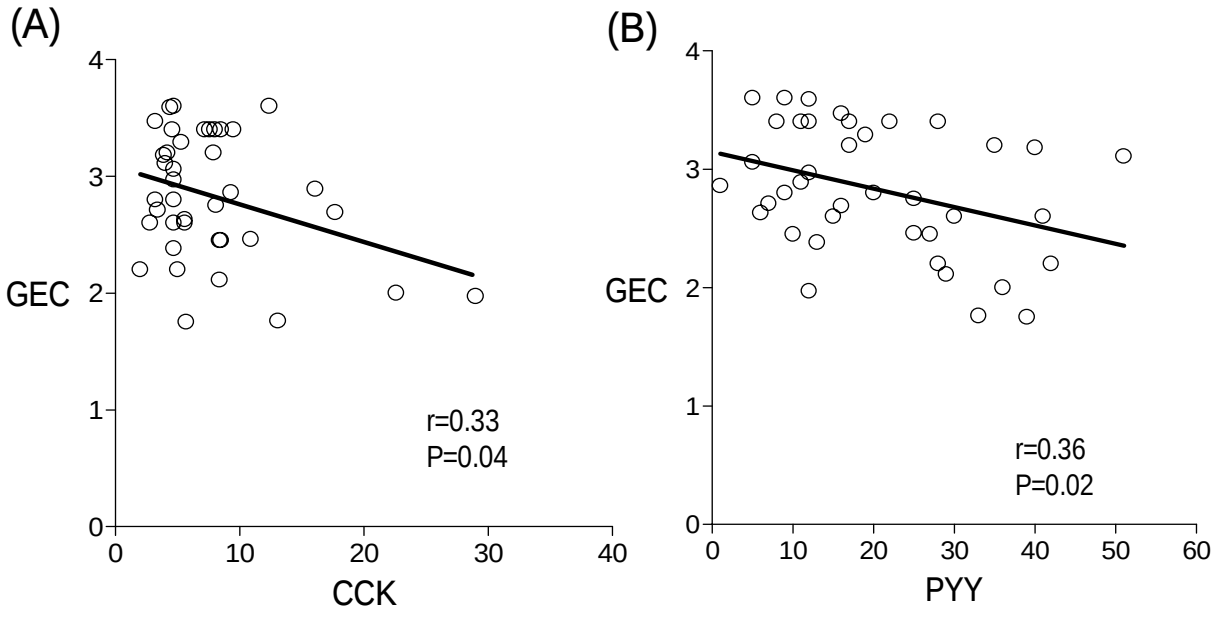


Figure 8.3.2 The relationship between the rates of gastric emptying assessed by GEC and baseline plasma concentrations of CCK (A) and PYY (B).

Similarly, nutrient-stimulated plasma concentrations of CCK (P=0.03) and PYY (P=0.02) were higher in patients with delayed gastric emptying at 60 and 120 minutes after meal. The GEC was inversely related to plasma concentrations of CCK (r= -0.32, P=0.049) and PYY (r = -0.30, P=0.06) at 120 minute, but not at 60 minute. There was a direct relationship between the GEC and both absolute changes in plasma CCK (r = 0.40, P=0.01) and PYY (r = 0.42, P<0.01) at 60 minute, and the integrated changes in plasma CCK (r = 0.36, P=0.03) and PYY over 120 minutes (r = 0.38, P=0.02) (Figure 8.3.3). The AUC for the plasma concentrations of CCK and PYY were, however, not significantly different between patients with delayed versus normal GE (CCK: AUC $_{0\text{-}120\ min}$: 130 ± 42 vs. 160 ± 38 pmol/L.min, P=0.61; PYY: AUC $_{0\text{-}120\ min}$: 174 ± 98 vs. 414 ± 155 pmol/L.min, P=0.16).

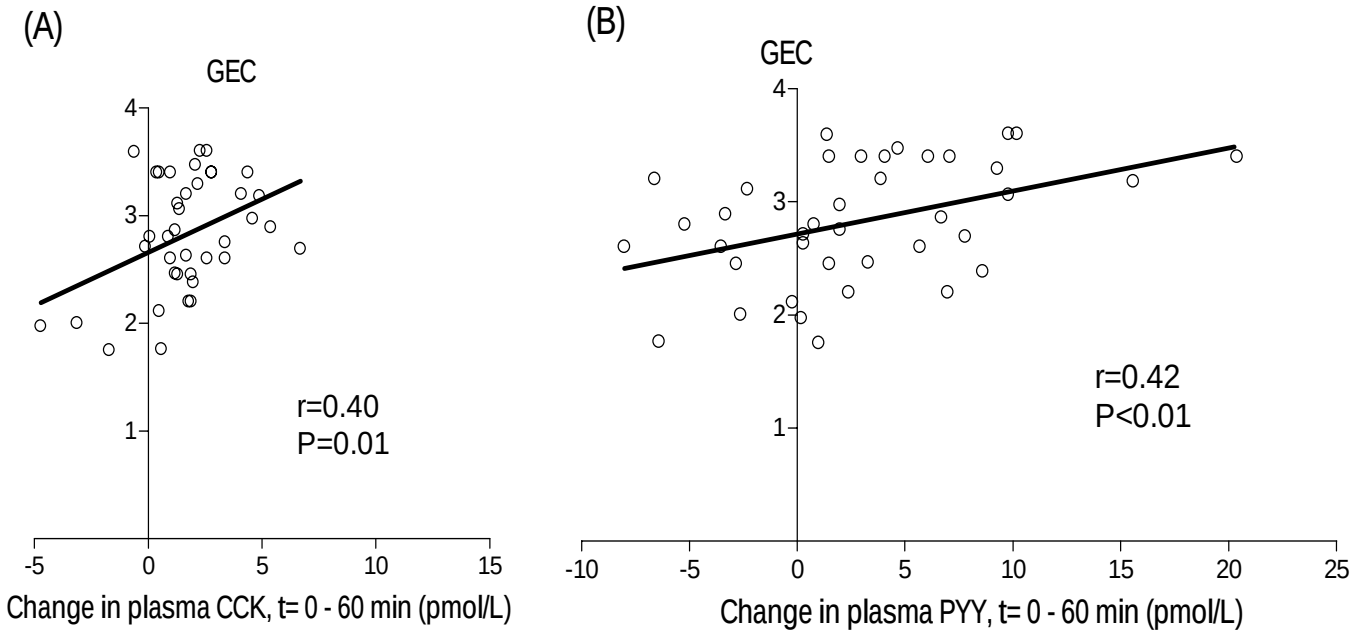


Figure 8.3.3 The relationship between the changes in plasma concentrations of CCK (A) and PYY (B) from baseline to 60 minutes, and the rate of gastric emptying assessed by GEC

8.3.4 DISCUSSION

The current study is the first to demonstrate an increase in plasma CCK and PYY concentrations in critically ill patients with delayed gastric emptying, supporting the hypothesis of a relationship between gastric emptying and plasma concentrations of CCK and PYY in critical illness. The major observations are that during critical illness, gastric emptying is inversely related to both fasting and postprandial plasma CCK and PYY concentrations, and that the postprandial increases in plasma CCK and PYY are also directly related to gastric emptying. Both plasma CCK and PYY concentrations were higher in patients with delayed gastric emptying, during both fasting and for 2 hours post-prandially. Although the strength of the correlation was only modest, the relationship should not be regarded as weak as this was a cross-sectional study. Furthermore, the fasting plasma CCK and PYY concentrations in the current study are comparable to those in Chapter 8.2 and others (Nematy, *et al.* 2005). Together, these findings suggest that a relationship between gastric emptying, plasma CCK and PYY concentrations during critical illness but that the interaction between these is complex.

The mechanisms underlying the elevated fasting levels of these hormones are unknown. Nutritional deprivation may be relevant since inadequate nutritional support is common in critically ill patients, fasting slows gastric emptying in healthy subjects, (Corvilain, *et al.* 1995) and plasma CCK and PYY concentrations are higher in patients with anorexic nervosa and malnutrition (Chance, *et al.* 1984; Baranowska, *et al.* 2000). The lack of difference in fasting CCK and PYY concentrations between patients with and without nutritional support in the current study is against nutrient deprivation as a cause. However, it is possible that the

duration of nutritional deprivation was insufficient for this to be demonstrated. Prolonged exposure of nutrients related to small intestinal hypo-motility (Dark and Pingleton 1989; Mutlu, *et al.* 2001) is unlikely as all patients in the current cohort were fasted for at least 8 hours. Renal impairment is also unlikely to contribute significantly to the current observations as the proportion of patients with renal impairment was small and the plasma CCK concentrations in this group did not differ from those with normal renal function. While the majority of the patients in the current study received acid suppression therapy and therefore, may have had increased serum gastrin levels, the cross-reactivity between gastrin and CCK is less than 2% (Santangelo, *et al.* 1998) and unlikely to contribute to the elevated CCK concentrations.

There was a weak but direct relationship between the rate of gastric emptying and postprandial increases in plasma CCK and PYY concentrations in critically ill patients. This has previously been shown in lean (Yamagishi and Debas 1978; Liddle, *et al.* 1986; Fried, *et al.* 1988; Fraser, *et al.* 1993; Borovicka, *et al.* 1996) and obese (Vazquez Roque, *et al.* 2006) healthy subjects. These data suggest that the release of these peptides is dependent on the amount of nutrient, particularly fat, delivered into the small intestine (Zhao, *et al.* 1999). This result differs from the data in Chapter 8.2, which showed that critically ill patients with feed intolerance had increased release of plasma CCK and PYY in response to duodenal nutrients compared to patients who tolerated feeds. The reason for the discrepancy is unclear but is likely to reflect differences in the site of nutrient administration. As the meal size and hence, nutrient load is relatively small, and delayed gastric emptying is common (64%), the relationship between GE and the hormonal release is probably related to the presence or absence of duodenal nutrient stimulation. This conclusion is supported by the observation

that the CCK concentrations in the current study were comparable to those seen during 1 kcal/min duodenal nutrition stimulation (Chapter 8.2). The heightened hormonal release in response to a similar nutrient load, particularly those with impaired motility (Chapter 8.2), was also observed in the current study. Thus, the increase in plasma concentrations of CCK and PYY in patients with delayed emptying was similar to those with normal gastric emptying. This suggests that although only a small amount of nutrients was delivered into the duodenum in patients with delayed gastric emptying, the "increased sensitivity" of the duodenal receptors leads to a greater hormonal release for the same nutrient load. Together, these findings confirm the complexity of the interaction between gastric emptying, intestinal nutrients and hormonal release in critically ill patients.

Consistent with the earlier study (Chapter 8.2), the postprandial release of PYY was related to the release of CCK, which supports the concept that CCK is an important proximal mediator for the release PYY (McFadden, *et al.* 1992; Lin, *et al.* 2000). As the release of PYY by nutrients in the proximal intestine is via direct neural stimulation of PYY-secreting cells (Greeley, *et al.* 1989), these data suggest the neural linkage is not disrupted in critical illness.

During the current study, blood glucose concentrations were adequately controlled by the standardized insulin therapy. However, insulin per se may have an effect on the entero-gastric feedback. In humans, insulin-induced hypoglycaemia has no significant effect on antro-pyloro-duodenal motor activity in humans (Fraser, *et al.* 1991), but accelerates gastric emptying (Russo, *et al.* 2005). Currently, there are no data on the impact of insulin on the release of CCK or PYY in humans. The impact of insulin on the entero-gastric feedback and

the hormonal release in the current study are, however, likely to be small as all patients received insulin therapy.

Whilst the current observations strengthen the rationale for the potential use of CCK antagonists in the management of feed intolerance in the critically ill, it is possible that the efficacy of such agents will be limited as many factors are involved in the regulation of gastric emptying during critical illness. Nevertheless, CCK-A antagonists such as loxiglumide accelerate gastric emptying of lipid-rich liquid meals in healthy subjects (Fried, *et al.* 1991; Schwizer, *et al.* 1997; Kreiss, *et al.* 1998) as well as patients with functional dyspepsia (Chua, *et al.* 1994) and irritable bowel syndrome (Cremonini, *et al.* 2005); suggesting a potential role of such agents in critical illness. Currently, there are no PYY antagonists available in human.

In conclusion, there is a complex relationship between gastric emptying, plasma CCK and PYY in the critically ill patients. Whilst gastric emptying is inversely related to fasting and postprandial plasma CCK and PYY concentrations, it may also be a determinant of CCK and PYY responses to a meal. The role of these entero-gastric hormones in the pathogenesis of impaired gastric emptying during critical illness, however, requires further evaluation with specific antagonists.

8.4 SUMMARY AND CONCLUSIONS

The work in the current chapter has demonstrated that the humoral response of entero-gastric feedback inhibition is abnormal in critically ill patients. Compared to healthy volunteers, both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations are significantly elevated in these patients. More importantly, plasma concentrations of CCK and PYY are greatest in patients with delayed gastric emptying or feed intolerance, a clinical manifestation of slow gastric emptying. Overall, an inverse relationship exists between the rate of gastric emptying and both fasting and postprandial plasma CCK and PYY concentrations after a gastric liquid meal. In view of the enhanced entero-gastric inhibitory feedback on both proximal (Chapter 7) and distal (Chapman, *et al.* 2005) gastric motility during critical illness, these findings strongly support the potential role of plasma CCK and PYY in the pathogenesis of gastric dysmotility in these patients. However, demonstration of a causal relationship requires the use of specific antagonists. As currently available prokinetic agents have major limitations, further evaluation of such agents, especially CCK-A antagonists, may potentially provide alternative avenues for the treatment of feed intolerance in critically ill patients.

CHAPTER 9: FACTORS THAT CONTRIBUTE TO DISTURBED GASTRIC EMPTYING AND FEED INTOLERANCE DURING CRITICAL ILLNESS

9.1 INTRODUCTION

Although the pathogeneses of disturbed gastrointestinal motility during critical illness are yet to be elucidated, a number of factors have been implicated in the aetiology of slow gastric emptying in critically ill patients, including admission diagnosis, mechanical ventilation, drugs (especially opiates and catecholamines), hyperglycaemia, hypotension and circulating inflammatory cytokines. The supporting data for the majority of these factors, however, have been inferred from studies performed in either animals (Dubois, *et al.* 1975; Lodato, *et al.* 1999; Emch, *et al.* 2000) or non-critically ill population (Mittal, *et al.* 1986; Crighton, *et al.* 1998; Kao, *et al.* 1998; Yuan, *et al.* 1998; Hammas, *et al.* 2001; Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003). In addition, nutritional deprivation from delaying feeds in these patients has also been suggested to be a contributing factor to the gastric dysmotility because short-term fasting slows gastric emptying in healthy humans (Corvilain, *et al.* 1995). As indicated in Chapter 4, there are limited data in critically ill patients that directly examine the relationship between these factors and disturbed gastric motor function or feed intolerance (Mutlu, *et al.* 2001).

The work described in this chapter, therefore, aimed to clarify the role of several of the proposed risk factors in the delay in gastric emptying seen during critical illness. Specifically, the potential impacts of (i) admission diagnosis, (ii) type of sedation, (iii) delay in initiating enteral feeding and (iv) degree of blood glucose control on either gastric emptying or feed intolerance were examined in critically ill patients.

9.2 THE IMPACT OF ADMISSION DIAGNOSIS ON GASTRIC EMPTYING

9.2.1 INTRODUCTION

Critically ill patients admitted with traumatic brain injury and burns are believed to be at the highest risk of delayed gastric emptying and feed intolerance with a prevalence of up to 80% (Hu, *et al.* 1993; Kao, *et al.* 1998; McArthur, *et al.* 1999; Mutlu, *et al.* 2001). Data on the incidence of delayed gastric emptying in patients with other diagnoses such as sepsis and multi-trauma, however, are limited and the techniques used to measure gastric emptying in some previous studies were suboptimal (Hu, *et al.* 1993; McArthur, *et al.* 1999; Ott, *et al.* 1999). The aims of this study were to examine: (i) the impact of admission diagnosis on delayed gastric emptying and (ii) factors associated with delayed gastric emptying in critical illness, using a validated and reliable technique to measure gastric emptying, the ^{13}C-octanoic acid breath test (Ghoos, *et al.* 1993; Zahn, *et al.* 2003; Nguyen, *et al.* 2006).

9.2.2 METHODS

9.2.2.1 Subjects

Data from an unselected cohort of critically ill patients, who were admitted to the intensive care unit at the Royal Adelaide Hospital from 1999 to 2005, were pooled from 6 previous clinical studies that involved measurement of gastric emptying by ^{13}C-octanoic acid breath tests. Four of the studies examined the impact of critical illness on gastric emptying: *study 1* – to evaluate the prevalence of delayed gastric emptying (n=45, Ritz, *et al.* 2001); *study 2*- to

examine the relationship between gastric emptying and antro-pyloro-duodenal motility (n=18, Chapman, *et al.* 2005); *study 3*- to assess the impact of morphine versus propofol on gastric emptying (n=14); and *study 4*- to examine the impact of delayed feeding on gastric emptying in critical illness (n=24). The other two studies were randomized, placebo-controlled trials that assessed the effects of a single dose of cefazolin (50mg; n=14; Chapman, *et al.* 2003) and erythromycin (200mg; n=30; Ritz, et al. 2005) on gastric emptying. In both of these latter trials, only the results of gastric emptying assessment during administration of placebo therapy (20 mL normal saline) were included. Although the outcome measures in each trial varied, the inclusion and exclusion criteria, the test meal and technique used to assess gastric emptying, ^{13}C-octanoic acid breath test, were identical (Chapter 6).

9.2.2.2 Protocol

All relevant details related to the patients and the ICU admission were obtained from case-notes and intensive care charts. Patients demographics, admission diagnosis, APACHE II score, medication (prior and during admission), past medical history, blood glucose concentrations, blood biochemistry, ventilation details, length of stay prior to the assessment of gastric emptying and length of hospital stay on the study day were recorded. The mean rate of naso-gastric feed delivery, before and after the assessment of gastric emptying, was also documented. In the current study, delayed gastric emptying was defined as a GEC of less than 3.2 (Ritz, *et al.* 2001).

The patients were categorized into 6 major admission diagnoses: (i) intra-cerebral injury; (ii) burns; (iii) multi-system trauma resulting from either motor vehicle accident or fall; (iv) sepsis; (v) respiratory failure after a non-abdominal surgery requiring ventilation in ICU; and

(vi) ischemic myocardial injury, with cardiogenic shock and significant pulmonary oedema. The intra-cerebral injury category encompassed open or closed head injury related to mechanical trauma, sub-dural, sub-arachnoid or intra-cerebral haemorrhage and major ischemic cerebral events. A patient was deemed to have sepsis if there were clinical signs of systemic inflammatory response syndrome (SIRS) with documented evidence of infection on bacteriological assessment (Balk 2000). SIRS was recognized by the presence of two or more of the following: temperature >38ºC or <36ºC; heart rate >90 beats/min; respiratory rate > 20 breaths/min or $PaCO_2$ <32 mmHg; white cell count greater than 12,000 cells/mm^3, or less than 4000 cells/mm^3, or a blood picture showed more than 10% immature white cell (Balk 2000).

9.2.2.3 Statistical Analysis.

Differences in demographic data and gastric emptying variables between the patients groups were compared using Chi-square test with Yates' correction and Student's t-test. Risk factors associated with delayed gastric emptying, such as APACHE II score, age, serum creatinine, length of ICU stay prior to the breath testing, ventilation parameters and blood glucose concentration, were assessed using Pearson's linear regression analysis. The linear relationship between these risk factors and gastric emptying variables were confirmed by histograms and Q-Q plots. After controlling for these risk factors, the influence of admission diagnosis on gastric emptying variables was assessed using linear and hierarchical regression model analyses. The relative risk of delayed gastric emptying, as compared to that of patients with cardiac injury, was also calculated with 95% confidence interval. Statistics were determined using SAS/STAT software (version 9.1, NC 27513, USA).

9.2.3 RESULTS

Completed breath test data were available for 145 patients. Thirteen of these patients were excluded from further analysis as their case notes and/or ICU charts could not be retrieved. Thus, the final analysis was performed on 132 critically ill patients. Overall patient characteristics and details related to their ICU admission are summarized in Table 9.2.1. The three most common admission diagnoses were: sepsis (n=44), head injury (n=30), and multi-system trauma (n=29). Seven of the 29 multi-system trauma patients had also sustained a head injury. All, except 4 patients, were sedated within 24 hours of gastric emptying measurement using morphine and/or midazolam alone (n=48), propofol alone (n=18) or a combination of these drugs (n=62). The mean interval between ICU admission and the day of gastric emptying measurement was 7.3 ± 0.6 days.

9.2.3.1 Critical illness factors associated with delayed gastric emptying

Overall, 60% of the patients had delayed gastric emptying, with a mean t50 of 163±7 minutes and GEC of 2.9±0.1. Table 9.2.2 summarizes the characteristics of patients who had delayed gastric emptying. Slow gastric emptying was more common in patients who were older, and those who had higher admission APACHE II scores, higher admission blood glucose and bilirubin concentrations, and who received SIMV mode ventilation. On linear regression analysis, gastric emptying (both t50 and GEC) correlated with older age, higher admission APACHE II scores, longer length of stay in ICU prior to GE, higher FiO2 requirement and higher serum creatinine (Table 9.2.3). There was no relationship between gastric emptying and patient gender, body mass index, ventilatory pressure, APACHE II score on study day, the type of sedation or requirements for inotropic support.

Table 9.2.1 Demographics and details related to the admission of critically ill patients included in the analysis.

	Critically ill patients (n=132)
Age (yr)	54.4 ± 1.5
Gender (M:F)	95:37
Body mass index (kg/m^2)	27.4 ± 0.6
Days in ICU prior to study	8.0 ± 0.6
APACHE II score	
Admission	23.9 ± 0.5
Study day	17.6 ± 0.6
Enteral feeding rate (mL/hr)	
Prior to breath testing	51.1 ± 2.9
After breath testing	56.6 ± 2.8
DIAGNOSIS (%(n))	
Sepsis	33% (44)
Head injury †	23% (30)
Multi-trauma †	22% (29)
Burns	7% (9)
Non-GI post-operative respiratory compromise	9% (12)
Cardiac injury (ischemia and failure)	11% (15)
Blood glucose level (mmol/L)	
Admission	9.7 ± 0.9
Study day	8.0 ± 0.3
Biochemistry	
Albumin (g/L)	23.6 ± 0.5
Bilirubin (μmol/L)	19.5 ± 2.5
White cell count (x 10^9/L)	12.6 ± 0.5
Serum creatinine (mmol/L)	0.134 ± 0.01
Medications (%(n))	
Opioid ± Benzodiazepine	83% (110)
Propofol	60% (80)
Inotropes	69% (91)
Mechanical ventilation	
SIMV: pressure support ventilation (n)	74:58
Fraction of inspired oxygen (FiO_2)	0.5 ± 0.01
Positive end expiratory pressure (PEEP, cmH_2O)	6.5 ± 0.3
Peak inspiratory pressure (cmH_2O)	24.5 ± 0.8

† 7 patients had head injury due to multi-trauma. SIMV synchronised intermittent mandatory ventilation. Pressure support ventilation - self triggered mode.

Table 9.2.2 Characteristics of patients who had normal and delayed gastric emptying on ^{13}C-octanoic acid breath test.

	Delayed gastric emptying (n=79)	**Normal gastric emptying (n=53)**
Age (yr)	57.8 ± 2.2 *	52.2 ± 2.0
Gender (M:F)	58:21	37:16
Body mass index (kg/m^2)	27.1 ± 0.8	27.9 ± 0.9
Days in ICU prior to study	7.3 ± 0.6	7.4±0.7
APACHE II score		
Admission	24.6 ± 0.6	22.9 ± 0.7
Study day	17.4 ± 0.4	17.8 ± 0.9
Enteral feeding rate (mL/hr)		
Prior to breath testing	44 ± 4 *	61± 5
After breath testing	55 ± 4 *	60 ± 4
Blood glucose level (mmol/L)		
Admission	9.7 ± 0.9 **	7.8 ± 0.2
Study day	8.5 ± 0.5	7.7 ± 0.3
Biochemistry		
Albumin (g/L)	23.8 ± 0.6	23.3 ± 0.9
Bilirubin (μmol/L)	24.2 ± 4.0 *	12.0 ± 1.5
White cell count (x 10^9/L)	12.3 ± 0.6	13.1 ± 0.7
Serum creatinine (mmol/L)	0.148 ± 0.02	0.113 ± 0.01
Medications (%(n))		
Opioid ± Benzodiazepine	87% (67)	81% (43)
Propofol	63% (50)	57% (30)
Inotropes	66% (52)	73% (39)
Mechanical ventilation		
SIMV: pressure support (n)	49:30 *	25:28
FiO_2	0.49 ± 0.02	0.46 ± 0.02
PEEP (cmH_2O)	6.4 ± 0.4	6.8 ± 0.4
Peak inspiratory pressure (cmH_2O)	24.6 ± 1.0	24.2 ± 1.2
Length of stay (day)		
In ICU	21.0 ± 1.6**	13.8 ± 1.2
In hospital	37 ± 2 **	28 ± 3

* P<0.05; versus normal gastric emptying.

** P<0.01; versus normal gastric emptying.

Table 9.2.3 Factors correlated with delayed gastric emptying in critical illness, derived from univariate analyses.

	P-value	r
Age	<0.01	0.32
Admission APACHE II score	<0.01	0.27
Fraction of inspiratory oxygen	0.02	0.27
Serum creatinine	0.04	0.17
Length of stay in ICU prior to the study	0.02	0.14

9.2.3.2 Impact of admission diagnosis on gastric emptying

The impact of admission diagnoses on gastric emptying in critical illness is summarized in Table 9.2.4 and Figure 9.2.1 & 2. After controlling for other factors that influence gastric emptying, admission diagnosis had a modest effect on gastric emptying ($r = 0.48$; $P=0.02$) using linear and hierarchical regression analysis. Gastric emptying was most delayed in patients with burns. In addition to patients with intra-cerebral and burn injuries, delayed gastric emptying was also common in patients who were admitted with multi-system trauma and sepsis. Patients with myocardial injury and non-GI post-operative respiratory failure had the lowest incidence of delayed gastric emptying.

9.2.3.3 Impact of pre-existing illness on gastric emptying

Gastric emptying was delayed in 58% of patients with no known co-morbidity prior to their ICU admission ($t50 = 167 \pm 11$ minutes, and $GEC = 2.9 \pm 0.1$). When controlled for age and admission APACHE II scores, there was a trend for slow gastric emptying to be more common in patients who had pre-existing alcoholic liver disease (80%; $P=0.04$), chronic renal

failure (75%; P=0.06), and to be less common in patients with known diabetes mellitus (38%; P=0.05).

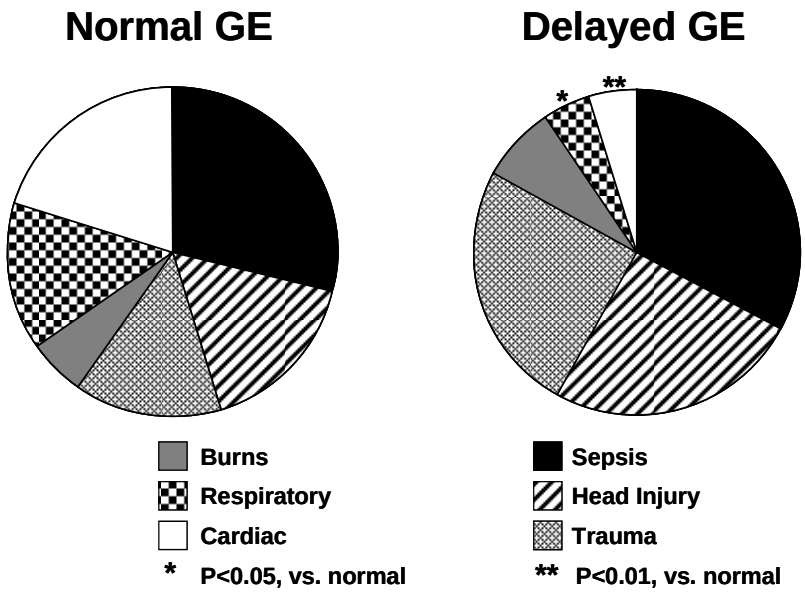


Figure 9.2.1 Summary of admission diagnosis in critically ill patients with normal (left) and delayed (right) gastric emptying (GE).

9.2.3.4 Outcome of delayed gastric emptying in critical illness

Patients who had delayed gastric emptying received feeds at a lower rate, both before and after the gastric emptying assessment (Table 9.2.2). The lengths of stay in ICU and overall duration of hospital admission were significantly longer for patients with delayed gastric emptying than for those who had normal gastric emptying (Table 9.2.2). Patients with the most delayed emptying (those with burns and multi-system trauma) had the longest stays in both ICU and hospital (Table 9.2.4). On the other hand, patients with a higher incidence of normal gastric emptying (ie. cardiac injury group) had a significantly shorter length of stay in hospital.

Table 9.2.4 Gastric emptying measurements, demographics and patient's characteristics in various groups of diagnosis

	Intra-cerebral injury † (n=30)	**Burns (n=9)**	**Multi-trauma (n=29)**	**Sepsis (n=44)**	**Non-GI post-op respiratory failure(n=12)**	**Cardiac injury (n=15)**
Slow gastric emptying (%)	67%	77%	72%	61%	33% *	27% **
Relative risk of delayed GE § (CI; confidence interval)	1.8 (1.1-2.8)	4.2 (1.1-15.0)	2.0 (1.2-3.5)	1.5 (1.02-2.0)	1.1(0.5-2.8)	—
Age (yr)	51.5 ± 1.5	37.2 ± 0.9	47.5 ± 1.8	65.8 ± 0.9	59.3 ± 1.2	58.8 ± 1.3
Days in ICU prior to study	9.8 ± 0.6	9.5 ± 1.5	7.0 ± 0.5	7.7 ± 0.5	6.3 ± 0.4	7.5 ± 2.1
APACHE II score						
Admission	23.7 ± 0.4	24.1 ± 0.5	23.2 ± 0.6	25.9 ± 0.5	22.3 ± 0.6	21.9 ± 0.6
Study day	17.5 ± 0.5	14.3 ± 0.6	16.4 ± 0.6	18.5 ± 0.6	17.8 ± 0.5	17.5 ± 0.5
Blood glucose concentrations on study day (mmol/L)	7.9 ± 0.2	8.9 ± 0.3	7.5 ± 0.2	8.5 ± 0.3	7.3 ± 0.4	8.7 ± 0.3
Medications (% (n))						
Opioid ± Benzodiazepine	80% (24)	89% (8)	89% (26)	82% (36)	83% (10)	73% (11)
Propofol	83% (25)	33% (3)	69% (20)	57% (25)	58% (7)	40% (6)
Inotropes	63%(19)	89% (8)	52%(15)	91%(40)	58% (7)	53% (8)
Enteral feeding rate (mL/hr)						
Prior to breath testing	28 ± 2	47 ± 3	29 ± 3	52 ± 3	53 ± 3	76 ± 3
After breath testing	58 ± 3	67 ± 2	40 ± 2	64 ± 3	55 ± 2	76 ± 2
Length of stay (days)						
In ICU	20 ± 3	34 ± 9	19 ± 2	20 ± 2	20 ± 2	16 ± 3
In hospital	46 ± 6	70 ± 5	52 ± 6	37 ± 3	37 ± 2	29 ± 2
Prokinetic therapy for feeding during admission # (% (n))	40% (12)	33% (3)	35% (10)	32% (14)	0% (0)	20% (3)

† 7 patients had head injury due to multi-trauma. * P<0.05, versus other 4 groups on hierarchical regression analysis. ** P<0.01, versus other 4 groups on hierarchical regression analysis. § Compared with patients with cardiac injury (CI – 95% confidence interval). # In all patients, prokinetic agents were ceased ≥ 24 hours prior to the assessment of gastric emptying.

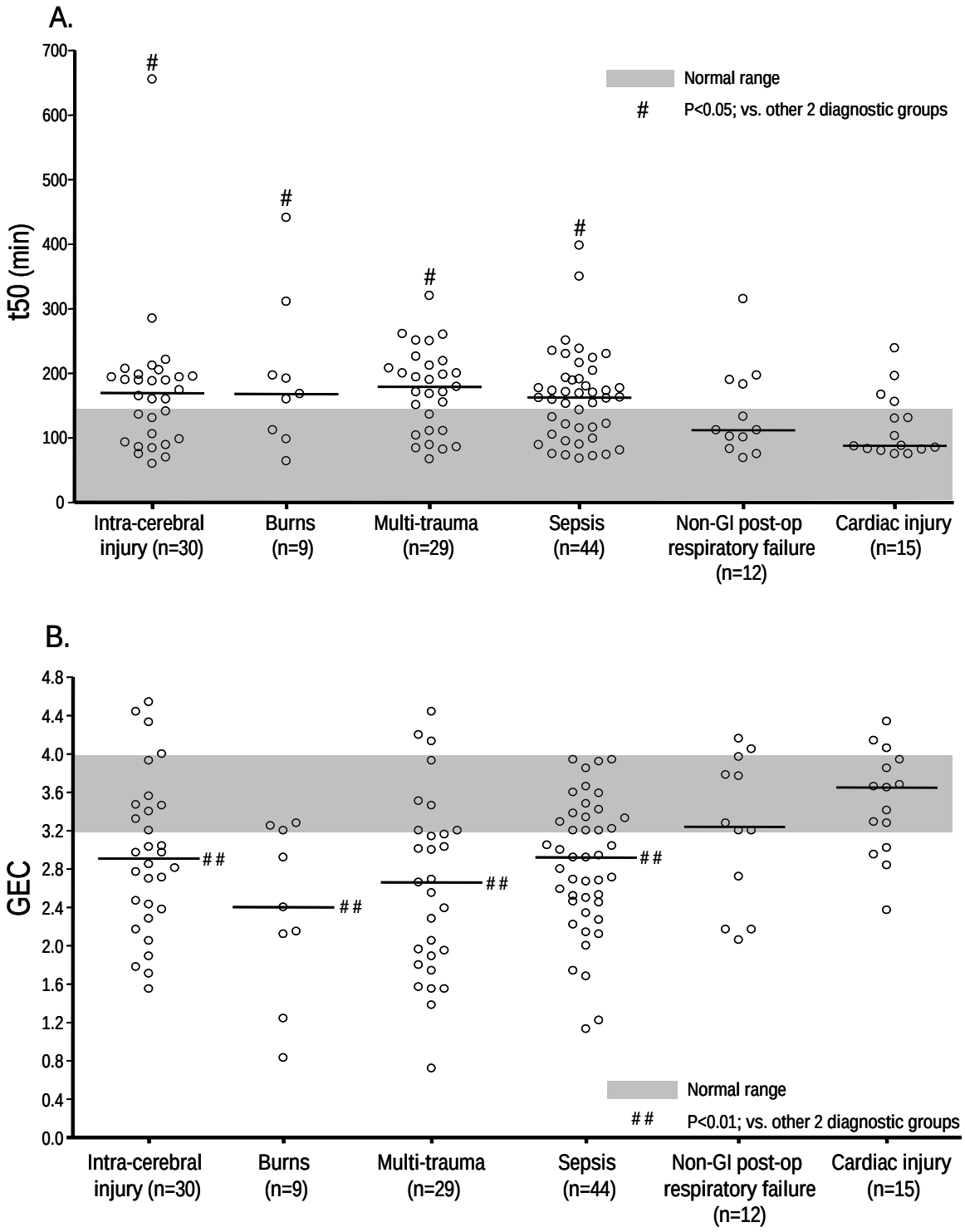


Figure 9.2.2 The impact of admission diagnoses on gastric emptying in critically ill patients, reflects by either (A) gastric half emptying time (t50) or (B) gastric emptying coefficient (GEC). Bars (—) indicate median values.

9.2.4 DISCUSSION

The current study is the first large scale systematic examination of the impact of admission diagnosis on gastric emptying in unselected critically ill patients using a standardized technique to measure gastric emptying. The results show that admission diagnosis has a significant but modest impact on gastric emptying in critically ill patients, after controlling for other potential variables that may influence gastric emptying. Consistent with previous reports (Hu, *et al.* 1993; Kao, *et al.* 1998; Mentec, *et al.* 2001; Mutlu, *et al.* 2001), factors such as APACHE II scores, age, length of ICU stay, blood glucose concentrations on admission, renal function, and SIMV mode of mechanical ventilation were also associated with delayed gastric emptying.

The high prevalence of delayed gastric emptying in patients with burns and head injury in the current study is consistent with previous reports (Hu, *et al.* 1993; Kao, *et al.* 1998; McArthur, *et al.* 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; Heyland, *et al.* 2003). Apart from factors known to slow gastric emptying such as a high APACHE II score and the use of opioid and inotropic agents, the mechanisms underlying disturbed emptying in patients with burns and head injuries are unknown. Several neuro-humoral abnormalities related to these injuries, however, may contribute to gastric dysmotility (Alican, *et al.* 1995; McArthur, *et al.* 1999). Thermal injury has been shown to relax the fundus, reduce antral motility and slow gastric emptying (Chen, *et al.* 1982; Alican, *et al.* 1995) due to increases in both sympathetic and opiatergic neural activity, and release of systemic inflammatory cytokines (Takakura, *et al.* 1997; McArthur, *et al.* 1999). In head injured patients, raised intra-cranial pressure is thought

to be the major factor responsible for impaired gastric motility and emptying, but the precise pathophysiology is unclear (McArthur, *et al.* 1999).

Previous data related to the impact of sepsis and trauma on gastric emptying in critical illness have been limited (Zaricznyj, *et al.* 1977; Carlin, *et al.* 1999; Kimura, *et al.* 2002). In the current study, the observation that gastric emptying was delayed in 61% of septic patients has significant clinical implications as up to 50% of admissions to ICU are due to sepsis and its complications (Montejo 1999; Mentec, *et al.* 2001; Heyland, *et al.* 2003). Early detection and management of feed intolerance in these at-risk patients is important to prevent the subsequent complications. In animals, release of inflammatory mediators and cytokines during sepsis have been shown to impair gastric and small intestinal motor activity and are likely to contribute to the negative effects of sepsis on gut function (Montuschi, *et al.* 1994; de Jonge, *et al.* 2003).

The results from the current study are also consistent with previous reports on gastric emptying in patients admitted to ICU following multi-system trauma (Carlin, *et al.* 1999). The mechanisms underlying the impact of trauma on gastric function are also unknown, but could relate to the inhibitory effects of inflammatory mediators and cytokines released from damaged tissue sustained during injury (Zaricznyj, *et al.* 1977). This speculation is supported by the observation that gastric emptying rates after limb fracture are related to the severity of pain, swelling and shock associated with the injuries (Zaricznyj, *et al.* 1977). However, it is likely that the analgesia requirements in these patients also contribute to impaired gastric emptying, as both opioids and benzodiazepines impair gastric motility and emptying (Nimmo, *et al.* 1975; Steyn, *et al.* 1997).

In contrast, less than one third of the patients with acute ischemic myocardial injury had delayed gastric emptying. The reason for the low prevalence of delayed gastric emptying in this group of patients is unclear. However, it is unlikely to relate to a lesser degree of illness severity or less frequent requirement for opioid and inotropic drugs, as the use of these was similar to that in the other diagnostic groups. In rats, acute myocardial injury delays both gastric emptying and intestinal transit of liquids (Nimmo, *et al.* 1975). The hypotension and the release of atrial natriuretic peptide induced by the myocardial infarction are thought to be the main mechanisms that mediate the inhibition of gut motility, possibly via the non-adrenergic and non-cholinergic pathways (Gondim, *et al.* 1999; Camurca, *et al.* 2004). Whether the similar neuro-hormonal mechanisms occur in humans during acute myocardial injury, further study is warranted.

In the current study, pre-existing co-morbidity had a moderate effect on gastric emptying, and diseases previously reported to be associated with slow gastric emptying, such as liver disease (Usami, *et al.* 1998) and chronic renal failure (Wang, *et al.* 1996), increased the likelihood of delayed gastric emptying during critical illness. These findings suggest that critical illness may have an 'additive' adverse effect on gastric emptying in these patients. The relatively normal gastric emptying seen with diabetes mellitus is intriguing, as slow gastric emptying is common in patients with both type 1 and 2 diabetes mellitus (Horowitz, *et al.* 1996; Kong, *et al.* 1996). The lower frequency of delayed gastric emptying in the diabetic patients is, however, consistent with findings that suggest gastric emptying of liquid is relatively normal in critically ill patients with type 2 DM (Chapter 10.2). The reason for this difference may relate to differences in proximal gastric motor function during critical illness in these patients (Chapter 10.3). In addition, hyperglycemia is associated with slowing of gastric emptying in

DM and it is possible that tight control of blood glucose concentrations, which is now routine in the ICU, may reduce the incidence of delayed gastric emptying in this group of patients (Fraser, *et al.* 1990).

The current study also confirmed that delayed gastric emptying in critically ill patients is associated with suboptimal delivery of enteral feeds and a longer length of stay in ICU and hospital (Mullen, *et al.* 1980; Dempsey, *et al.* 1988; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; Heyland, *et al.* 2003). The adverse effect on successful enteral feeding was most pronounced prior to the assessment of gastric emptying (ie. in the first week of critical illness), with mean feeding rates as low as 28 ± 3 mL. As the current study is retrospective, the relationship between delayed gastric emptying, illness and its impact on admission outcomes such as length of stay in ICU and hospital could not be determined, and this requires further study. However, feed intolerance, an indirect marker of delayed gastric emptying, is known to be associated with prolonged ICU stay (Heyland, *et al.* 1995; Montejo 1999; Mentec, *et al.* 2001). It is possible that this is related, in part, to the increased risk of gastro-oesophageal reflux and subsequent aspiration pneumonia due to large gastric residuals (Montejo 1999; Mentec, *et al.* 2001; Heyland, *et al.* 2003; Metheny, *et al.* 2004).

There are a number of limitations to the current study. Due to its retrospective nature, selection bias cannot be totally excluded. However, such bias is likely to be minimal as the studies into which patients were recruited had similar inclusion and exclusion criteria, and data for over 90% of patients were available for analysis. As gastric emptying was assessed on only a single occasion, approximately a week after admission, variations in the severity of illness and prescribed medications throughout the ICU course could have led to fluctuations in

gastric emptying in critically ill patients over time. The relatively wide time window between admission and measurement of gastric emptying could have potentially weakened the strength of association between admission diagnosis and gastric emptying. However, since the association was still seen on day 8, when other factors known to alter gastric emptying in critical illness had accounted for, the relationship between admission diagnosis and gastric emptying may have been even stronger if gastric emptying had been assessed earlier in the admission. Currently there are no data on the temporal relationship between the impact of admission diagnosis and gastric emptying in critically ill patients. Finally, the use of the ^{13}C octanoic acid breath test to measure gastric emptying is also a potential source of error. However, a number of studies, in both healthy humans and critically ill patients, have demonstrated a strong correlation between this technique and the current gold-standard gastric scintigraphy (Kim, *et al.* 2000; Zahn, *et al.* 2003).

In conclusion, admission diagnosis has a modest impact on gastric emptying in critically ill patients, even after controlling for factors known to influence this function. Apart from burns and head injury, patients with sepsis and multi-system trauma are also at high risk of delayed gastric emptying. Patients with these "at-risk" admission diagnoses should be monitored careful for signs of feed intolerance during enteral feeding, so that treatment for feed intolerance can be instituted early to prevent reflux complications and optimize nutritional support.

9.3 THE IMPACT OF TYPE OF SEDATION ON GASTRIC EMPTYING AND MEAL DISTRIBUTION IN CRITICAL ILLNESS

9.3.1 INTRODUCTION

The most commonly used sedative regimens in critical illness are either combination of morphine and midazolam (M&M) or propofol alone (Fraser and Riker 2007; Payen, *et al.* 2007). Both gastric motility and emptying in health are significantly impaired by opioids such as morphine (Mittal, *et al.* 1986; Crighton, *et al.* 1998; Yuan, *et al.* 1998) but not low doses of propofol (Hammas, *et al.* 1998; Chassard, *et al.* 2002). The choice of sedative agents is, therefore, believed to be an important determinant of gastric emptying (Mutlu, *et al.* 2001). However, whilst sedation with M&M impairs antro-duodenal motility (Bosscha, *et al.* 1998), slows gastric emptying (Heyland, *et al.* 1996) and increases feed intolerance (Heyland, *et al.* 1996; Montejo 1999; Mentec, *et al.* 2001), avoiding M&M does not improve gastric emptying in head injured patients (McArthur, *et al.* 1999). The effect of propofol on gastric motor function in critically ill patients is unknown, although the combination of propofol and morphine does not worsen gastric emptying (Hammas, *et al.* 2001).

Currently, there are no studies that have directly compared the impact of M&M and propofol sedation on gastric emptying and intra-gastric meal distribution in critically ill patients. The aim of this study was, therefore, to evaluate the effects of M&M compared to propofol as sedative drugs on gastric emptying and intra-gastric meal distribution in critically ill patients.

9.3.2 METHODS

9.3.2.1 Subjects

Gastric scintigraphic data from 36 mechanically ventilated, critically ill patients (55.4 ± 2.7 yr; 23 M; BMI: 28.0 ± 1.2 kg/m^2), who were admitted to the intensive care unit at the Royal Adelaide Hospital between May 2005 to September 2006, were reviewed. These gastric scintigraphic studies had been performed as part of clinical research to evaluate the impact of critical illness on gastric emptying. All patients received an insulin infusion for control of hyperglycemias according to a standard protocol, able to receive enteral nutrition and shared the common exclusion criteria outlined in Chapter 6, except for the type of sedation. The mean duration from admission to gastric emptying assessment was 5.8 ± 1.0 days.

9.3.2.2 Study protocol and techniques

All patients were sedated with either (i) propofol (n=16) or (ii) a combination of morphine and midazolam (n=20), during and for at least 24 hours prior to the study. The choice of sedation was not randomised and was individually prescribed by the intensivist(s) in charge of the patient, as judged most suitable for the patient's requirements. The depth of sedation during the study and 8 hours prior to the study was assessed by Sedation-Agitation Scale (SAS) score (Riker, *et al.* 1999). In all patients, a 14 to 16 French Levin naso-gastric (NG) feeding tube (Pharma-Plast, Lynge, Denmark) had been inserted into the stomach, as part of clinical care, and the correct gastric position of the feeding tube confirmed by radiology.

Gastric scintigraphy was performed for 240 minutes in an identical fashion in all patients and the details of this assessment are outlined in Chapter 6. Blood samples were collected from

an arterial line at timed intervals following test meal delivery for assessment of plasma glucose concentrations, using a portable glucometer (Precision Plus, Abbott Laboratories, Bedford, USA). On completion of the study, nasogastric feeding was re-commenced as clinically indicated.

All relevant details of the patient's ICU admission were recorded, including demographics, admission diagnosis, inotropic support, the number of days in ICU prior to study, APACHE II score on admission and on study day, and prior history of enteral feeding (Table 9.3.1). The degree of illness severity was also assessed, by using Sequential Organ Failure Assessment (SOFA) score (Vincent, *et al.* 1998), on admission and the study day.

9.3.2.3 Data analysis

The scintigraphic measurements were analysed as outlined in Chapter 6, with correction for radionuclide decay and γ-ray attenuation. A region of interest was drawn around the total stomach. This was subsequently divided into proximal and distal gastric regions. Gastric emptying curves (expressed as percentage retention over time) were derived. The amount of feed remaining in the total, proximal and distal stomach at 0, 5, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes were calculated (Collins, *et al.* 1983; Collins, *et al.* 1988). Standard gastric $t_{1/2}$ could not be determined and is not reported as one third (12/36) of the patients had less than 50% of the meal emptied by 240 minutes. Based on normal data using an identical meal in healthy humans, "delayed" gastric emptying was defined as greater than 10% retention at 240 minute (Nguyen, *et al.* 2006).

9.3.2.4 Statistical analysis

The differences in demographic characteristics, APACHE II score, length of stay in ICU prior to study, inotropic support, admission diagnosis and baseline blood glucose concentrations between critically ill groups were compared using Student's unpaired t-test and Fisher's exact test. A two-way repeated measures analysis of variance (ANOVA) with post-hoc comparisons was used to compare the: (i) overall meal retention; (ii) regional meal retention; and (iii) blood glucose concentrations in the two groups. The relative risk of delayed gastric emptying between the types of sedation was also determined.

9.3.3 RESULTS

Twenty-eight (78%) patients in the cohort had delayed gastric emptying, with mean meal retention at 240 minute of 31 ± 5%. Nineteen (53%) patients had received enteral feeds for a mean duration of 5.2 ± 1.3 days, and 20 (55%) patients had received inotropic therapy during and at least 24 hour before the study. Seventeen (47%) patients did not receive any nutritional support prior to the study (mean duration after ICU admission of 4.0 days).

There was no difference in meal retention between patients who: (i) received enteral feeds versus no prior enteral feeds (P=0.47), and (ii) received inotropes versus no inotropes (P=0.66). Overall, there was a positive correlation between age and gastric retention at 240 minute (r= 0.51; P=0.002). There was no relationship between gastric meal retention and gender, BMI and APACHE II scores (either on admission or day of study), or the duration of stay in ICU prior to gastric emptying assessment.

9.3.3.1 Impact of sedation on gastric emptying and meal distribution

In the 24 hours prior to the study, 20 patients were sedated with morphine (0.10 ± 0.009 mg/kg/hr) and midazolam (0.05 ± 0.005 mg/kg/hr); and 16 patients with propofol (1.8 ± 0.2 mg/kg/hr).

There were no differences in age, gender, BMI, duration of ICU stay prior to study, admission diagnosis, APACHE scores, and prior enteral feeding between patients who received M&M or propofol (Table 9.3.1). In particular, the depth of sedation as reflected by the SAS score, the need for inotropic therapy and SOFA scores were comparable between patients who received M&M or propofol. The proportion of patients with head injury was also similar between the groups (35% (7/20) vs. 31% (5/16)).

In patients sedated with M&M, total gastric meal retention at 240 minute was significantly longer than in patients sedated with propofol ($P<0.01$; Figure 9.3.1A). Meal retention in the proximal stomach was also significantly greater in patients sedated with M&M ($P=0.02$; Figure 9.3.1B), although retention in the distal stomach was similar ($P=0.80$; Figure 9.3.1C). Overall, patients receiving M&M (95% (19/20)) were more likely to have delayed gastric emptying than those who received propofol (56% (9/16); $P=0.01$).

Table 9.3.1 Demographic data and characteristics of critically ill patients

	Morphine and midazolam (n=20)	**Propofol (n=16)**	**P-value**
Age (yr)	53.9 ± 3.6	57.9 ± 3.9	0.40
Gender (M:F)	15:5	8:8	0.17
Body mass index (kg/m^2)	28.5 ± 1.3	27.4 ± 1.1	0.65
Days in ICU prior to study	4.1 ± 0.1	6.9 ± 1.2	0.11
Admission APACHE II score	22.7 ± 1.1	22.4 ± 1.1	0.70
Study day APACHE II score	22.7 ± 1.1	21.2 ± 0.8	0.46
Inotropes [a]	11 (55%)	9 (56%)	0.99
- Mean 24h cumulative dose	199 ± 43	189 ± 32	0.86
- Admission SOFA score	5.0 ± 0.6	4.8 ± 0.9	0.81
- Study day SOFA score	6.0 ± 0.8	5.4 ± 0.6	0.54
Baseline blood glucose level (mmol/L)	7.0 ± 0.2	7.1 ± 0.2	0.89
Sedation-Agitation Scale score			
- During gastric emptying study	1.8 ± 0.3	2.0 ± 0.4	0.65
- 8 hours prior to study	1.6 ± 0.2	2.0 ± 0.4	0.40
Admission diagnosis [b]			
Sepsis	5 (25%)	4 (25%)	0.99
Respiratory failure	5 (25%)	4 (25%)	0.99
Multi-trauma	4 (20%)	5 (31%)	0.25
Head injury [c]	7 (35%)	5 (31%)	0.93
Burns	1 (5%)	0 (0%)	0.99
Aortic dissection	4 (20%)	2 (13%)	0.67
Prior enteral feeding	10 (50%)	9 (56%)	0.74
- Mean 24h feed volume received (mL)	1158 ± 76	1300 ± 156	0.54
- Administered: prescribed ratio (%)	81 ± 5	85 ± 8	0.62

[a] Adrenaline or nor adrenaline infusion. [b] One patient may have more than 1 diagnosis.
[c] Including sub-arachnoid haemorrhage and massive cerebral ischemic events

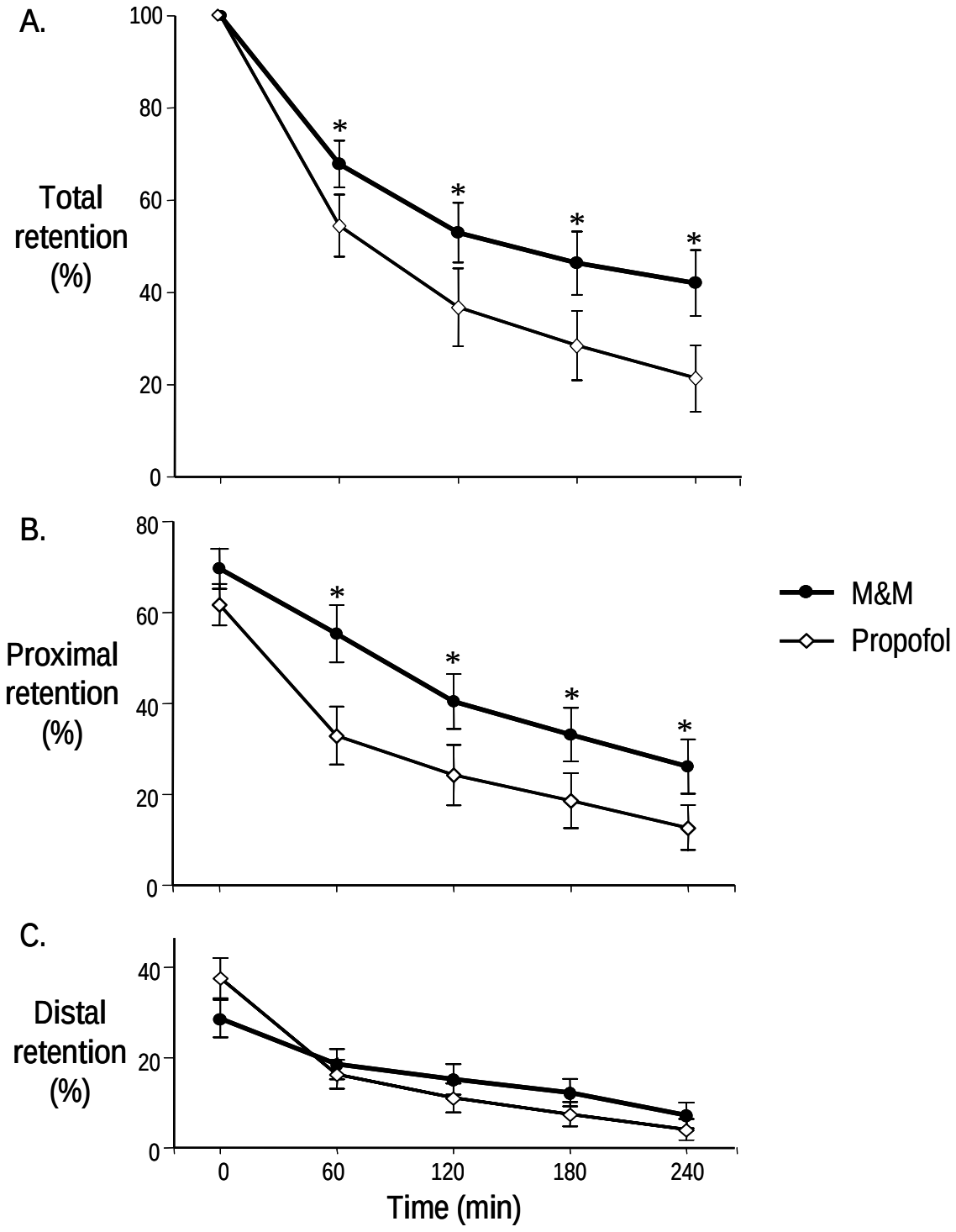


Figure 9.3.1 Total and regional gastric emptying as measured by % retention in (A) the whole stomach, (B) proximal stomach and (C) distal stomach of critically ill patients who were sedated with either morphine and midazolam (M&M) or propofol. * $P < 0.01$ vs. propofol.

9.3.3.2 Impact of sedation on gastric emptying and meal distribution in patients without head injury

As the type of sedation has been reported to have no impact on gastric emptying of critically ill patients with head injury (McArthur, *et al.* 1999), these patients were excluded in a sub-analysis, to assess the impact of sedation on gastric emptying in non-head injured patients. After excluding patients with head injury, 13 patients were sedated with M&M (58.0 ± 3.0 yr; 9M; APACHE II: 24.7 ± 2.2) and 11 patients with propofol (60.4 ± 3.9 yr; 5M; APACHE II: 23.3 ± 3.1). In patients sedated with M&M, the total gastric meal retention over 240 minutes was significantly greater than those sedated with propofol (P=0.04; Figure 9.3.2).

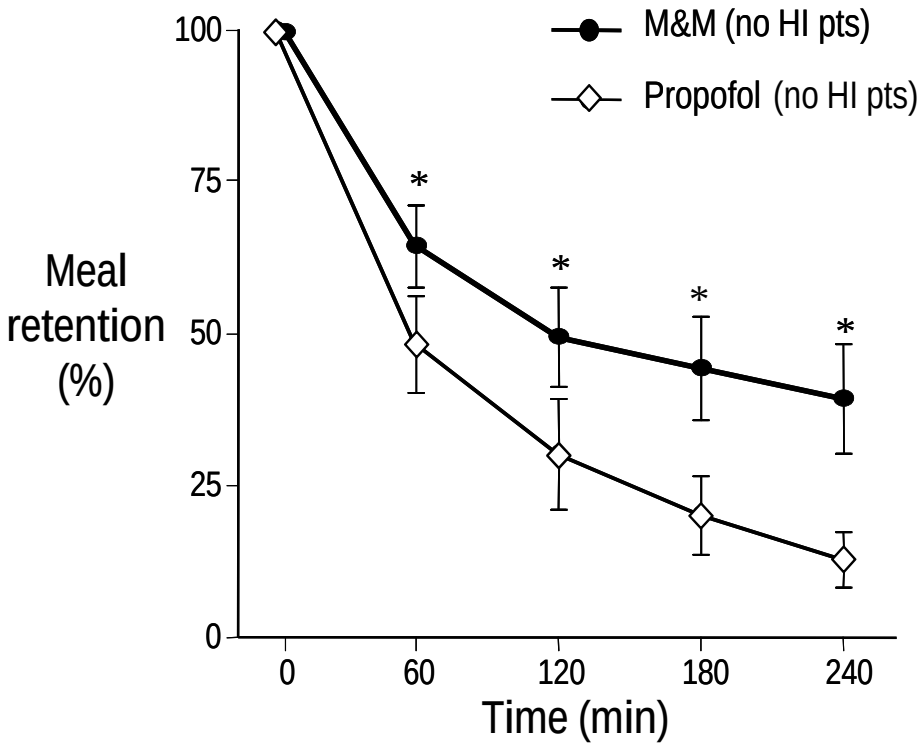


Figure 9.3.2 Gastric emptying in critically ill, non-head injured patients who were sedated with either morphine and midazolam (M&M; n=13) or propofol (n=11). * $P < 0.05$; vs. propofol.

9.3.3.3 Blood glucose concentrations

Fasting blood glucose concentrations were similar in the two groups (7.0 ± 0.2 mmol/L vs. 7.1 ± 0.2 mmol/L; P=0.89). After the meal, there was a small but significant increase in blood glucose concentrations in all patients that peaked at 8.1 ± 0.3 mmol/L. However, there were no differences in blood glucose concentration responses between patients receiving M&M and propofol.

9.3.4 DISCUSSION

This study evaluated the relationship between two commonly used sedative regimens and gastric emptying and intra-gastric meal distribution measured by scintigraphy, in an unselected group of critically ill patients. The results demonstrate that in patients who were well matched for factors known to alter gastric emptying, such as age, admission diagnosis, blood glucose concentration, illness severity and inotrope use, and the level of sedation, reflected by the SAS score, patients who were sedated with morphine/midazolam have slower gastric emptying and more proximal gastric meal retention than those sedated with propofol. These effects persisted even when head injured patients were excluded from the analysis. These observations suggest that in critical illness, gastric emptying may be influenced by the choice of sedation and that propofol-based sedation may be preferable, especially in patients who are intolerant of gastric feeding.

The adverse effects of M&M on gastric emptying and intra-gastric meal distribution in the current study are consistent with the known motor effects of morphine (Mittal, *et al.* 1986; Crighton, *et al.* 1998; Yuan, *et al.* 1998). In healthy subjects, even at low dose, morphine

markedly inhibits gastric emptying by enhancing proximal gastric relaxation, increasing pyloric tone and retrograde duodenal contractions (Mittal, *et al.* 1986). The enhanced proximal gastric relaxation induced by morphine (Mittal, *et al.* 1986) is likely to explain the excessive proximal gastric retention in patients sedated with M&M, contributing to slow gastric emptying (Yuan, *et al.* 1998). The contribution of motor disturbances in the distal stomach due to morphine are also likely to be important (Dubois 1987) as a number of antral motor abnormalities have been reported in critically ill patients sedated with M&M (Bosscha, *et al.* 1998), including a persistence of the fasting pattern during gastric feeding and a reduction in antral motility. These distal gastric motor disturbances have been reported to inversely relate to the rate of gastric emptying in critically ill patients (Bosscha, *et al.* 1998).

In contrast, the impact of propofol on gastric motility and emptying in humans is less well defined. Whilst propofol inhibits gastric emptying in a dose dependent fashion in mice (Inada, *et al.* 2004), infusion of propofol up to 5 mg/kg/hr over 1 to 3 hours has no effect on gastric emptying in either healthy subjects (Hammas, *et al.* 1998; Chassard, *et al.* 2002) or patients who have undergone minor surgery (Jellish, *et al.* 1995). In the current study, 56% of patients sedated with propofol, at a mean rate of ~ 2 mg/kg/hr, had delayed gastric emptying. Without a "control group" of no sedation, it is not possible to determine whether the delayed gastric emptying was an effect of propofol or of critical illness. Nevertheless, it is clear from the current study that the incidence of delayed gastric emptying in patients receiving propofol was significantly lower than in patients sedated with M&M. McArthur (1999) demonstrated that in patients with head injuries, replacing sedation with M&M by propofol did not improve gastric emptying. In this group of patients, raised intra-cranial pressure rather than sedation may have had a greater influence over gastric emptying (McArthur, *et al.* 1999). However,

even when head injured patients were excluded from the current analysis, gastric retention in patients who were sedated with propofol remained lower than that of sedated with M&M, suggesting the type of sedation had an impact on gastric emptying.

Lower proximal gastric meal retention in patients sedated with propofol may relate to an effect of propofol on proximal gastric motility. Barostat studies in 40 patients before elective abdominal surgery have shown that addition of propofol to morphine increases fasting gastric tone and decreases proximal gastric volume (Hammas, *et al.* 2001). In addition, proximal gastric relaxation in response to duodenal nutrients is initially impaired in critically ill patients sedated with propofol (Chapters 7 and 10). Together, these findings suggest that propofol reduces proximal gastric volume, while M&M is likely to increase proximal gastric relaxation (Mittal, *et al.* 1986). As distal gastric retention appears to be unaffected by the type of sedation, a lesser degree of proximal gastric relaxation with propofol is likely to result in faster gastric emptying of liquids than does M&M. Although the effects of propofol on the distal gastric motor activity have not been examined, delayed gastric emptying, increased pyloric contractions, persistence of fasting motility patterns and retrograde duodenal contractions have been previously reported in unselected critically ill patients who were sedated with propofol only (Chapman, *et al.* 2005).

The current study has several potential clinical implications for critical care practice. Firstly, the lower incidence of delayed gastric emptying with propofol compared to M&M suggests that propofol may be the preferred sedative agent in patients who are at greater risk of delayed gastric emptying and feed intolerance. Unfortunately, many at-risk patients such as those with multi-trauma also require analgesia. In these patients, minimizing the opiate dose and

combining propofol with analgesic agents that have less adverse effects on gastric motor function such as ketamine (Fass, *et al.* 1995) may improve feed tolerance. Furthermore, in patients sedated with M&M who develop feed intolerance, there may be a benefit in substituting propofol, if possible, in addition to prokinetic therapy. However, the prolonged use of high dose propofol (> 4mg/kg/h) should be avoided due to the potential mitochondrial adverse effects, especially in patients with head-injury (Ernest and French 2003; Corbett, *et al.* 2006). Secondly, the increased proximal gastric meal distribution in patients sedated with M&M is likely to predispose these patients to an increased risk of gastro-esophageal reflux and aspiration pneumonia (Montejo 1999; Mentec, *et al.* 2001; Metheny, *et al.* 2004), and provides a possible explanation for the high incidence of such complications in enterally fed patients who receive M&M. In addition to the increased proximal distribution, morphine also reduces lower esophageal sphincter pressure (Mittal, *et al.* 1986) which would amplify this risk. It is possible that the incidence of these complications is lower with the use of propofol, however, this speculation requires further investigation.

As this is an observational study which was not randomized, the results should be interpreted with some caution. In particular, the choice of sedation in critical illness is influenced by many factors such as admission diagnosis, analgesic requirements, duration of sedation, cardiovascular stability, illness severity, presence of renal failure, head injury and hepatic dysfunction (Gehlbach and Kress 2002; Hogarth and Hall 2004). Nevertheless, these and other factors that are known to alter gastric emptying appeared to have been relatively well matched between the two patient groups. Furthermore, although gastric emptying in the propofol group was assessed 2 days later than that of M&M group, the impact of this difference is likely to be minimal given that there was no relationship between gastric

emptying and duration of stay in ICU prior to its assessment. In addition, most feed intolerance (an indirect marker of slow gastric emptying) occurs in the first 3 days of admission (Chapter 9.2) (Heyland, *et al.* 1996; Montejo 1999; Mentec, *et al.* 2001). Finally, risk factors for slow gastric emptying other than type of sedation were similar between the groups. Nevertheless, the apparent beneficial effects of propofol-based sedation on gastric function need confirmation by prospective randomized controlled studies.

In conclusion, slow gastric emptying is more common in patients sedated with M&M than in those receiving propofol, with a greater retention of enteral feed in the proximal stomach. These findings suggest that patients sedated with M&M may be at higher risk of feed intolerance, gastro-oesophageal reflux and aspiration pneumonia. Thus, in patients at risk or with a history of feed intolerance, propofol may be a better 'sedative agent' than M&M. These observations, however, need confirmation by a randomised clinical trial.

9.4 THE IMPACT OF DELAYED ENTERAL FEEDING ON GASTRIC EMPTYING, AND CHOLECYSTOKININ AND PEPTIDE YY RESPONSES

9.4.1 INTRODUCTION

Both acute (Corvilain, *et al.* 1995) and chronic (Dubois, *et al.* 1979; Hutson and Wald 1990; Lee 1993; Nelson and Walsh 2002; Stompor, *et al.* 2002; Strid, *et al.* 2004) nutritional deprivation are associated with reduced gastric emptying in humans. Nutrient deprivation and malnutrition are well recognised problems in critically ill patients (Adam and Batson 1997; De Jonghe, *et al.* 2001) because the ability to provide adequate caloric needs, via enteral feeding, is frequently compromised by: (i) delays in commencement of feeds (Adam and Batson 1997) and (ii) interruptions of feeds due to impaired gastrointestinal motility and procedure related fasting (McClave, *et al.* 1999; De Beaux, *et al.* 2001). Depending on the techniques of gastric emptying assessment, delayed gastric emptying occurs in 40% to 80% of critically ill patients and is manifest clinically as intolerance to enteral feeding (Heyland, *et al.* 1996; McClave, *et al.* 1999; Montejo 1999; Mentec, *et al.* 2001; Heyland, *et al.* 2003). Consequently, it has been estimated that up to 45% of critically ill patients are not fed in the first 3-5 days of admission (Adam and Batson 1997; McClave, *et al.* 1999; Montejo 1999) and only 50% to 68% of daily requirement is delivered to these patients (Adam and Batson 1997; McClave, *et al.* 1999; De Beaux, *et al.* 2001; De Jonghe, *et al.* 2001; Krishnan, *et al.* 2003).

Whilst the mechanisms underlying delayed gastric emptying in critical illness remain poorly defined, heightened inhibitory feedback on gastric emptying arising from the interaction of nutrients with the small intestine is likely to be important (Chapman, *et al.* 2005). This concept is further supported by findings which suggest that both fasting and nutrient-stimulation plasma CCK and PYY concentrations are elevated in critically ill patients (Chapter 8). Given the known relationship between nutritional status and gastric emptying in healthy subjects, the impact of delayed enteral nutrition and the associated malnutrition on gastric motor dysfunction in these patients are also likely to be important. Although delayed nutritional support has been shown to increase septic complications and mortality (Heyland, *et al.* 2003; Artinian, *et al.* 2006), its impact on gastric emptying or plasma concentrations of entero-gastric feedback hormones has not been studied. This study, therefore, aimed to evaluate the effects of delayed enteral feeding on gastric emptying and plasma concentrations of CCK and PYY in the critically ill patients.

9.4.2 METHODS

9.4.2.1 Subjects

Studies were performed in 28 unselected critically ill patients (55.3±3.3 yr; 17M; APACHE II: 22.4 ± 1.2), who were admitted to the intensive care unit at the Royal Adelaide Hospital. Patients were sedated, mechanically ventilated, able to receive enteral nutrition and shared the common exclusion criteria outlined in Chapter 6. No patient received parenteral nutrition.

9.4.2.2 Study Protocol

Patients were enrolled within the first 10 hours after admission to the ICU and were randomized to receive either "*early feeding*" within 24 hours of admission or "*delayed feeding*" on day 4 of admission after gastric emptying assessment. Patients who were randomized to the "delayed feeding" group did not receive any other form of nutritional support including parenteral nutrition. A naso-gastric (NG) tube was inserted on admission in all patients and correct position of the tube was confirmed by X-ray. In the early feeding group, enteral nutrition was delivered to the patients according to the Unit feeding protocol, described in Chapter 6. If an aspirate > 250 mL occurred, the feeding rate was reduced to half or to the minimum rate of 20 mL/h. Prokinetic therapy was, however, not administered before or during the gastric scintigraphy. For patients in the 'late' feeding group, the NG tube was placed on free-drainage. For patients who received early feeds, the amount of calorie administered as well as the administered: prescribed caloric ratio over the first 4 days prior to the assessment of gastric emptying was collected.

In patients receiving enteral nutrition, feeding was ceased 6 hours prior to the study. The stomach was emptied by aspiration via the NG tube and the volume of aspirate obtained was recorded. Gastric emptying of a 100 mL of Ensure®, labelled with 20MBq ^{99m}Tc-sulphur colloid, was measured by gastric scintigraphy over 240 minutes (Chapter 6). Arterial blood samples (5mL) for the measurement of plasma CCK and PYY concentrations were collected into chilled EDTA tubes, immediately before and at 60 minute and 120 minute after the delivery of the intra-gastric meal (Chapter 6). Blood samples for the measurement of blood glucose concentrations were also collected at baseline, every 15 minutes for the first hour and

every 30 minutes for the subsequent 3 hours. On completion of the study, NG feeding was re-commenced as clinically indicated.

All relevant details of the patient's ICU admission were recorded, including demographics, admission diagnosis, type and level of sedation, inotropic support, days in ICU prior to study, APACHE II score on admission and on study day, and prior history of enteral feeding. The depth of sedation during and for 8 hours prior to the study was assessed by SAS score (Riker, *et al.* 1999). SOFA scores (Vincent, *et al.* 1998) on admission and on the study day were assessed and recorded. Data regarding the patient's secondary outcomes were also collected prospectively. These included: duration of mechanical ventilation, occurrence of ventilated associated pneumonia, length of ICU and hospital stay, and ICU and hospital mortality. Ventilator-associated pneumonia was defined as the presence of a new or progressive infiltrate along with at least two of the following signs and symptoms: a) purulent respiratory secretions; b) fever (body temperature >38°C) or hypothermia (body temperature <35°C); and c) leukocytosis (white blood cell count $\geq$10,000/mm^3) or leucopoenia (total white blood cell count <4500/mm^3 or >15% immature neutrophils (bands) regardless of total peripheral white blood cell count) (Luna, *et al.* 1997).

9.3.2.3 Data analysis

The scintigraphic measurements were analysed as outlined in Chapter 6, with correction for radionuclide decay and γ-ray attenuation (Collins, *et al.* 1983; Collins, *et al.* 1986). As the emptying did not reach 50% at 240 minute in approximately one third of patients, the standard

gastric $t_{1/2}$ could not be determined in all patients and is not reported. Delayed gastric emptying was defined as > 10% meal retention at 240 minute (Chapter 6).

Plasma CCK and PYY concentrations were measured using the radioimmunoassay techniques described in Chapter 6. Blood glucose concentrations were also measured using a portable glucometer (Precision Plus, Abbott Laboratories, Bedford, USA).

9.4.2.4 Statistical Analysis

Differences in the demographic characteristics, APACHE II score, SAS score, SOFA score, baseline blood glucose, CCK and PYY concentrations between the two groups of critically ill patients were compared using Student's unpaired t-test. The differences in the proportion of patients with delayed gastric emptying, use of inotropes or morphine, and the secondary outcomes between the 2 groups were compared using a Chi-square test, with Yate's correction where appropriate. A two-way repeated measures analysis of variance (ANOVA) was used to evaluate the differences in: (i) the gastric retention of meal; and (ii) CCK and PYY responses to gastric nutrients between patients received early versus delayed feeds. The integrated changes in plasma CCK and PYY concentrations over the 120 minutes after meal ingestion were expressed as area under the curve ($AUC_{0\text{-}120min}$) and the differences between the groups were compared by Student's unpaired t-test. The relationships between the % retention of meal and (i) the total number of calories received prior to the gastric emptying assessment and, (ii) plasma CCK and PYY concentrations during fasting and after feeds were assessed using Pearson's simple linear correlation.

9.4.3 RESULTS

After randomization, 14 patients (54.9 ± 3.3 yr; 8M) received enteral feeding within 24 hours of admission. From ICU admission to the assessment of gastric emptying, the "early feeding" patients were fed for 60.4 ± 2.4 hours and received a mean total calorie load of 2894 ± 198 kcal per patient, with an administered/prescribed caloric ratio of 72 ± 4%. All patients in the early feeding group had feeds intermittently interrupted due to diagnostic imaging, therapeutic interventions or nursing care activities (bed baths and dressing changes), all of which required fasting. The other 14 patients (56.3 ± 3.4 yr; 10M) did not receive any form of nutrition prior to the measurement of gastric emptying on day 4. There were no differences in either age, gender, BMI, APACHE score, admission diagnosis, types of sedation, the use of inotrope, SAS and SOFA scores between the 2 groups (Table 9.4.1).

9.4.3.1 Gastric emptying

Gastric emptying was delayed in 18/28 (64%) of patients. In 32% (9/28) of patients, more than 50% of meal remained in the stomach at 240 minute after meal ingestion. The proportion of patients with delayed gastric emptying was similar between the groups ("early feeding" = 9/14 vs. "delayed feeding" = 9/14). Overall, there were no differences in the percentage of meal retained in the whole (P=0.93; Figure 9.4.1A), proximal (P=0.53; Figure 9.4.1B) or distal stomach (P=0.54; Figure 9.4.1C) between patients who received delayed or early feeding. The percentage of meal retained in the stomach did not correlate with the total number of calories received prior to the gastric emptying assessment at any time points (at 0 minute: r=0.22, P=0.19; at 60 minute: r=0.22, P=0.13; at 120 minute: r=0.15, P=0.22; at 240 minute: r=0.21, P=0.22).

Table 9.4.1 Demographic data and characteristics of critically ill patients who received early and delayed enteral feeding.

	Early feeding (n=14)	**Delay feeding (n=14)**	**P-value**
Age (yr)	54.9 ± 3.3	56.3 ± 3.4	0.78
Gender (M:F)	8:6	10:4	0.69
Body mass index (kg/m^2)	28.3 ± 1.7	27.4 ± 1.9	0.70
APACHE II score			
Admission	24.0 ± 1.7	22.9 ± 1.7	0.46
Study day	22.5 ± 1.7	21.2 ± 1.7	0.48
DIAGNOSIS [a] n (%)			
Head injury	6 (42%)	7 (50%)	0.99
Sepsis	6 (42%)	6 (42%)	0.99
Respiratory failure	5 (36%)	4 (29%)	0.70
Trauma	4 (29%)	6 (42%)	0.45
Dissecting aortic aneurysm	1 (7%)	2 (14%)	0.38
Burns	1 (7%)	0 (0%)	0.32
Baseline blood glucose level (mmol/L)	7.3 ± 0.2	7.8 ± 0.2	0.86
Sedations			
Opioid ± Benzodiazepine (n (%))	8 (58%)	10 (71%)	0.69
Propofol (n (%))	6 (42%)	4 (29%)	0.69
SAS score on study day	2.0 ± 0.2	1.9 ± 0.2	0.95
Inotropes (n (%))	6 (42%)	7 (50%)	0.99
SOFA score on study day	5.3 ± 0.9	4.8 ± 0.8	0.72
Number of calories received prior to gastric emptying assessment (kcal)	2894 ± 198	0	NA
Administered: prescribed calorie ratio (%)	72 ± 4%	0	NA

[a] More than one diagnosis possible in any patient. SAS score –Sedation-Agitation Scale (SAS) score. SOFA score - Sequential Organ Failure Assessment score.

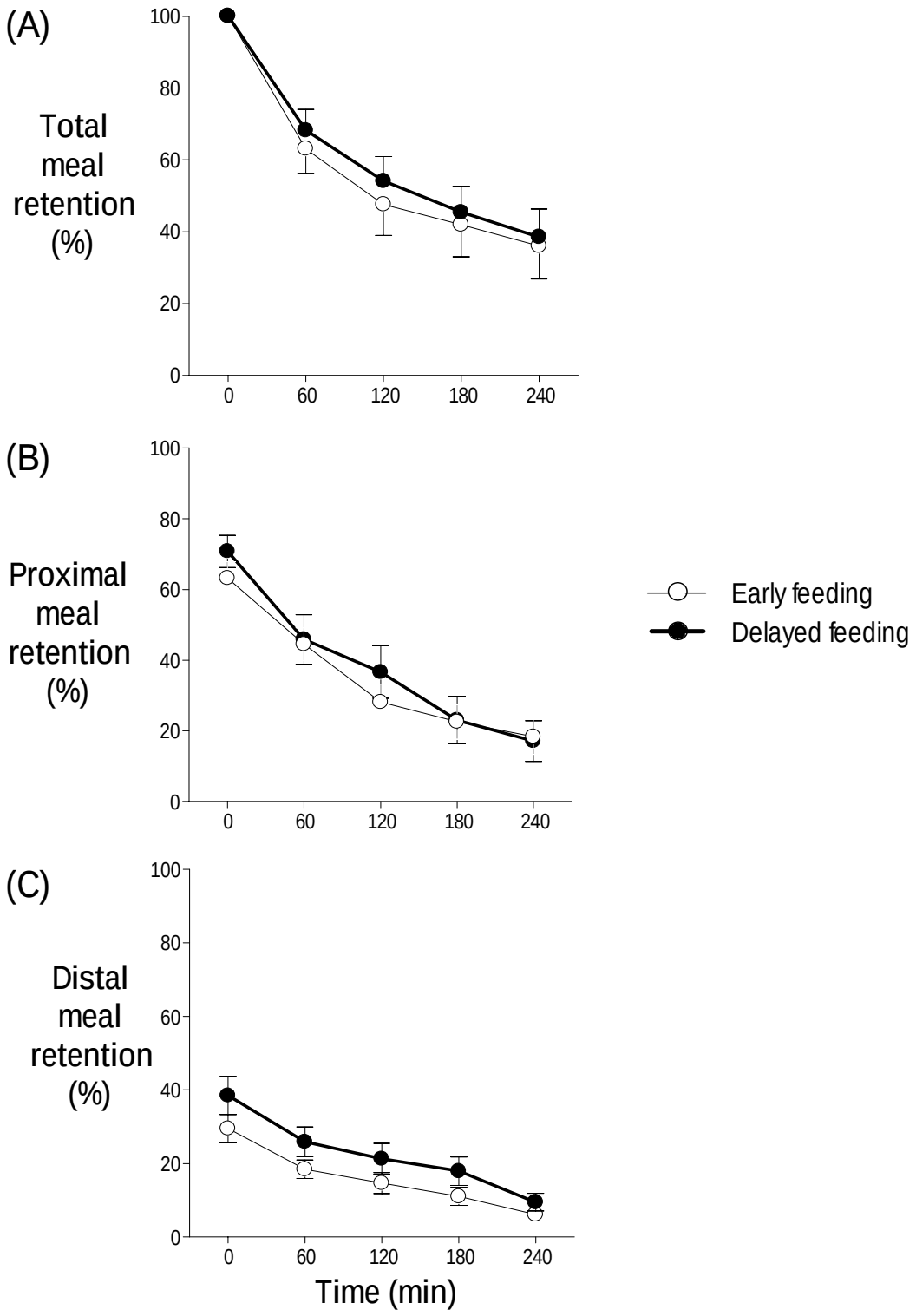


Figure 9.3.1 Total (A), proximal (B) and distal (C) gastric retention of meal in critically ill patients who received early (○) and delayed (●) enteral feeding.

9.4.3.2 Plasma CCK and PYY concentrations

Both plasma CCK and PYY concentrations increased after the gastric meal in both the early feeding and delayed feeding groups (Figure 9.4.2). However, there were no differences in fasting or post-prandial plasma CCK and PYY concentrations between patients in either group (Figure 9.4.2). Between t = 0 - 120 minute, the integrative changes in plasma CCK ($AUC_{0\text{-}120min}$: 190 ± 47 pmol/L.min vs. 141 ± 44 pmol/L.min, respectively; P=0.45) and PYY ($AUC_{0\text{-}120min}$: 360 ± 126 pmol/L.min vs. 266 ± 99 pmol/L.min, respectively; P=0.53) were also similar between patients who received delayed or early enteral feeding.

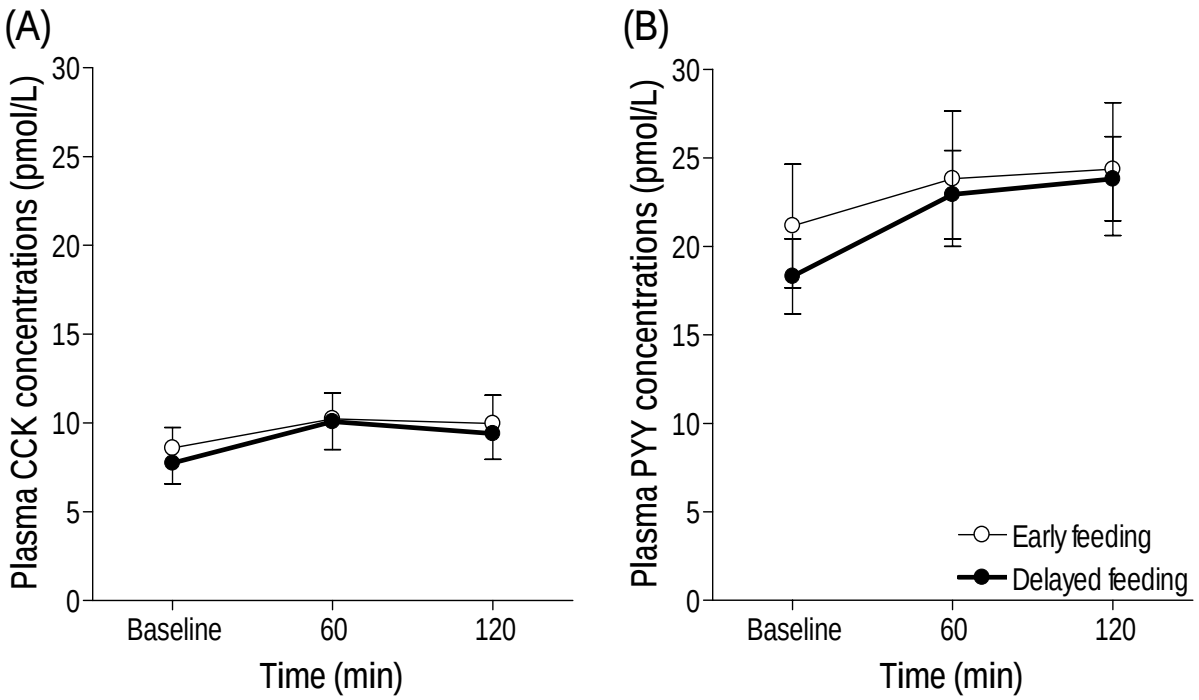


Figure 9.4.2 Plasma concentrations of CCK (A) and PYY (B) during fasting and post-prandially in critically ill patients who received early (○) and delayed (●) enteral feeding.

9.4.3.3 Relationship between gastric emptying and entero-gastric hormones

Both baseline and post-prandial plasma CCK and PYY concentrations were higher in patients with delayed GE than those with normal GE (Figure 9.4.3). There was a trend for a positive correlation between fasting plasma CCK concentrations and meal retention at 60 minute (r=0.35; P=0.07), 120 minute (r=0.33; P=0.09), 180 minute (r=0.31; P=0.10) and 240 minute (r=0.34; P=0.07). Similarly, there was a positive correlation between fasting plasma PYY concentrations and meal retention at 60 minute (r=0.43; P=0.02) and 120 minute (r=0.42; P=0.02). There was a trend for an inverse relationship between the integrated changes in plasma CCK, but not PYY, concentrations and meal retention at 180 minute (P=0.13) and 240 minute (P=0.12). Overall, there was no difference between the integrated changes in plasma CCK and PYY levels in patients with delayed and normal GE (CCK: AUC $_{0\text{-}120\ min}$: 158 ± 42 pmol/L.min vs. 179 ± 48 pmol/L.min, P=0.76; PYY: AUC $_{0\text{-}120\ min}$: 265 ± 100 pmol/L.min vs. 344 ± 71 pmol/L.min, P=0.60).

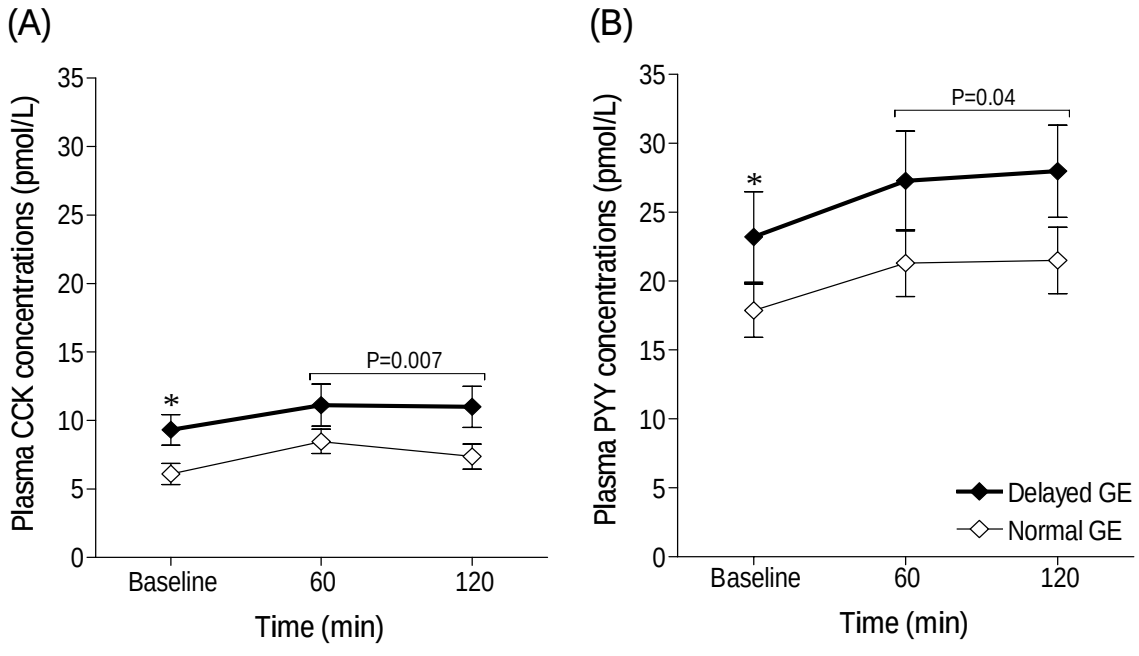


Figure 9.4.3 Plasma concentrations of CCK (A) and PYY (B) during fasting and after feed in critically ill patients with normal (◊) and delayed (♦) gastric emptying (GE). * P<0.05, vs. patients with normal GE.

9.4.3.4 Secondary outcomes

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

9.4.3.5 Blood glucose concentrations

The mean fasting blood glucose concentrations was 6.8 ± 0.3 mmol/L. After feeds, there was a small, but significant, increase in blood glucose in all patients, with a peak of 8.2 ± 0.4 mmol/L at 60 minute. There were, however, no differences in either fasting (6.9 ± 0.3 mmol/L vs. 6.8 ± 0.5 mmol/L, P=0.84) or nutrient-stimulated (P=0.36) blood glucose concentrations between patients who received delayed compared to early feeding.

9.4.4 DISCUSSION

This is the first randomised controlled study to examine the impact of delaying enteral feeding on gastric emptying and the entero-gastric hormonal responses. In critically ill patients who were well matched for age, gender, and other factors that are known to influence gastric emptying, delaying enteral feeds for 4 days had no effect on either gastric emptying or plasma

concentrations of CCK and PYY. Delaying enteral feeding was, however, associated with prolonged mechanical ventilation and length of study in ICU but no difference in mortality. These observations indicate that whilst the timing of initiation of enteral feeding is not be a significant determinant of gastric emptying during critical illness, delaying enteral feeding adversely influences short-term outcomes in the critically ill, and supports the current recommendation that nutrition support should be commenced as early as possible.

Despite the relatively small sample size, the current study has a number of strengths. Firstly, the randomization of patients in the timing of enteral feeding is likely to minimize selection bias. Secondly, gastric emptying was assessed by the gold standard technique, gastric scintigraphy (Camilleri, *et al.* 1998). Thirdly, the '4-day' criterion in the delayed feeding group was clinical relevant as this is the mean duration for which enteral nutrition was delayed in many studies reported in the literature (Adam and Batson 1997; McClave, *et al.* 1999; Montejo 1999; Heyland, *et al.* 2003).

In contrast to healthy subjects (Corvilain, *et al.* 1995), short-term nutritional deprivation of 4 days did not slow gastric emptying or disturb entero-gastric hormonal feedback activity in critically ill patients. There are a number of possible reasons that may account for this discrepancy. Although the similarity in gastric emptying between the "early" and "delayed" feeding groups could represent a type 2 error due to the small sample size, the differences in secondary outcomes between the groups argue against this possibility. As recent data suggest that gastric emptying in critically ill patients is related to the plasma concentrations of CCK and PYY (Chapter 8), the lack of difference in the entero-gastric hormonal responses between the early and delayed feeding groups are in accordance with the similarities in gastric

emptying between the groups. Furthermore, the high prevalence of delayed gastric emptying (64%) in these patients with no apparent difference between the groups indicates that even with a very large sample size, there is unlikely to be any effect. Thus, the lack of impact of timing of feeding on gastric emptying suggests that other factors such as sedation, inotropic therapy, admission diagnosis and illness severity are more likely to be important in mediating gastric motor dysfunction in critical illness (Heyland, *et al.* 1996; Montejo 1999; Mentec, *et al.* 2001), and overriding any effect of acute fasting on gastric emptying.

As only 72 ± 4% of prescribed nutrients were delivered to the patients, it is possible that the patients in the "early feeding" group received insufficient amount of nutrients to prevent the inhibitory effect of nutritional deprivation. Whilst this amount of delivered calories appears inadequate, it does reflect the true performance of nutritional support in the clinical setting with the reasons for the interruption of feed consistent with those described by McClave et al (1999). The "threshold" of nutrient deprivation necessary to impair gastric motor function is currently unknown. It is also unclear whether the 4-day duration of deprivation in the current study was sufficient to alter gastric emptying. Re-feeding data from patients with anorexia nervosa suggest that the adaptive changes underlying fasting-induced slow gastric emptying may take as long as 2 weeks to develop or revert (Rigaud, *et al.* 1988). Although determination of the "threshold" and "duration" of nutritional deprivation required to induce gastric dysmotility is of interest, it is of limited relevance to nutritional support during critical illness because of the adverse effects of delayed feeding on the duration of ventilation and ICU stay in these patients.

Fasting and post-prandial plasma CCK and PYY concentrations were evaluated in the current study because of recent data suggesting that delayed gastric emptying in critically ill patients

may be related to an enhanced entero-gastric inhibition by duodenal nutrients (Chapman, *et al.* 2005) and that elevated plasma CCK and PYY concentrations in these patients may have a role in this phenomenon (Chapter 8). In the current study, the higher fasting and post-prandial plasma CCK and PYY concentrations in patients with delayed gastric emptying are in agreement with this concept. In addition, in keeping with a recent report (Chapter 8), there was a positive correlation between both fasting plasma CCK and PYY concentrations and meal retention. Thus, given the relationship between gastric emptying and entero-gastric hormones, it is probably that the similarity in entero-gastric hormonal responses between the groups reflects comparable rates of gastric emptying. However, it is not possible to formally test this hypothesis without specific neuro-humoral antagonists such as loxiglumide (Schwizer, *et al.* 1997).

In the current study, although delaying enteral feeding had no effect on gastric emptying or entero-gastric hormonal response, it was associated with prolongation of both mechanical ventilation and length of stay in the ICU and the hospital. The reasons underlying the prolonged mechanical ventilation are unclear, but could theoretically relate to a higher occurrence of ventilation-associated pneumonia in the patients in whom enteral feeding was delayed. In animals, delaying enteral nutrition is associated with a disruption of intestinal mucosal integrity. It has been proposed that this predisposes the patients to bacterial translocation and subsequent infectious complications (DeWitt and Kudsk 1999; Alpers 2002). Whilst the number of patients who developed ventilation-associated pneumonia was increased in the “delayed feeding” group, the difference did not reach statistical significance possibly due to the small sample size. Nevertheless, these observations are consistent with earlier data that suggest that delaying enteral feeding in critically ill patients is associated with a higher rate of infectious complications (Heyland, *et al.* 2003). The lack of difference in mortality in the current study is also likely to relate to insufficient power in light of the 20%

increase in mortality reported in a previous large study (Artinian, *et al.* 2006). Overall, the findings in the current study support the current recommendation that in patients without contraindications to enteral nutrition, this should be commenced within 24-48 hours of admission (Heyland, *et al.* 2003).

In conclusion, delayed commencement of enteral nutrition for 4 days has little impact on either the rate of gastric emptying or entero-gastric hormonal feedback in patients with critical illness. However, the adverse impacts on the duration of mechanical ventilation, ICU and hospital stay support the current recommendation that enteral nutrition should be commenced as early as possible in these patients, unless specific contraindications are present.

9.5 THE RELATIONSHIP BETWEEN BLOOD GLUCOSE CONTROL AND FEED INTOLERANCE

9.5.1 INTRODUCTION

Over the last 8 years, the importance of insulin therapy to control hyperglycemia in the critically ill has been recognized as this reduces both in-hospital mortality and morbidity (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003; Krinsley 2004). Whilst the impact of tighter blood glucose control on gastric emptying or the success of feeding have not been formally evaluated, the incidence of delayed gastric emptying and feed intolerance in these patients has not significantly changed since the introduction of standardized insulin therapy, and these complications still develop in over 50% of critically ill patients (Chapter 8.3; Chapter 9.2; and Chapter 10.2). These findings suggest either that (i) there is no relationship between blood glucose contractions and gastric emptying or feed intolerance during critical illness; or (ii) the degree of blood glucose control achieved with current insulin regimens is insufficient to prevent hyperglycemia-induced slow gastric emptying. The aims of the current study were, therefore, to examine the (i) presence and (ii) nature of the relationship between blood glucose concentrations and feed intolerance in critical illness during standard insulin therapy.

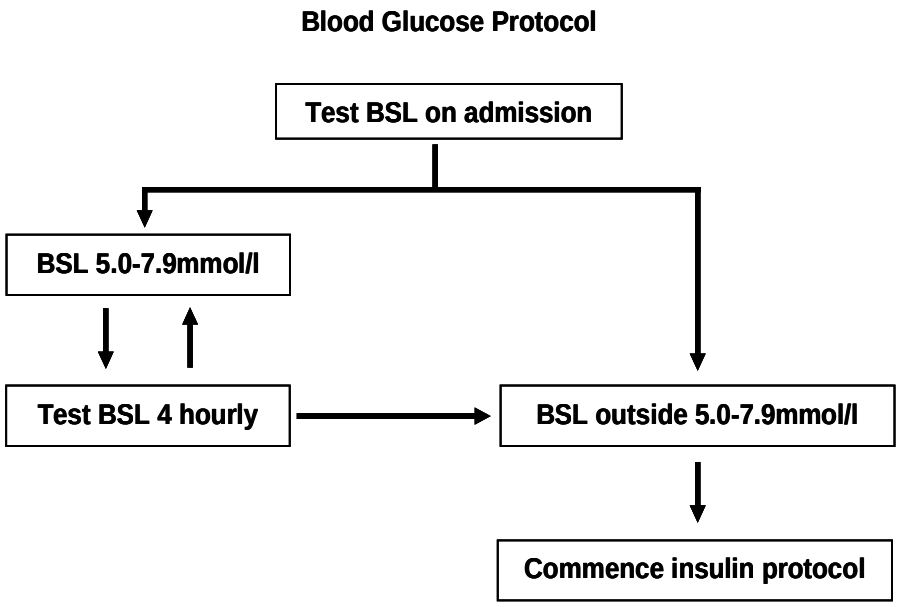
9.5.2 METHODS

9.5.2.1 Subjects

Data from 95 consecutive feed-intolerant critically ill patients, with no prior history of type 1 or II diabetes mellitus (DM) were compared with 50 feed-tolerant patients, who were admitted to the intensive care unit at the Royal Adelaide Hospital, between June 2004 and June 2005. The groups were matched for age, gender, BMI and admission APACHE II score. All patients were mechanically ventilated and received nasogastric feeding for at least 3 days according to the feeding protocol outlined in Chapter 6. As feed intolerance may take up to 3 days to develop (Heyland, *et al.* 1995; Mentec, *et al.* 2001), patients who received enteral feeds for less than 3 days were excluded from the current study in order to minimize the risk of wrongly categorising patients as 'feed tolerant'. Patients who were ineligible for the study were excluded using the common criteria outlined in Chapter 6.

9.5.2.2 Insulin infusion protocol

In all patients, hyperglycemia was managed according to a standardized insulin infusion protocol that aimed to maintain the blood glucose concentration between 5.0 and 7.9 mmol/L (Chapter 6). Two- to 4-hourly blood glucose concentrations were measured throughout the admission. The insulin infusion protocol (Figure 9.5.1) was commenced if the concentration was above the target range at any time. Once insulin therapy commenced, blood glucose concentrations were measured 1-2 hourly for insulin titration.



Insulin Protocol

BSL (mmol/l)	Initial IV bolus (units)	Starting infusion (units/hr)	Subsequent infusion (units/hr)	Repeat BSL (hrs)
>15.0	2	2	Increase by 1	1
10.0-14.9	1	1	Increase by 1	1
8.0-9.9	0	0.5	If BSL dropping; continue current rate. If static or rising; increase by 0.5	1
5.0-7.9	0	0	Continue current rate *If BSL drops for 2 consecutive hrs decrease rate by 0.5.*	1 (2hrly if BSL stable >6 hrs)
3.5-4.9	0	0	Cease	1 (4hrly if off insulin >6hrs)
<3.5	Call doctor	0	Cease	1

Figure 9.5.1 Outline of blood glucose monitoring protocol and the associated insulin protocol at the Intensive Care Unit of the Royal Adelaide Hospital.

9.5.2.2 Data collection and analysis.

In all patients, the relationship between blood glucose concentrations and feed intolerance was assessed by documenting 2-hourly blood glucose concentrations and insulin requirements for the 24 hours immediately prior to and the 96 hours following commencement of feeding. In addition, for feed-intolerant patients, 2-hourly blood glucose concentrations and insulin

requirements were also determined for the 24 hours immediately prior to the development of intolerance. The time from admission until feed intolerance occurred and the rate of naso-gastric feed delivery were also recorded. Blood glucose concentrations for each 24 hour period were expressed as peak, mean and trough levels. For each patient, the highest and lowest blood glucose concentrations recorded within the 24-h period were defined as the "peak" and "trough" blood glucose levels, respectively.

All relevant details related to the patient's ICU admission, blood glucose concentrations and insulin requirement were also obtained by careful examination of patient's case-notes and intensive care charts. Patient demographics, admission APACHE II score, admission diagnosis, medication, past medical history, mode of ventilation, and length of ICU stay were also recorded.

9.5.2.3 Statistical Analysis

Differences in the characteristics of patients between the groups were compared by chi-square test (with Yates' correction where appropriate) for categorical data and by Student's t-test for continuous data. As the time taken to develop feed intolerance after the commencement of enteral feeding was not normally distributed, the data was expressed as median and inter-quartile rang (IQR). Variation in blood glucose concentrations was defined as the mean change in blood glucose concentrations between the 2-hourly measurements within the 24 hours duration. Repeated measures analysis of variance (ANOVA) was used to evaluate the differences in blood glucose concentrations and insulin requirement between the feed-intolerant and feed-tolerant patients. After controlling for factors known to alter gastric motor function including APACHE II score, use of inotropes and opiate sedation

(morphine/midazolam), the difference in variation of blood glucose concentration between the groups was assessed over time using a mixed model ANOVA. The relationship between admission BSL and length of time fed before developing intolerance was assessed using Pearson's linear regression.

9.5.3 RESULTS

The patient characteristics in each cohort are summarised in Table 9.5.1. There were no differences in the demographics, the admission APACHE II scores, the admission diagnosis, the use of opioid ± benzodiazepine or inotropic therapy or the type of mechanical ventilation between the feed-intolerant and feed-tolerant groups.

In both groups, enteral feeds commenced 1.9 ± 0.6 days after patients were admitted to the ICU. The median time taken to develop feed intolerance after the commencement of enteral feeding was 23 (IQR: 10-62) hours. Compared to feed tolerant patients, feed-intolerant patients received less feed at a lower feeding rate (49 ± 2 mL/hr vs. 61 ± 2 mL/hr, $P<0.01$) and stayed longer in ICU (19.7 ± 1.7 days vs. 11.5 ± 0.8 days, $P<0.01$). Ten feed-intolerant patients eventually required insertion of post-pyloric feeding tube for ongoing enteral nutritional support.

9.5.3.1 Relationship between blood glucose concentrations and feed intolerance

There was a trend for feed-intolerant patients to have a higher admission blood glucose concentrations than feed-tolerant patients (10.3 ± 1.6 mmol/L vs. 8.3 ± 0.4 mmol/L; $P=0.08$; Figure 9.5.2). However, the proportion of patients with a fasting blood glucose concentration > 11.1 mmol/L on admission, a diagnostic criterion for diabetes mellitus (Kuzuya, *et al.*

2002), was similar between the groups (feed-intolerant: 15/95 (16%) vs. feed-tolerant: 10/50 (20%); P=0.41).

Table 9.5.1 Demographics and characteristics of feed-tolerant and feed-intolerant critically ill patients.

	Feed Intolerant (n=95)	**Feed Tolerant (n=50)**	P-value
Age (yrs)	53.5 ± 1.8	55.8 ± 2.3	0.76
Gender (M:F)	61:34	29:21	0.48
Body mass index (kg/m^2)	26.7 ± 0.4	27.0 ± 0.6	0.81
Admission APACHE II score	25.0 ± 0.6	24.5 ± 1.0	0.79
Admission diagnosis † (n (%))			
Sepsis	53 (56%)	25 (50%)	0.60
Multi-trauma	51 (54%)	23 (46%)	0.39
Multi-Organ Failure	18 (19%)	6 (12%)	0.35
Head injury	16 (17%)	10 (20%)	0.65
Burns	9 (10%)	5 (10%)	0.99
Cardiac	4 (4%)	0 (0%)	0.30
Non-GI post-operative respiratory failure	11 (12%)	2 (4%)	0.22
Medications (n (%))			
Opioid ± Benzodiazepine	70 (73%)	31 (62%)	0.19
Inotropes	47 (49%)	23 (46%)	0.73
Mechanical ventilation			
SIMV: pressure support	60 (63%)	35 (70%)	0.46

† Some patients had more than one diagnosis

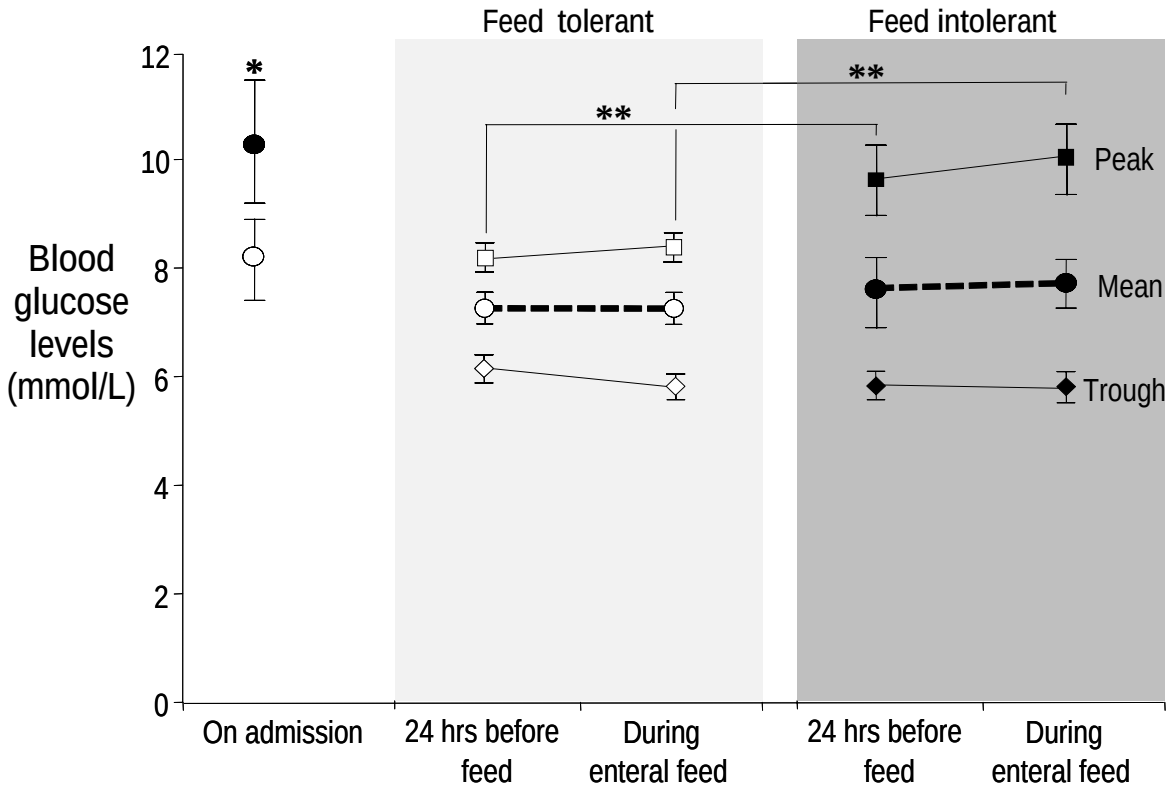


Figure 9.5.2 Comparison of blood glucose concentrations between feed-tolerant (white) and feed-intolerant (black) critically ill patients on admission, before and during enteral feeding. The peak (□), mean (○) and trough (◊) blood glucose levels before and during enteral feeding were compared between the groups. * P=0.08, vs. feed-tolerant; ** P<0.05, vs. feed-tolerant before and during enteral feeding.

In all patients, there was a significant reduction in the mean blood glucose concentrations after the initiation of insulin therapy (P<0.01). In both groups, neither *mean* nor *trough* blood glucose concentrations increased after enteral feeds; and the levels were similar between the groups in the 24 hours prior to feeding and during the first 4 days of feeding (Figure 9.5.2). However, *peak* blood glucose concentrations in the 24 hours prior to feeding and during enteral feeding in feed-intolerant patients were significantly higher than those of feed-tolerant patients.

Enteral feeding increased the proportion of patients with blood glucose concentrations > 10 mmol/L in the feed-intolerant group but not in the feed-tolerant group (Figure 9.5.3). Compared to feed-tolerant patients, a greater proportion of feed-intolerant patients had blood glucose levels > 10 mmol/L over the 4 days of enteral feeding (P<0.05). Furthermore, the duration of blood glucose concentrations > 10 mmol/L was greater in feed-intolerant patients than those of feed-tolerant patients (5.0 ± 0.3 hours vs. 4.0 ± 0.3 hours; P=0.02).

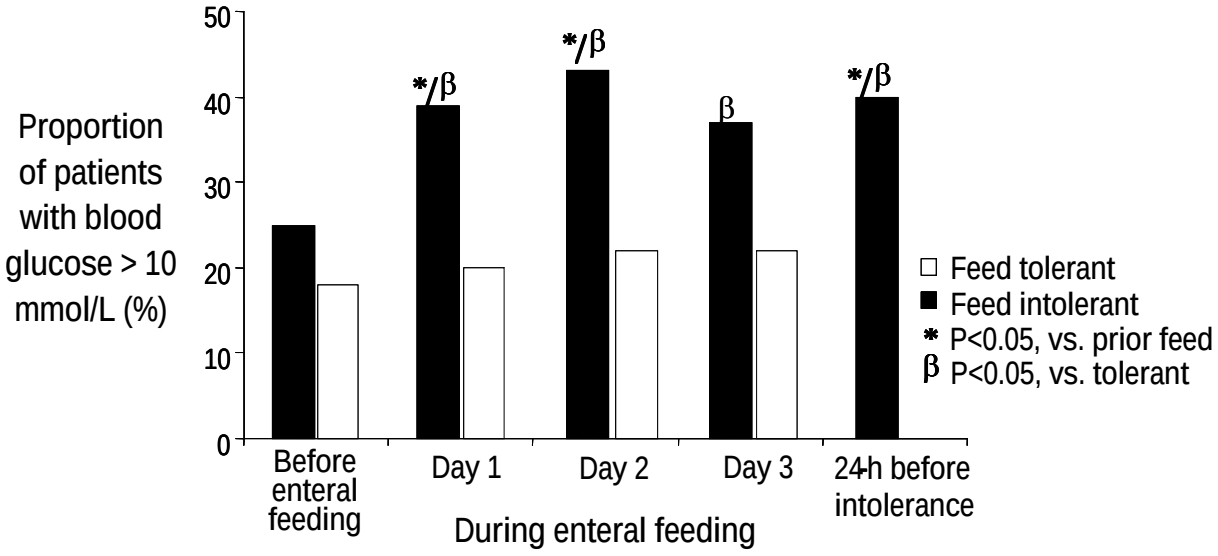


Figure 9.5.3 Percentage of patients with episodes in which blood glucose concentration > 10 mmol/L before and during enteral feeding, in feed-tolerant and feed-intolerant patients.

In feed intolerant patients, even after controlling for APACHE II score and the use of inotropes, and opiate sedation (morphine/midazolam), the variation in blood glucose concentrations both 24 hours before, and during, enteral feeding was significantly greater than in patients who tolerated gastric feed (P=0.044; Figure 4), and was highest in the 24 hours leading up to the development of feed intolerance (4.0 ± 0.2 mmol/l; P=0.025). Over the first 4 days of enteral feeding, the variation significantly diminished in the feed-tolerant group (P<0.0001) but increased in the feed-intolerant group (P<0.0001).

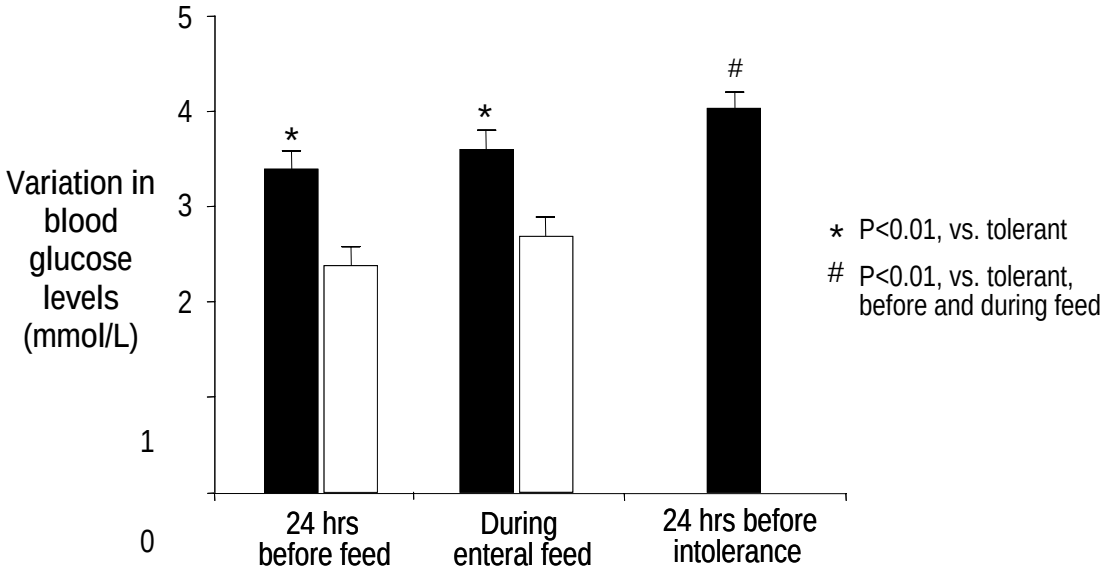


Figure 9.5.4 Comparison of hourly variation in BSL between feed tolerant (□) and feed-intolerant (■) patients, before and during enteral feeding, and immediately before intolerance.

There was however a negative correlation between blood glucose concentrations on admission and the time taken to develop feed intolerance after feeding started (r = -0.40, P=0.001; Figure 9.5.5), but no relationship between admission blood glucose level and hourly variations in blood glucose concentration 24 hours before feed (P=0.77).

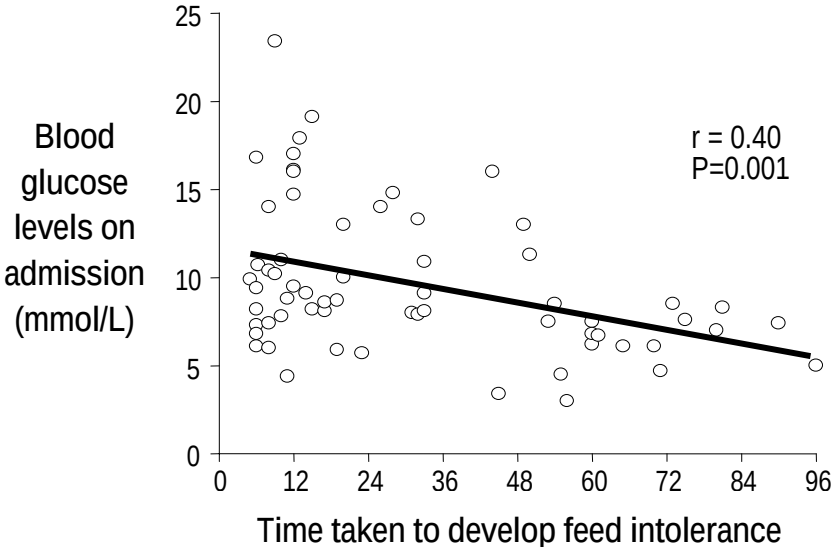


Figure 9.5.5 Relationship between admission BSL and the length of time taken to develop feed intolerance in critically ill patients, in the first 96 hours of admission.

9.5.3.2 Relationship between administered insulin and feed intolerance

Before the start of enteral feeding, there was a trend for more feed-tolerant than feed-intolerant patients to receive insulin therapy (46% (23/50) vs. 32% (30/95), respectively; P=0.09). Once enteral feeding was started, all patients received insulin therapy for blood glucose control, and insulin dose increased significantly. However, the total daily administered insulin before and during enteral feeding was similar between the groups (Figure 9.5.6).

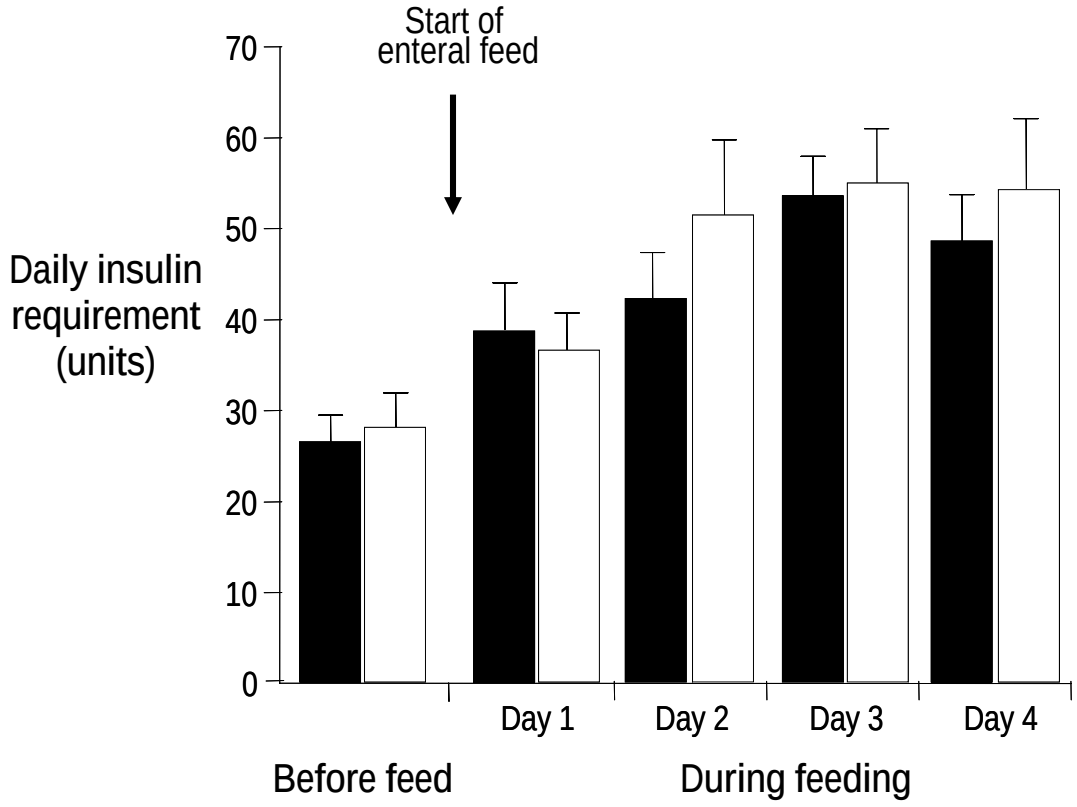


Figure 9.5.6 Comparison of mean daily insulin requirement between feed tolerant (□) and feed-intolerant (■) patients, before and during the first 4 days of enteral feeding.

9.5.4 DISCUSSION

This study demonstrated that critically ill patients who are intolerant of gastric feeding: (i) have a trend for higher blood glucose levels on admission, (ii) have higher peak blood glucose concentrations before and during feeding, (iii) exhibit greater variation in blood glucose concentration, especially within the 24 hours leading up to feed intolerance, and (iv) are more likely to have episodes of blood glucose concentration ≥ 10 mmol/L for a longer duration (i.e. 'episodic hyperglycemia') when compared to feed tolerant patients, despite administration of similar levels of insulin. These findings were demonstrated after controlling for factors known to alter gastric motor function in critical illness, such as age, illness severity, admission diagnosis and medications. This study supports the presence of a relationship between blood glucose concentrations and feed intolerance during critical illness, suggesting that more meticulous blood glucose control with an intensive insulin protocol may potentially be beneficial for feeding in these patients.

As the groups were well matched for factors that are known to alter gastric motor function in critical illness, the association between feed intolerance and the higher prevalence of episodic hyperglycemia may have clinical significance. Hyperglycaemic episodes were not only more common but more prolonged in feed-intolerant patients. The mean duration of hyperglycemia in patients with feed intolerance was approximately 5 hours, and in both healthy subjects and diabetic patients, transient hyperglycemia of similar magnitude and duration has been associated with disturbed gastric motility and delayed gastric emptying (Fraser, *et al.* 1990; Oster-Jorgensen, *et al.* 1990; Hebbard, *et al.* 1996; Samsom, *et al.* 1997). Thus, these data provide a potential link between 'sub-optimal' blood glucose control and feed intolerance and

suggest that a more intensive insulin regimen may be required in order to minimize the variation in blood glucose concentrations in these patients.

The reasons underlying the episodic hyperglycemia remain unclear. Up to a third of patients admitted to ICU have undiagnosed DM (Umpierrez, *et al.* 2002), a well recognised risk factor for disturbed gastric motility and delayed gastric emptying (Fraser, *et al.* 1990; Oster-Jorgensen, *et al.* 1990; Hebbard, *et al.* 1996; Samsom, *et al.* 1997). Thus, it is possible that there was a higher prevalence of undiagnosed DM in feed intolerant group. However, only 16-20% of patients in the current cohort had undiagnosed DM, as defined by fasting admission blood glucose levels > 11.1 mmol/L (Kuzuya, *et al.* 2002), and the proportion of patients with undiagnosed DM was similar between the groups. Furthermore, gastric emptying in critically ill patients with well controlled type 2 DM appears to be relatively normal (Chapter 10.2). Together, these findings argue against undiagnosed DM as the major cause and suggest that episodic hyperglycemia in feed-intolerant patients may relate to other factors.

The fact that feed intolerant patients required a similar amount of insulin for lesser amount of enteral feeds delivered compared to feed tolerant patients together with the greater variation in blood glucose supports the hypothesis that such patients may have greater susceptibility to stress-induced glucose-intolerance or insulin resistance during critical illness. Both hyperglycemia and gastric motor function in critical illness are related to the stress response (O'Neill, *et al.* 1991; Boord, *et al.* 2001; McCowan, *et al.* 2001) and the severity of acute illness (Mentec, *et al.* 2001). The greater degree of episodic hyperglycemia in the feed intolerant patients may thus reflect greater illness severity. Although the APACHE II scores

were similar between the groups, other markers of illness severity such as inflammatory cytokines, which may not be reflected by APACHE II scores and are known to both impair gastric motility in animals (Glatzle, *et al.* 2004) and increase insulin resistance in humans (Yudkin, *et al.* 1999), may be important. It is also possible that increased blood glucose concentrations in feed intolerant patients could be a surrogate for regulatory processes involved in nutrient-induced insulin secretion and other humoral factors such as glucagon-like peptide 1 and amylin, which are known to regulate gastric emptying (Mayer, *et al.* 2002; Meier, *et al.* 2004).

Clinically, the timing and dosage of the insulin protocol used in the current study may have been insufficient to prevent the episodic hyperglycemias. Although the protocol adopted in the current study has been shown to reduce in-hospital mortality (Krinsley 2004), the upper range of the target BSL (7.9mmol/L) is relatively high and the 'test and treat' interval is long. These factors allow a greater chance for the development of undetected episodes of hyperglycemia as well as a longer time to reduce blood glucose concentrations to target levels. The prolonged duration of up to 5 hours of hyperglycemia in the current study is in agreement with this. It is, therefore, conceivable that lower target blood glucose concentrations of 4.4-6.1 mmol/L with 1-hourly 'test and treat' interval (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003), may be more preferable to minimize episodic hyperglycemia and improve gastric motility, in addition to the beneficial effects of insulin on inflammation and immune response (Van den Berghe 2004; Langouche, *et al.* 2005). This protocol, however, has not been widely adopted because of concerns regarding the incidence of hypoglycaemia of between 5% to 25% (Van den Berghe, *et al.* 2001; Van den Berghe, *et al.* 2003). A recent

study reported the incidence of hypoglycaemia is only 0.5% (Bland, *et al.* 2005) suggests the earlier data may have overstated this risk.

In conclusion, feed intolerance during critical illness is associated with 'sub-optimal' blood glucose control and is characterized by a greater occurrence of episodic hyperglycaemia with a greater glycemic variation during enteral feeding. These findings suggest that tight blood glucose control in critical illness is not only beneficial in terms of increased survival, but may also potentially improve the success of enteral feeding, although this requires further prospective evaluation.

9.6 SUMMARY AND CONCLUSIONS

The work in the current chapter has substantially consolidated our understanding on the factors that potentially contribute to the pathogenesis of delayed gastric emptying during critical illness. Not only do these results confirm the adverse impact of factors such as admission diagnosis, type of sedation, and blood glucose control on gastric motor function, but it also refutes the current belief that delaying enteral feeding in critically ill patients slows gastric emptying. Overall, there are a number of clinical implications from these findings. The identification of subgroups based on admission diagnosis allows the caring physician to identify patients with burns, head injury, sepsis and multi-system trauma to be at-risk of delayed gastric emptying. These patients should be monitored closely for signs of feed intolerance so that treatment can be instituted early, and therefore, the associated complications can be prevented. In view of the differential impact of the type of sedation on gastric emptying and meal distribution, the choice of sedation in the at-risk patients should be carefully determined. Whilst propofol would be a preferred sedative for at risk patients, other factors such as analgesia need consideration. Furthermore, the prolonged use of high dose propofol (> 4mg/kg/h) should be avoided due to the potential mitochondrial adverse effects, especially in patients with head-injury (Ernest and French 2003; Corbett, *et al.* 2006). It is also important for tight blood glucose control in these patients, preferably with an intensive insulin protocol, to prevent episodic hyperglycemia, which appears to be a potential risk factor for feed intolerance. Although delaying enteral feeding for 4 days has little impact on gastric motor function in these patients, the adverse impact on the duration of ventilation and ICU stay strongly suggest that enteral nutrition should be commenced as early as possible in patients who have no contra-indications to enteral feeding.

CHAPTER 10: IMPACT OF PRE-EXISTING TYPE 2 DIABETES MELLITUS ON PROXIMAL GASTRIC MOTILITY, GASTRIC EMPTYING AND FEED INTOLERANCE DURING CRITICAL ILLNESS

10.1 INTRODUCTION

Gastro-paresis occurs in up to 50% of patients with either type 1 or 2 diabetes mellitus (DM) (Horowitz, *et al.* 1996). In these patients, abnormalities in motor function have been reported in both the proximal and distal stomach, including impaired proximal gastric relaxation in response to meal (Samsom, *et al.* 1995; Samsom, *et al.* 1998), reduced antral motility and antro-duodenal coordination (Fraser, *et al.* 1994; Samsom, *et al.* 1996) and increased pyloric motility (Fraser, *et al.* 1991). The pathogenesis of these abnormalities is unclear but factors such as autonomic neuropathy and hyperglycemia have been suggested to be important (Horowitz, *et al.* 1996; Samsom, *et al.* 1997; Rayner, *et al.* 2001).

Delayed gastric emptying is also common in critically ill patients (Heyland, *et al.* 1995; Heyland, *et al.* 1996; Montejo 1999; Mentec, *et al.* 2001; Ritz, *et al.* 2001), and manifests as intolerance to gastric feeding. Feed intolerance has an adverse impact on patient morbidity and mortality (Mullen, *et al.* 1980; Dempsey, *et al.* 1988; Montejo 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; McClave, *et al.* 2002; Heyland, *et al.* 2003; Metheny, *et al.* 2004), as it is a risk factor for pulmonary aspiration, delay in achieving nutritional goals and the necessity for prokinetic agents, post-pyloric feeding or parenteral nutrition (Heyland 1998; Heyland 2000; Mentec, *et al.* 2001; Heyland, *et al.* 2003). As discussed in Chapter 7, both proximal and distal gastric motility are disturbed in critically ill patients. The pathogenesis of this is unknown but medications used for sedation, neuromuscular paralysis and hemodynamic support, admission diagnosis, hyperglycemia, and mechanical ventilation have all been suggested to play a role (Heyland 1998; Heyland 2000; Mentec, *et al.* 2001; Heyland, *et al.* 2003). Premorbid conditions such as DM have also been suggested to be a risk factor for slow

gastric emptying in critically ill patients (Mutlu, *et al.* 2001). This is clinically relevant as approximately one third of patients admitted to intensive care units have DM (Umpierrez, *et al.* 2002). However, the data on the relationship between pre-existing DM and gastric motor function during critical illness are lacking.

The aims of the studies described in this chapter were, therefore, to evaluate the impact of pre-existing type 2 diabetes mellitus on: (i) proximal gastric motor function, (ii) gastric emptying and (iii) the occurrence of feed intolerance in critically ill patients who received enteral gastric feeding.

10.2 THE IMPACT OF PRE-EXISTING TYPE 2 DIABETES MELLITUS ON PROXIMAL GASTRIC MOTOR ACTIVITY

10.2.1 INTRODUCTION

As the proximal stomach is a major determinant of liquid gastric emptying in humans, the aim of the current study was to examine proximal gastric motor activity during fasting and in response to nutrients in critically ill patients with pre-existing type 2 DM. Given that both DM and critical illness are risk factors for disturbed gastric motility, it was hypothesized that in critically ill patients with pre-existing DM, the proximal gastric motor activity would be abnormal and differs from that of patients without DM. In order to reliably assess he entero-gastric feedback response on the proximal stomach, nutrients were delivered directly into the duodenum in all subjects, at a rate consistent with normal gastric emptying (Chapter 7).

10.2.2 METHODS

10.2.2.1 Subjects

Studies were performed in 25 mechanically ventilated critically ill patients, who were admitted to the intensive care unit at the Royal Adelaide Hospital, between January 2004 and September 2005. All patients were sedated, required enteral nutrition and shared the common exclusion criteria (except for diabetes mellitus) described in Chapter 6. Ten patients had documented type 2 DM with a mean duration of 7.9 ± 1.8 years. Seven of the DM patients had required insulin therapy prior to ICU admission. Formal testing for the presence of autonomic neuropathy was not performed. Data were compared to that obtained from (i) 15

critically ill patients without diabetes mellitus and (ii) 10 healthy volunteers, as were reported in Chapter 7.2. All patients had common exclusion criteria (Chapter 6) and received a standardized insulin infusion protocol for blood glucose control. The demographic characteristics of patients and healthy subjects are summarized in Table 10.2.1.

Table 10.2.1 Demographics and characteristics of the critically ill patients and healthy subjects

	DM ICU patients (n=10)	**Non-DM ICU patients (n=15)**	**Healthy subjects (n=10)**
Age (yrs)	59 ± 3 *	48 ± 5 *	28 ± 3
Gender (M:F)	5 : 5	12 : 3	7 : 3
BMI (kg/m^2)	35 ± 3 **	27 ± 1	25 ± 1
APACHE II score			
On admission	28.6 ± 1.5	23.2 ± 0.8	N/A
On study day	24.7 ± 1.5	21.1 ± 1.3	
Diagnoses	Sepsis (3); Pneumonia (3); Severe asthma (1); MVA (1); SAH (1); Angioedema (1)	Sepsis (3); Pancreatitis (2); Head trauma (2); MVA (3); Cardiac failure (2); Burn (1); Lung abscess (1); Meningitis (1)	N/A

MVA: Motor Vehicle Accident; N/A: not available; SAH- Sub-arachnoid haemorrhage

* $P<0.05$ vs. healthy subjects

** $P<0.05$ vs. healthy subjects and non-DM critically ill patients

10.2.2.2 Protocol

Proximal gastric motility in this study was assessed with a barostat technique (Chapter 6). In both patients and healthy subjects, the study was performed after at least 6 hours fasting and in a 30 degree recumbent position. Propofol alone was used for sedation in all patients; and opioids, benzodiazepines or prokinetic agents were not administered for 24h prior to and during the study. The placement of both the barostat catheter and post-pyloric feeding tube as well as the confirmation of the duodenal position of the feeding tube were identical as that outlined in Chapter 7.2 and Figure 7.2.1.

After determination of MDP, an *isobaric* study was performed continuously over 4 hours, at MDP + 2 mmHg (Azpiroz and Malagelada 1984, 1985). All studies began with a 15 minute baseline recording, during which normal saline (0.9% NaCl) was infused into the duodenum at a rate of 4 mL/min (baseline 1). In random order, each subject then received two 60 minute duodenal infusions of Ensure® at 1 or 2 kcal/min. Ensure® was diluted 1:4 with normal saline (0.9%) for the 1 kcal/min infusion and 1:2 for the 2 kcal/min infusion, and infused at a rate of 4 mL/min. The nutrient infusions were separated by a 2 hour "washout period" consisting of 1.5 hour of no infusion, followed by 30 minutes of intra-duodenal infusion of saline (baseline 2).

Blood samples for the measurement of blood glucose concentration were also collected at baseline and every 20 minutes during nutrient infusion.

10.2.2.3 Data analysis

The method of data analysis on the proximal gastric motility in the current study has been outlined in Chapter 6 and is identical to that described in Chapter 7.2. The time course for the proximal stomach to return to baseline volume after nutrient stimulation was assessed by analysis of the 2 hour "washout period"; and was defined as the time taken for the relaxed fundus to return to pre-stimulation level for > 5 min.

10.2.2.4 Statistical analysis

The differences in demographic characteristics, baseline volumes, MDPs and fundic volume waves between the healthy subjects and critically ill patients were compared using Student's unpaired t-test. As data were non-parametric, the time required for proximal stomach to return to baseline level after nutrient stimulation was expressed as median and inter-quartile range (IQR), and the differences between the groups were compared using Mann-Whitney test. Differences in (i) the proximal gastric bag volume response between the groups and (ii) the blood glucose responses between the groups, with time and treatment as the factors were compared by repeated ANOVA.

10.2.3 RESULTS

10.2.3.1 Proximal gastric volume response to duodenal nutrients

The MDP was higher in both patient groups compared with healthy subjects ($P<0.05$), but was similar between DM and non-DM patients (Table 10.2.2). Baseline proximal gastric volumes were similar between the three groups.

As in previous studies (Chapter 7), healthy volunteers demonstrated a "biphasic" proximal gastric volume response in response to duodenal nutrients. Following an initial rapid relaxation, the fundus partially contracted and then exhibited a sustained relaxation throughout the remainder of the infusion (Figure 10.2.1). In non-DM critically ill patients, there was impairment of both the initial and later phase of the response. In DM patients, however, there was an absence of the initial response in the first 20 minutes during both 1 and 2 kcal/min infusions. Thereafter, the proximal gastric volume increased to the level observed in healthy volunteers.

Table 10.2.2 Comparison of proximal gastric motor activity between critically ill patients and healthy subjects

	DM ICU patients (n=10)	**Non-DM ICU patients (n=15)**	**Healthy subjects (n=10)**
MDP (mmHg)	11.9 ± 1.0 *	11.3 ± 1.2 *	7.1 ± 0.6
Baseline intra-gastric volume (mL)	187 ± 43	197 ± 22	182 ± 19
Time to recovery of baseline volume following infusion (min)	41 ± 15 *	83 ± 11 **	15 ± 4

* P<0.05 vs. healthy subjects. ** P<0.05 vs. DM patients and healthy subjects

During the 1 kcal/min infusion there was no difference in the proximal gastric volume response between DM critically ill patients and the other two groups. However, during the first 20 minutes of the 2 kcal/min infusion, the proximal gastric volume was significantly smaller in DM critically ill patients than in non-DM critically ill patients and healthy subjects. Thereafter, the proximal gastric volume of DM patients was greater than that of non-DM patients and similar to healthy subjects (Figure 10.2.1).

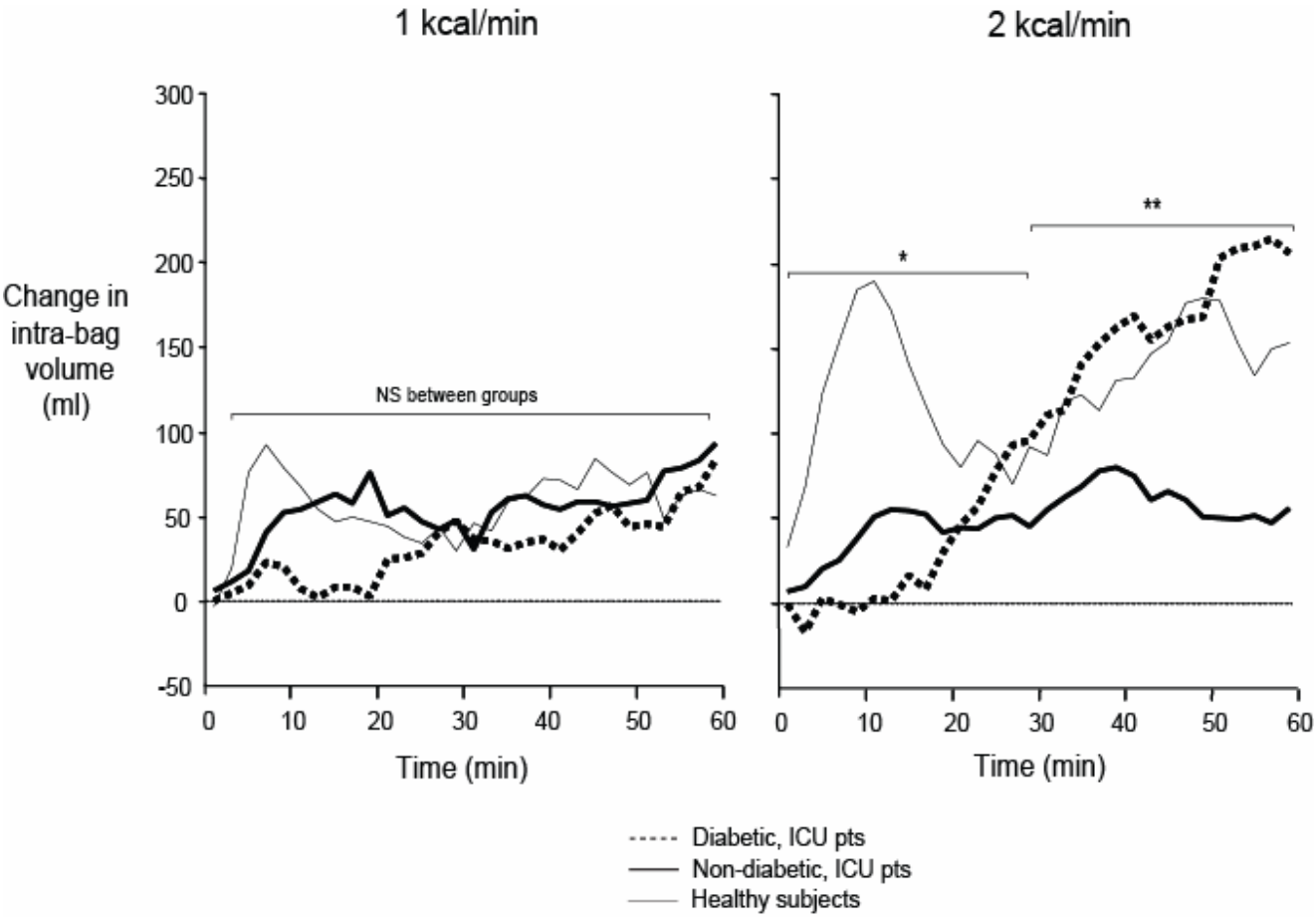


Figure 10.2.1 Changes in proximal gastric volume during duodenal nutrient stimulation (1 and 2 kcal/min) in critically ill patients and healthy subjects. * P<0.05 ICU patients vs. healthy subjects during 0- 30 min; ** P<0.05; non-DM patients vs. DM patients and healthy subjects during 30- 60 min

10.2.3.2 Recovery of proximal gastric volume after nutrient stimulation

The proximal gastric volume returned to baseline level within 60 minutes following cessation of nutrient stimulation in all DM patients and healthy subjects, but in only 2/15 (13%) non-DM patients. In DM patients, the time taken for the proximal gastric volume to return to baseline level was significantly shorter than in non-DM patients and longer than healthy subjects (Table 10.2.2).

10.2.3.3 Fundic volume wave activity

At baseline, the mean frequency of FWs in DM patients (10.2 ± 1.7 waves/10 min) was similar to that of healthy subjects (11.8 ± 0.9 waves/10 min; P=0.38), but was higher than non-DM patients (7.0 ± 0.8 waves/10 min; P=0.04; Figure 10.2.2).

The effect of duodenal nutrient stimulation on the frequency of FWs in DM patients was similar to that of healthy subjects but differed from non-DM patients (Figure 10.2.2). Nutrient stimulation with 1 kcal/min infusion did not reduce the mean frequency of FWs in either DM patients (9.0 ± 2.0 waves/10 min; P=0.68) or healthy subjects (9.9 ± 1.0 waves/10 min; P=0.10), in contrast to non-DM patients (4.4 ± 0.9 waves/10 min; P=0.04). However, in all 3 groups the 2 kcal/min nutrient infusion significantly reduced the mean frequency of FWs compared to baseline (DM: 3.9 ± 1.1 waves/10 min, P=0.02; healthy: 7.6 ± 0.8 waves/10 min, P<0.001; non-DM: 4.2 ± 0.9 waves/10 min, P=0.03). The magnitude of reduction in FW frequency during 2 kcal/min was greatest in DM patients (-6.6 ± 1.7 waves/10 min), compared to healthy subjects (-4.0 ± 0.7 waves/10 min, P=0.03) and non-DM patients (-1.9 ± 0.6, P<0.001; Figure 10.2.2).

Overall, the frequency of FWs in DM patients during 1 kcal/min infusion was similar to that of healthy subjects, but was higher than non-DM patients. In contrast, due to the greater magnitude of reduction in FW frequency by a higher nutrient load, fundic wave activity during 2 kcal/min infusion in DM patients was similar to that of non-DM patients, but less than that of healthy subjects (Figure 10.2.2).

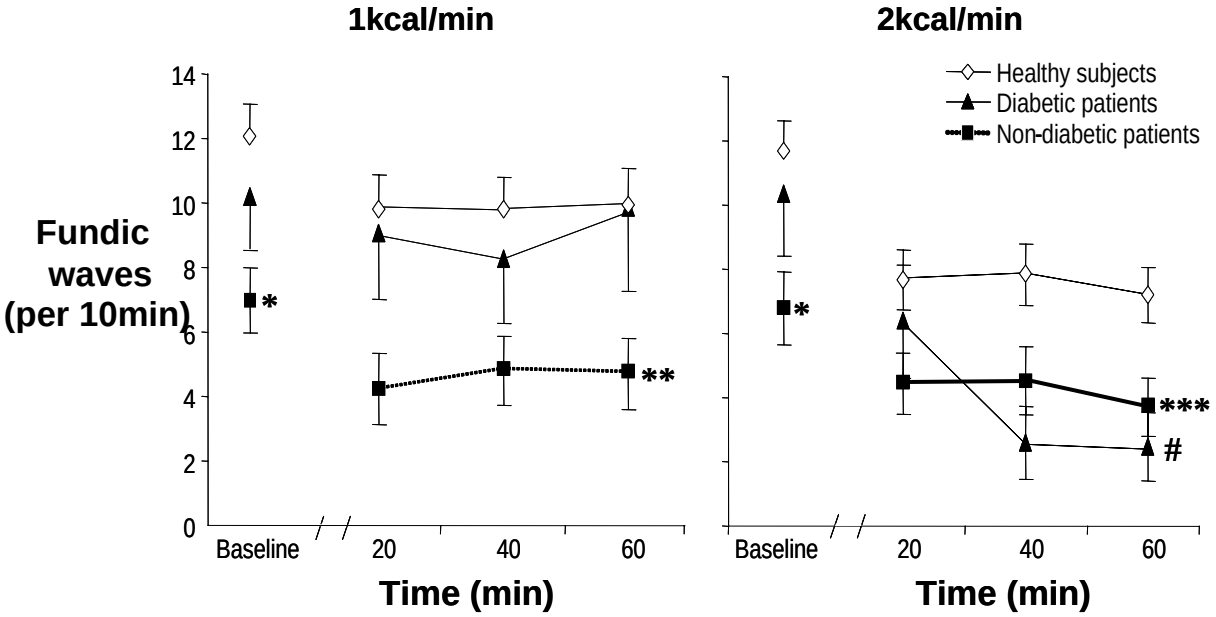


Figure 10.2.2 Number of fundic slow waves during fasting and duodenal nutrient stimulation (1 and 2 kcal/min) in critically ill patients and healthy subjects. * P<0.05 vs. healthy subjects and DM patients (at baseline); ** P<0.05 vs. healthy subjects and DM patients (during infusion); *** P<0.05 vs. healthy subjects (during infusion); # P<0.05 vs. healthy subjects (during infusion).

10.2.3.4 Blood glucose concentrations

Overall, both fasting and nutrient-stimulated blood glucose concentrations were higher in critically ill patients than in healthy subjects (Figure 10.3). There were no significant differences in blood glucose concentrations between DM and non-DM patients, reflecting the use of the insulin infusion protocol in the ICU.

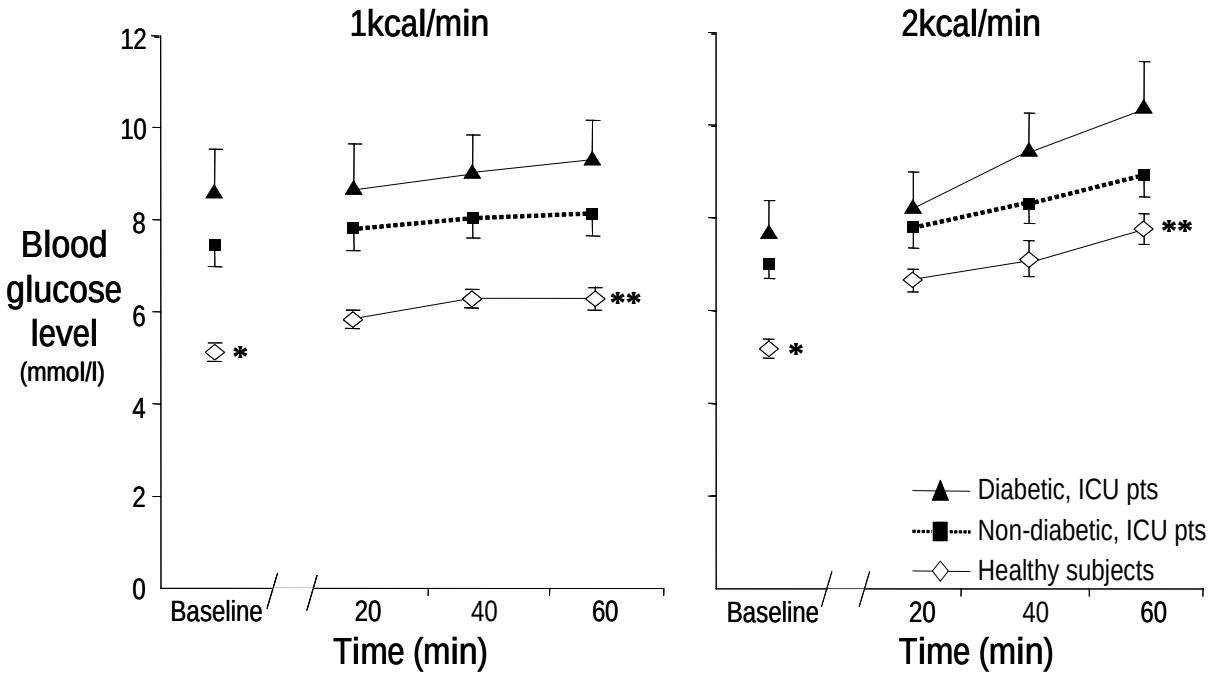


Figure 10.2.3 Blood glucose concentrations at baseline and during nutrient infusions in critically ill patients and healthy subjects. * P<0.05 vs. healthy subjects (at baseline); ** P<0.05 vs. healthy subjects (during infusion).

10.2.4 DISCUSSION

The findings of this study suggest that proximal gastric motor activity in critically ill patients with type 2 DM is different from that of non-DM patients and characterized by: (i) an initial absence of proximal gastric relaxation, after which the volume increased to a level similar to that seen in healthy volunteers, (ii) a nutrient load-dependent reduction in fundic wave activity and (iii) a slightly impaired recovery of the proximal gastric volume to baseline level.

In health, enterogastric feedback is regulated by neuro-hormonal pathways (Azpiroz and Malagelada 1985; Heddle, *et al.* 1988; Lin, *et al.* 1989; Lin, *et al.* 1993), and proximal gastric tone is modulated by a balance between the excitatory cholinergic nerves and the inhibitory

nitrergic neural inputs from the vagus (Paterson, *et al.* 2000). The complete absence of proximal gastric relaxation during the first 20 minutes of nutrient infusion in the diabetic patients was characteristic but the reason for this response is unclear. Autonomic dysfunction may be important as it is common in patients with both DM (Tougas, *et al.* 1992; Rayner, *et al.* 2001; Valensi, *et al.* 2003) and critical illness (Schmidt, *et al.* 2001; Schmidt, *et al.* 2005), and is associated with impaired relaxation of the proximal stomach (Samsom, *et al.* 1998). In the current study, the greater degree of impaired gastric relaxation may relate to an 'additive-effect' of DM and critical illness on the autonomic nervous system (Paterson, *et al.* 2000; Kellow, *et al.* 2006). Disturbances in the metabolism of nitric oxide, a key transmitter in the regulation of gastrointestinal motor function, may also be important (Kellow, *et al.* 2006). Impaired proximal gastric relaxation is associated with altered levels of nitric oxide (Toma, *et al.* 1992; Lefebvre 1993; Undeland, *et al.* 1998; Kuiken, *et al.* 2002; Leclere and Lefebvre 2002), and has been reported in both patients with diabetes mellitus (Samsom, *et al.* 1995; Samsom, *et al.* 1998) and those with critical illness (Argaman, *et al.* 2003). Furthermore, whilst elevated inflammatory cytokines during critical illness (Souba 1994) can also contribute to impaired relaxation (Emch, *et al.* 2000), these are less likely to account for the differences seen between the groups as the proportion of patients with sepsis and trauma were similar between patient groups.

The subsequent normalization of the proximal gastric volume in DM critically ill patients has not been observed previously either in patient with critical illness or with diabetes mellitus alone. The mechanism underlying this observation is unknown. Only proximal gastric motor responses to gastric, not duodenal, nutrients have been previously evaluated in non-critically ill patients with DM. Although a number of factors such as hyperglycaemia (Hebbard, *et al.*

1996; Hebbard, *et al.* 1996; Rayner, *et al.* 2000) and opioid sedation (Mittal, *et al.* 1986) can potentially induce excessive gastric relaxation, these factors are unlikely to have contributed significantly as absolute increase in blood glucose level was small and morphine was avoided for 24 hours prior to the study. Although the diabetic patients had a higher BMI than the non-diabetic patients in the current study, previous work has showed no difference in either proximal gastric volume or compliance between obese and lean subjects (Kim, *et al.* 2001; Park and Camilleri 2005); thus, the difference in BMI is unlikely to have contributed to the differences in proximal gastric motility.

In addition to the proximal volume response, fundic wave activity during nutrient stimulation was also different between critically ill patients with and without DM. While an inhibitory effect on fundic wave activity was evident at 1 kcal/min in the non-diabetic patients, fundic wave activity in diabetic patients was only reduced at 2 kcal/min infusion. These findings suggest a dose-dependent reduction in fundic wave activity in diabetic critically ill patients, similar to that seen with healthy volunteers, which indicate that entero-gastric feedback is not increased in diabetic critically patients. This is in contrast to the enhanced entero-gastric feedback in response to duodenal nutrient stimulation seen in non-DM critically ill patients (Chapman, *et al.* 2005).

Whether differences in the 'accommodative' response to nutrients between the patient groups affect the tolerance to bolus or continuous gastric feeds remains to be determined and requires further study. It is conceivable that slow continuous feeds would be better tolerated in the non-DM critically ill patients where proximal gastric relaxation is small and slow during nutrient stimulation. This is consistent with most studies on non-selected critically ill patients

(Heyland, *et al.* 2003; Chang, *et al.* 2004). In contrast, the relatively normal 'biphasic' proximal gastric response in the DM critically ill patients may allow better tolerance to bolus gastric feeds.

In conclusion, proximal gastric motor responses to duodenal nutrient are relatively normal in patients with type 2 DM during critical illness. Whilst these findings suggest these patients may have normal gastric emptying and may be less prone to developing naso-gastric feed intolerance than non-diabetic, critically ill patients, further study is required.

10.3 THE IMPACT OF PRE-EXISTING TYPE 2 DIABETES MELLITUS ON GASTRIC EMPTYING DURING CRITICAL ILLNESS

10.3.1 INTRODUCTION

Although it is generally believed that gastric emptying is likely to be slower in critically ill patients with DM compared to those without DM as both conditions are risk factors for delayed gastric emptying (Horowitz, *et al.* 1996; Kong, *et al.* 1996; Rayner, *et al.* 2001; Horowitz, *et al.* 2002; Samsom, *et al.* 2003), data on gastric emptying in critically ill patients with DM are currently lacking. The proximal stomach is a major regulator of liquid gastric emptying (Kelly 1980; Collins, *et al.* 1988; Collins, *et al.* 1991). As motor activity in this region of the stomach differs between diabetic and non-diabetic critically ill patients (Chapter 10.2), it is possible that the rate of gastric emptying would also be different. The aim of this study was, therefore, to evaluate the effect of pre-existing type 2 DM on gastric emptying of a liquid nutrient meal in critically ill patients, using a ^{13}C-octanoic acid breath test.

10.3.2 METHODS

10.3.2.1 Subjects

A retrospective audit was performed on a complete cohort of 59 mechanically ventilated, critically ill patients, pooled from 3 clinical trials, who had undergone ^{13}C-octanoic acid breath tests in order to assess their gastric emptying. All studies had been performed in the Intensive Care Unit of the Royal Adelaide Hospital over a 4-year period. Within this cohort, a subgroup of 12 patients with a history of type 2 DM (62 ± 3yr; 7M) was identified. Three

patients with type 1 DM were excluded from the analysis. The mean duration of DM was 10.5 ± 2.1 years. Four patients had documented neuropathy and 7 patients were insulin-dependent prior to admission. Of the 44 critically ill patients without a history of diabetes mellitus (50 ± 3 yr; 36M), a subgroup of 15 age and sex matched patients (61 ± 4 yr; 9M) were selected for comparison with the diabetic group. Breath tests on 15 healthy volunteers (30 ± 2 yr; 8M) were also assessed. The demographic data are summarized in Table 10.3.

10.3.2.2 Protocol

Patient demographics, admission details, current and past medical history and medication were obtained by careful examination of patient's case-notes and intensive care charts. A diagnosis of diabetes mellitus in an individual patient was accepted if there was a clear documentation of the disease prior to admission to the ICU. In all patients, gastric emptying was assessed using an identical standardized technique of 13C-octanoic breath test, as described in Chapter 6. Both healthy subjects and critically ill patients were studied in the morning after an overnight fast. The $^{13}CO_2$ concentration over time was plotted and the resultant curves used to calculate gastric emptying coefficient (GEC) and gastric half emptying time (t50) (Chapter 6). In the current study, delayed gastric emptying was defined as a GEC of less than 3.2 (Ritz, *et al.* 2001).

10.3.2.3 Statistical Analysis.

Differences in demographic data and gastric emptying variables between the studied groups were compared using unpaired Student's t-test. Comparison of the proportion of patients with delayed gastric emptying amongst the groups was performed using Fisher's exact test.

Table 10.3.1 Demographics and characteristics of critically ill patients and healthy subjects.

	Critically ill DMs (n=12)	**Matched, critically ill non-DMs (n=15)**	**Unselected critically ill non-DMs (n=44)**	**Healthy volunteers (n=15)**
Age (yrs)	62 ± 3 *	61 ± 4 *	50 ± 4 *	28 ± 3
Gender (M:F)	7:5	12:3	36:8	12:3
BMI	35 ± 3 **	27 ± 1	29 ± 1	25 ± 1
APACHE II score				
On admission	28.6 ± 1.5	23.2 ± 0.8	23.2 ± 0.8	NA
On study day	24.7 ± 1.5	21.1 ± 1.3	21.1 ± 1.3	NA
Blood glucose level (mmol/L)				
On admission	7.6 ± 0.7	7.2 ± 0.6	7.5 ± 0.2	NA
On study day	7.8 ± 0.7	7.4 ± 0.6	7.6 ± 0.2	
Sedation (% (n))				
Morphine ± midazolam	42% (5)	40% (6)	57% (25)	NA
Propofol	50% (6)	27% (4)	43% (19)	
Inotropic support (% (n))				
(adrenaline or noradrenalin)	75% (9)	67% (10)	68% (30)	NA
Diagnoses	Sepsis (3), pneumonia (3), severe asthma, MVA (2), SAH (2), angioedema.	Sepsis (3), pancreatitis (2), head trauma (2), MVA (3), cardiac failure (2), burn, lung abscess, meningitis.	Sepsis (21), pancreatitis (4), head trauma (10), MVA (15), cardiac failure (6), burn (4), pneumonia (12), lung abscess (2), meningitis (3).	NA

* P<0.05, vs. healthy subjects; ** P<0.05, vs. healthy subjects and critically ill, non-DM

NA = not applicable; MVA = motor vehicle accident; SAH = sub-arachnoid haemorrhage

10.3.3 RESULTS

There was no difference in the median APACHE II scores on the study day between the 3 groups of critically ill patients. The proportions of patients who were sedated using morphine and/or midazolam, propofol and inotropic agents were also similar amongst the 3 critically ill groups. No patients received prokinetic therapy within 24 hours of gastric emptying measurements. The mean blood glucose concentrations among the groups did not differ either on admission or on the study day (Table 10.3.1). The proportion of patients who received insulin infusion therapy for blood glucose control was also similar among the groups.

10.3.3.1 Gastric emptying

In critically ill patients with DM, the gastric half emptying time (t50 = 122 ± 11 minutes) was shorter than in both the matched non-DM patients (165 ± 13 minutes; P=0.02) and the unselected patients without DM (168 ± 16 minutes; P=0.02). There was no difference in gastric half emptying time between patients with DM and healthy volunteers (148 ± 13 minutes, NS) (Figure 10.3.1).

In critically ill patients with DM, the gastric emptying coefficient (GEC=3.8 ± 0.3) was significantly higher than in both the matched non-DM patients (GEC=2.7 ± 0.2; P=0.03) and the unselected patients without DM (GEC=2.8 ± 0.1; P=0.02). Gastric emptying coefficients were similar between critically ill patients with DM and healthy subjects (3.5 ± 0.1; NS) (Figure 10.3.1).

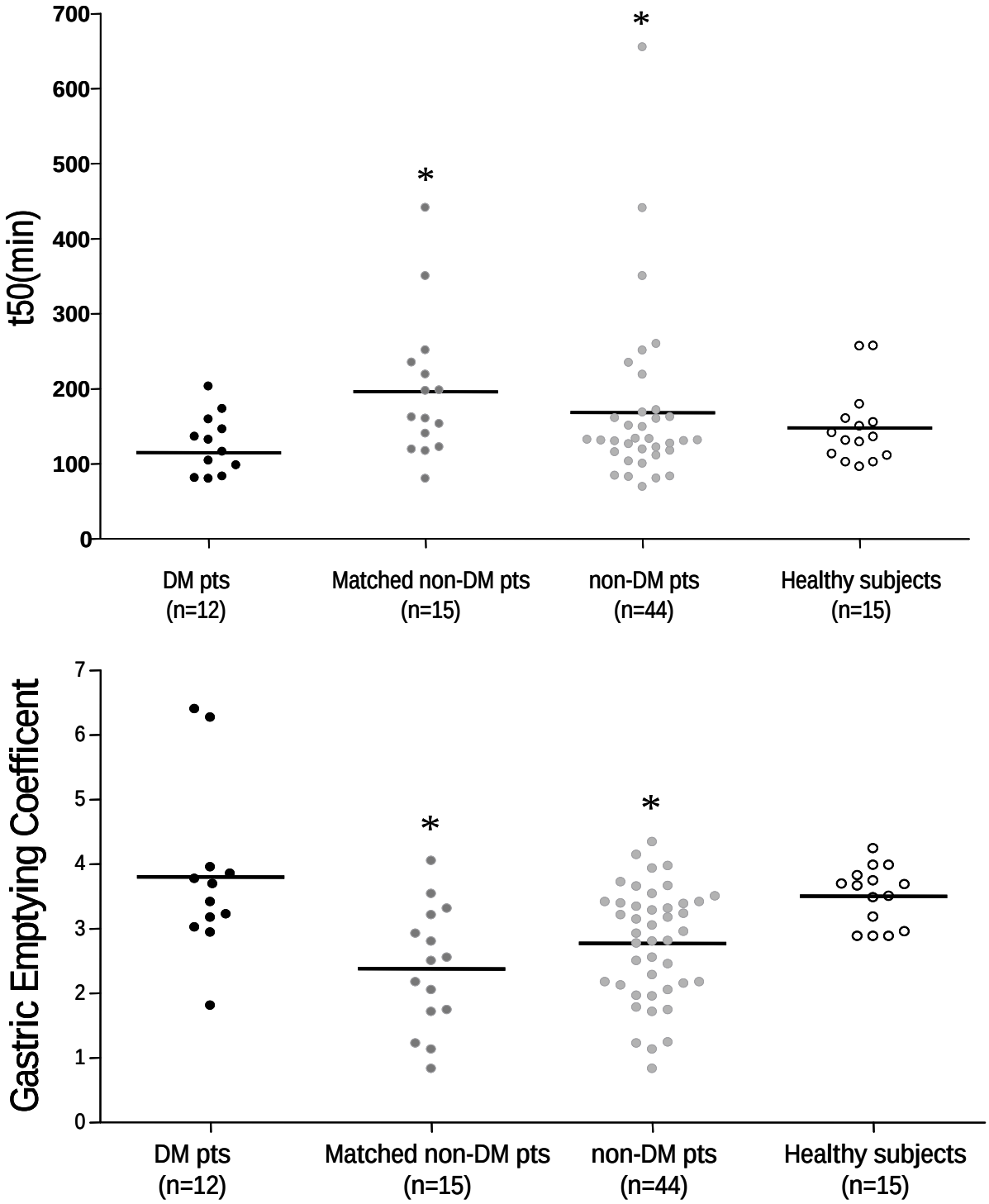


Figure 10.3.1 Gastric emptying half times (t50; upper panel) and gastric emptying coefficient (GEC; lower panel) in critically ill patients and healthy subjects. * $P<0.05$, vs. DM critically ill and healthy subjects.

10.3.3.3 Proportion of subjects with slow gastric emptying

The proportion of DM patients with a GEC < 3.2 (25% (3/12)) was similar to that of healthy subjects (26% (4/15); NS) but significantly less than that of the non-diabetic patients (matched = 60% (9/15), P=0.06; unselected = 56% (25/44), P=0.05) (Figure 10.3.2).

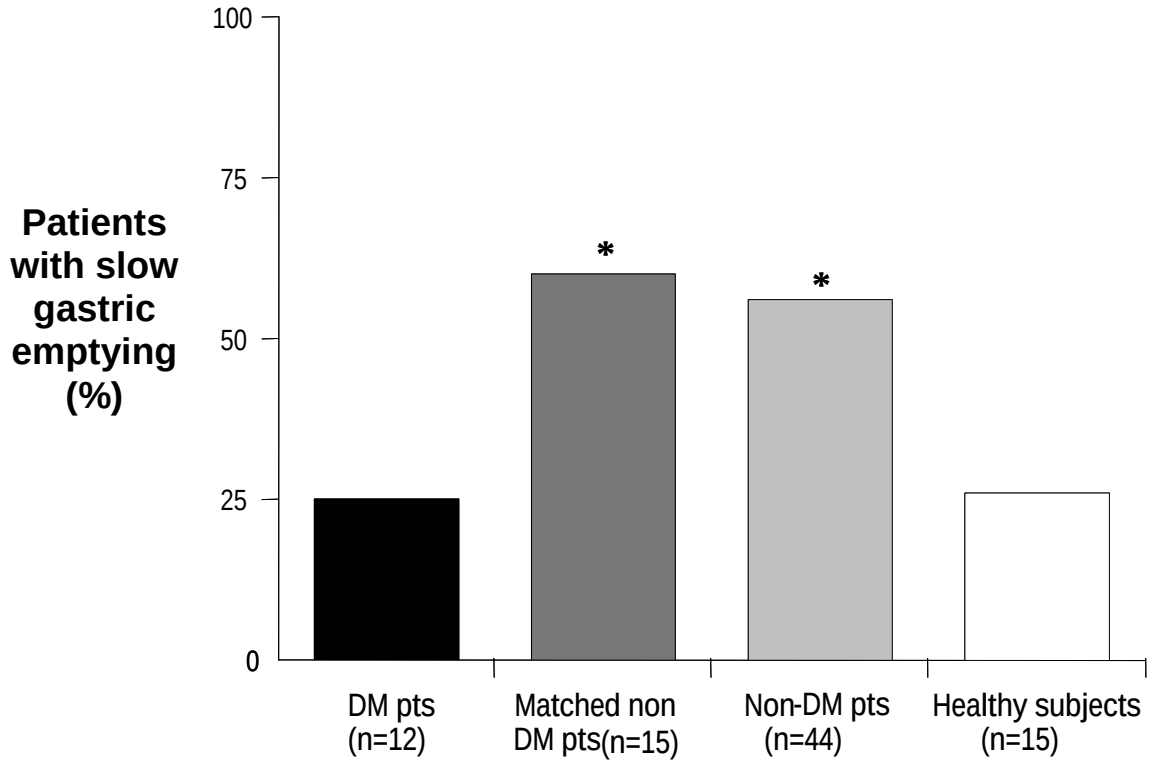


Figure 10.3.2 Percentage of subjects with slow gastric emptying in diabetic, non-diabetic and healthy groups. * P<0.05, vs. DM critically ill and healthy subjects.

10.3.4 DISCUSSION

The current study demonstrates that gastric emptying of a liquid meal in critically ill patients with longstanding type 2 DM is comparable to that in healthy subjects and is less likely to be delayed than patients without DM. These data concur with those reported previously in non-critically ill diabetic patients (Phillips, *et al.* 1991, 1992; Frank, *et al.* 1995; Jones, *et al.* 1996; Schwartz, *et al.* 1996; Bertin, *et al.* 2001). The findings are also consistent with the proximal gastric motor activity of these patients (Section 10.2).

Although gastric emptying of solids is frequently delayed in both type 1 and 2 DM patients (Campbell, *et al.* 1980; Jones, *et al.* 1995; Kong and Horowitz 1999; Jones, *et al.* 2001; Samsom, *et al.* 2003), a variable rate of liquid gastric emptying has been reported, ranging from delayed (Wegener, *et al.* 1990; Chang, *et al.* 1996; Samsom, *et al.* 1997; Vaisman, *et al.* 1999; Darwiche, *et al.* 2001), to normal or even accelerated (Phillips, *et al.* 1991; Frank, *et al.* 1995; Jones, *et al.* 1996; Schwartz, *et al.* 1996; Lipp and Schnedl 1997; Bertin, *et al.* 2001). The reasons underlying this discrepancy amongst the studies and between liquids versus solids emptying remain unclear. The different results in liquid gastric emptying amongst studies, however, may relate to the presence or absence of hyperglycemia and autonomic neuropathy. Studies that did not control for marked hyperglycemia at the time of gastric emptying would be expected to have excessive proximal gastric relaxation (Horowitz, *et al.* 1996) and thus, may have delayed gastric emptying as the liquids pools in the proximal stomach. In the present study, the differences in gastric emptying rate between the critically ill groups are unlikely to be attributed to blood glucose control as the levels were similar between the groups on both admission and study day.

On the other hand, a high proportion of non-critically ill patients with autonomic neuropathy were found to have impaired proximal gastric relaxation (Samsom, *et al.* 1997), resulting in a smaller proximal stomach, more distal redistribution of liquid and thus more rapid gastric emptying (Hebbard, *et al.* 1996; Rayner, *et al.* 2001). The prevalence of autonomic neuropathy in the current cohort could not be accurately identified as the data were collected retrospectively. However, based on a previous study in DM population with a similar mean duration of disease (Valensi, *et al.* 2003), a prevalence of 50% would be expected. Autonomic neuropathy may, therefore, contribute to the impaired proximal gastric relaxation (Chapter 10.2) and subsequent rapid gastric emptying in the current study, although the magnitude of its impact remains unknown. As described previously in this Chapter 10.2, proximal gastric relaxation in diabetic critically ill patients is markedly reduced in the first 20 minutes after meal. Interestingly, increased fundic wave activity in non-critically ill patients has been associated with accelerated gastric emptying (Frank, *et al.* 1995). The impaired relaxation in conjunction with a relatively normal fundic wave activity in the diabetic critically ill patients could thus result in an enhanced distal distribution of meal for emptying, and potentially lead to more rapid gastric emptying.

There are a number of limitations with the current study. As it is a retrospective study with a relatively small sample size, the possibility of selection bias cannot be excluded. However, this appears unlikely as results from all patients included in the earlier studies were included. The assessment of gastric emptying was performed using ^{13}C-octanoic acid breath test. Whilst this is less accurate than the gold standard scintigraphic technique, a good correlation has been shown to exist between the two techniques (Chapman, *et al* 2004; Nguyen, *et al*

2006) and it appears unlikely that the choice of this methodology would influence the gastric emptying results selectively (Zahn, *et al.* 2003).

In conclusion, gastric emptying of a liquid meal in critically ill patients with DM is normal and the proportion of patients with delayed gastric emptying is less than in non-diabetic patients. When taken together with findings described in Chapter 10.2, the presence of longstanding type 2 diabetes mellitus does not appear to constitute a further risk factor for impaired gastric motor function in these patients.

10.4 THE IMPACT OF PRE-EXISTING TYPE 2 DIABETES MELLITUS ON THE DEVELOPMENT OF FEED INTOLERANCE

10.4.1 INTRODUCTION

Contrary to the traditional belief that critically ill patients with DM are at greater risk of disturbed gastric motility, slow emptying and intolerance to gastric feeding (Mutlu, *et al.* 2001; Metheny, *et al.* 2004), the findings in Chapters 10.2 and 10.3 have demonstrated that the presence of pre-existing type 2 DM in these patients has only a minor impact on proximal gastric motility and gastric emptying. In critical illness, impaired gastric emptying is manifested as intolerance to naso-gastric feeds (Montejo 1999; Mentec, *et al.* 2001; Mutlu, *et al.* 2001; Metheny, *et al.* 2004). It is, therefore, important to clinically confirm the relevance of these recent findings in terms of the incidence of feed intolerance. The aim of this study was to examine the impact of pre-existing type 2 DM on the occurrence of feed intolerance in critically ill patients who received enteral gastric feeding.

10.4.2 METHODS

10.4.2.1 Subjects

All patients admitted to the intensive care unit at the Royal Adelaide Hospital and who received enteral feeding between January 2003 and July 2005 were identified from a discharge coding database. This database records and stores the details of (i) admission diagnosis, (ii) investigations performed and (iii) treatments administered to all patients admitted to the hospital. For every patient on this database, each diagnosis, procedure or therapy (including ICU admission and enteral nutrient infusion) is coded as a number. The following criteria (based on the coding number) were used to search the database to identify the patients for the

current study: (i) admitted between 1 January 2003 and 1 July 2005, (ii) admitted to ICU during the hospital admission, and (iii) received any enteral nutrition for during ICU admission. Of the patients identified during the study period, only patients who had received gastric feeding for at least 72 hours were included in the final analysis. Other exclusion criteria were: previous oesophageal or gastric surgery; gastrointestinal surgery during the current admission; post-pyloric feeding and type 1 DM.

The outline of the patient selection process is summarised in Figure 10.4.1. Of the 649 patients identified, 118 (18%) patients had pre-existing diabetes mellitus. Sixty-eight of these patients were excluded from the final analysis because of: feeding duration < 72 hours (n=34), gastrointestinal surgery (n=16), post-pyloric feeding (n=4), type 1 diabetes mellitus (n=3), history of gastric or oesophageal surgery (n=1), incomplete data or missing case notes (n=10) (Figure 10.4.1). Prior to ICU admission, 19 DM patients were managed by diet alone, 21 patients were taking oral hypoglycaemics and 10 patients were receiving insulin.

Five hundred and thirty-one enterally fed, non-diabetic patients were identified during the study period. Three hundred and nine patients were excluded from this group due to: feeding duration < 72 hours (n=182), gastrointestinal surgery (n=50), history of gastro-oesophageal surgery (n=13), post-pyloric feeding (n=2), incomplete data or missing case notes (n=62) (Figure 10.4.1). Of the 222 non-DM patients who received enteral feeds for more than 72 hours without other exclusion criteria, 50 age, sex and APACHE II score matched patients were selected for comparison to the DM patients. The final analysis, therefore, included 3 groups of patients: (i) DM group (n=50); (ii) matched non-DM group (n=50) and (iii) unselected non-DM group (n=222).

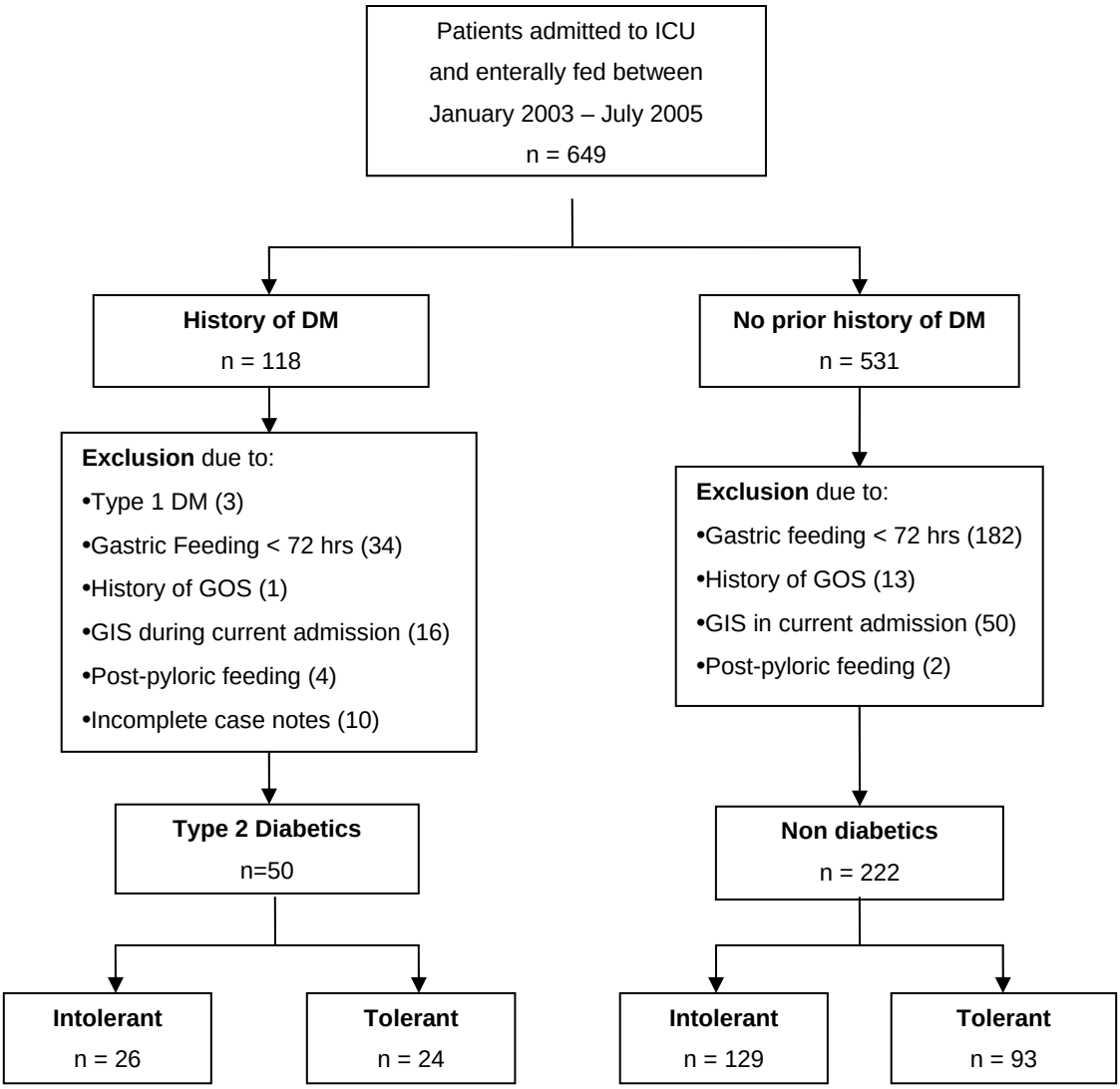


Figure 10.4.1 Outline of study protocol and patient selection. DM = Diabetes mellitus; GOS = previous gastro-oesophageal surgery; GIS = Gastro-intestinal surgery

10.4.2.2 Protocol

The case notes and critical care charts of all patients were reviewed to determine: (i) the presence of pre-existing diabetes mellitus and (ii) the duration of feeding. The following data were also obtained: age, gender, admission diagnosis and APACHE II score, duration of ICU stay, duration of feeding, type of diabetes and treatment, feeding rate, time to development of feed intolerance, blood glucose concentrations (admission and immediately before

development of feed intolerance), and the use of morphine and/or midazolam, and vasopressor support therapy (either adrenaline or nor adrenaline). The use of prokinetic agents (either metoclopramide or erythromycin) other than for treatment of feed intolerance was also recorded. All patients in the cohort received (i) standardized insulin infusion therapy and (ii) protocol-driven enteral nutrition, as described in Chapter 6. Enteral feeding was continuous, and interrupted only if clinically indicated.

10.4.2.3 Statistical analysis

Categorical data were compared by chi-square test with Yates' correction and continuous data were compared by Student's t-test. The data on the duration of feed and the time to develop feed intolerance were, however, not distributed normally and are expressed as median and inter-quartile range (IQR). These parameters were compared using Mann Whitney test.

10.4.3 RESULTS

The demographics and characteristics of the 3 groups of patients are summarized in Table 10.4.1. Diabetic patients were older than the unselected non-diabetic patients, but the gender, APACHE II score, the use of morphine/midazolam and inotropes and duration of gastric feeding were similar between the groups. In addition to being of similar age, gender and having comparable APACHE II scores to the matched non-diabetic patients, the diabetic patients also had similar admission diagnoses, use of morphine/midazolam and inotropes, and duration of gastric feeding. The blood glucose concentrations in diabetic patients were higher on admission than the non-DM groups, but the blood glucose concentrations amongst the groups were comparable immediately before the development of feed intolerance as a result of effective therapy with insulin.

The incidence of feed intolerance in diabetic patients was 52% (26/50) and was similar to that seen in both the entire non-diabetic patient group (58% (129/222); P=0.35) and the matched non-diabetic patients (50% (25/50); P=0.96). There was no difference in the duration of feeding prior to the development of intolerance between patients with and without DM (DM: 62.6 ± 43.8 hours vs. matched non-DM: 45.3 ± 54.6hours vs. unselected non-DM: 50.6 ± 59.5 hours; P=0.25). There was a trend for DM patients to receive feeds at a slightly lower rate than matched non-DM patients (DM: 53.0 ± 15.3 mL/hr vs. matched non-DM: 58.2 ± 14.2 mL/hr; P=0.09) but at a similar rate to that of unselected non-DM patients (55.7 ± 15.8 mL/hr; P=0.29).

Overall, 155 (57%) patients did not tolerate gastric feed. Diabetes mellitus was present in 26 (17%) feed-intolerant patients and 24 (20%) feed-tolerant patients. Patients who failed gastric feeding were more likely to be: (i) sedated with morphine and/or midazolam, (ii) treated with inotropic therapy, and (iii) admitted with intra-cranial injury (Table 10.4.2). There was a trend for more patients with burns to develop feed intolerance. There was no relationship between feed intolerance and age, gender, APACHE II score, and blood glucose concentrations on admission.

Amongst patients with similar demographics and admission APACHE II scores, patients who had feed intolerance received significantly less feeds (52.5 ± 16.7 mL/hr vs. 58.2 ± 14.4 mL/hr; P=0.01) and stayed significantly longer in ICU (19.3 ± 34.6 days vs. 11.7 ± 8.2 days, P=0.02). These adverse effects were most pronounced in DM critically ill patients with feed intolerance (Table 10.4.2).

Table 10.4.1 Demographics and admission characteristics of patients with and without type 2 diabetes mellitus (DM).

	Type 2 Diabetics (n=50)	**Matched non-DM (n=50)**	**Unselected non-DM (n=222)**
Age (yr)	62.8 ± 14.0 *	62.9 ± 14.7	48.6 ± 19.0
Gender (M:F)	33:17	33:17	123:99
APACHE II score (on admission)	20.3 ± 7.3	20.5 ± 5.2	19.5 ± 6.8
Blood glucose (mmol/L)			
On admission to ICU	10.6 ± 5.2 *	7.5 ± 2.4	7.9 ± 3.2
At intolerance	7.7 ± 2.9	8.2 ± 5.0	7.3 ± 2.6
Duration of feeding prior to intolerance (hr)	62.6 ± 43.8	41.3 ± 54.6	50.6 ± 59.5
Duration of enteral feeding (hr)	179.3 ± 105.0	179.8 ± 154.2	184.0 ± 190.4
Medications (n (%))			
Morphine ± midazolam	26 (52%)	26 (52%)	148 (67%)
Propofol	24 (48%)	24 (48%)	74 (33%)
Inotropic therapy #	21 (42%)	22 (44%)	102 (46%)
Diagnosis (n (%))			
Medical	26 (52%)	22 (44%)	88 (40%)
Surgical†	3 (6%)	9 (18%)	23 (10%)
Burns	2 (4%)	1 (2%)	11 (5%)
Trauma	9 (18%)	10 (20%)	49 (22%)
Intracranial injury	10 (20%)	8 (16%)	51 (23%)
Length of ICU stay (days)	18.0 ± 15.1	16.3 ± 15.3	15.6 ± 28.9

† Non-abdominal surgery; # includes adrenaline and nor-adrenaline

* $P<0.01$, versus unselected non-diabetic patients

Table 10.4.2 Demographics and admission characteristics of feed-tolerant and intolerant patients.

	Feed-intolerant (n=155)	**Feed-tolerant (n=117)**	P-value
Age (yrs)	53.3 ± 19.6	56.8 ± 16.5	0.13
Gender (M:F)	96:59	60:57	0.08
APACHE II score (on admission)	19.9 ± 7.4	19.2 ± 6.4	0.43
- DM	21.7 ± 8.0	18.7 ± 6.1	0.18
- Non-DM	19.6 ± 7.2	19.3 ± 6.4	0.66
Morphine and/or midazolam (%)	119 (77%)	67 (57%)	<0.01
- DM	17/26	13/24	0.56
- Non-DM	102/129	54/93	<0.01
Inotropic therapy (%)	81 (52%)	43 (37%)	0.01
- DM	14/26	8/24	0.17
- Non-DM	67/129	35/93	0.04
Admission blood glucose (mmol/L)	8.2 ± 3.8	8.5 ± 3.8	0.60
- DM	10.6 ± 4.9	10.4 ± 5.7	0.88
- Non-DM	7.7 ± 3.4	8.0 ± 3.0	0.56
Diagnosis			
Medical	52 (34%)	62 (53%)	<0.01
Surgical †	15 (10%)	11 (9%)	0.99
Burns	9 (6%)	4 (3%)	0.13
Trauma	36 (24%)	22 (18%)	0.20
Intracranial injury	43 (27%)	18 (15%)	0.01
Feeding rate (mL/hr)	52.5 ± 16.7	58.2 ± 14.4	0.01
- DM	45.4±12.8	62.2 ± 14.1	<0.01
- Non-DM	54.0±17.1	57.5 ± 14.6	0.11
Length of ICU stay (days)	19.3 ± 34.6	11.7 ± 8.2	0.02
- DM	25.1 ± 17.6	10.2 ± 4.5	<0.01
- Non-DM	18.1 ± 37.0	12.1 ± 8.8	0.13

† Non-abdominal surgery

10.4.4 DISCUSSION

The similarity in the rate of feed intolerance between the groups is in-keeping with the lack of effect of diabetes mellitus on proximal gastric motility (Chapter 10.2) and rates of gastric emptying seen in these patients during critical illness (Chapter 10.3). However, these findings are in contrast to those seen in non-critically ill patients (Horowitz, *et al.* 1996; Kong and Horowitz 1999). The reasons for the discrepancy between the effects of DM in critically ill and other patients are unclear.

Although the aetiology of slow gastric emptying in non-critically ill patients with DM remains unclear, both autonomic neuropathy and hyperglycemia are thought to be important contributing factors (Horowitz, *et al.* 1996; Kong and Horowitz 1999). The impact of autonomic neuropathy in unknown in the current study as its prevalence could not be accurately identified retrospectively. Based on a previous study in diabetic population with a similar duration of disease (Valensi, *et al.* 2003), a prevalence of 50% would be expected. Although the presence of autonomic neuropathy is known to increase the risk of gastroparesis in non-critically ill patients (MacGregor, *et al.* 1976; Fraser, *et al.* 1990), this did not appear to slow gastric emptying in the critically ill patients (Chapter 10.3). It is possible that the impairment in autonomic function in diabetes blunts the effects of critically illness on proximal gastric function (Chapter 10.2). Furthermore, some of the delay on gastric emptying seen with diabetic patients may be related to elevated blood glucose concentrations (Horowitz, *et al.* 1996; Kong and Horowitz 1999). In the current study, standardized insulin therapy was used to maintain euglycemia in both groups and hence, is likely to explain the similar rate of feed intolerance and supports the concept that hyperglycemia per se is important in diabetic gastroparesis. On the other hand, as reported

by other investigators (Mittal, *et al.* 1986; Heyland, *et al.* 1995; Heyland, *et al.* 1996; Yuan, *et al.* 1998; Hammas, *et al.* 2001; Mentec, *et al.* 2001), factors such as the use of morphine and/or midazolam and vasopressor support with inotropes are more likely to be associated with feed intolerance, and potentially of greater importance than pre-existing type 2 DM, on gastric motor function in critically ill patients.

The current study focused on critically ill patients who required gastric feeding for at least 72 hours for two reasons. First, as feed intolerance may occur up to 72 hours after the start of feeding (Heyland, *et al.* 1995; Yuan, *et al.* 1998; Montejo 1999; Mentec, *et al.* 2001), including patients who were fed for less than 72 hours would increase the risk of falsely labelling patients as 'feed tolerant'. Second, it is more clinically relevant to study these patients as they are more likely to be sicker, at a higher risk of malnutrition and thus, are likely to benefit most from nutritional support (Heyland, *et al.* 1995; Yuan, *et al.* 1998; McClave, *et al.* 1999; Mentec, *et al.* 2001; Metheny, *et al.* 2004). Successful feeding of these patients is also likely to have a greater impact on outcomes than in those who require nutritional support for only a few days (Heyland, *et al.* 2003).

Consistent with previous studies (Heyland, *et al.* 1996; Adam and Batson 1997; Mentec, *et al.* 2001; Heyland, *et al.* 2003; Metheny, *et al.* 2004), the patients who did not tolerate enteral feeding had a longer ICU length of stay and lower feed rates. While patients with a prior history of type 2 DM were not at an increased risk of feed intolerance, diabetic patients who developed this complication had significantly longer ICU stays than those without DM. The reason for this observation is unclear, but it may relate to the greater susceptibility of

these patients to infections and venous thrombo-embolism (Langdon and Shriver 2004; Butler, *et al.* 2005).

In summary, although delayed gastric emptying is common in patients with type 2 diabetes mellitus, these patients do not appear to be at increased risk of either slow gastric emptying (Chapter 10.3) or gastric feed intolerance during critical illness. This may relate to the use of standardized insulin protocols to minimize hyperglycemia. Thus, provided that euglycemia is to be maintained by insulin therapy, the presence of pre-existing DM 2 in critically ill patients should not influence the standard practices of gastric feeding.

10. 5 SUMMARY AND CONCLUSIONS

The data in the current chapter argue against the traditional belief that a prior history of type 2 DM is a risk factor for disturbed upper gastrointestinal motility and feed intolerance during critical illness. The evidence presented demonstrates that critically ill patients with a pre-existing diagnosis of type 2 DM have only a minor disturbance in the proximal gastric motility, relatively normal gastric emptying and are at no higher risk of feed intolerance than patients without DM.

These findings have a number of therapeutic implications. Firstly, the presence of pre-existing type 2 DM in critically ill patients should not influence the standard practice of gastric feeding and, in the absence of contraindications, enteral feeding should be commenced as early as possible (Heyland, *et al.* 2003). Secondly, given the characteristic proximal gastric response to nutrients in these patients, the role of bolus cyclical enteral feeds should be investigated, as this pattern of feeding is deemed to be more physiological than continuous feeds and may minimize interruption due to procedures and clinical care (van Berge Henegouwen, *et al.* 1997). Although enteral feeds are currently delivered continuously at a low rate in critically patients to avoid the development of high gastric residue, this method of feeding may itself cause a delay in gastric emptying through an on-going activation of enterogastric feedback mechanism (van Berge Henegouwen, *et al.* 1997). This may be particularly relevant in the intensive care units as the inhibitory effects of enterogastric feedback by duodenal nutrients on the antro-pyloric region are enhanced during critical illness (Chapman, *et al.* 2005). A bolus cyclical feeding approach could potentially reduce constant

inhibitory effects on the stomach by entero-gastric feedback. Thirdly, whilst the incidence of feed intolerance in these patients is not higher, this complication should be treated promptly when it occurs due to the associated morbidity, particularly prolonged length of stay in ICU. Finally, gastric emptying function of these patients is as susceptible to general risk factors of critical illness, such as morphine sedation and inotropic support as non-diabetic patients, and such factors should be avoided whenever possible.

CHAPTER 11: PROKINETIC THERAPY WITH ERYTHROMYCIN FOR THE TREATMENT OF FEED INTOLERANCE IN CRITICALLY ILL PATIENTS

11.1 INTRODUCTION

Several therapeutic options are available for the management of feed intolerance in critically ill patients, including prokinetic therapy, post-pyloric feeding and total parenteral nutrition (Chapter 4). Whilst prokinetic agents are usually regarded as first line therapy for feed intolerance (Dove and Sahn 1995; Booth, *et al.* 2002; Doherty and Winter 2003; Kattelmann, *et al.* 2006; Davies 2007), data supporting the effectiveness of prolonged prokinetic therapy in feed intolerant critically ill patients are lacking. Currently, the prokinetic agents available for the treatment of feed intolerance are erythromycin and metoclopramide. There are, however, no studies that directly compare the effectiveness of these agents and the optimal approach to the treatment of feed intolerance; in particular the role of combinations of drugs has not been addressed. In addition, the adverse effects of these prokinetic agents are also not well characterized in critically ill patients (Chapter 4).

The work described in the current chapter, therefore, aimed to examine the effectiveness of erythromycin and metoclopramide as a single agent for 7-day treatment of feed intolerance in critically ill patients, as well as the effectiveness of "rescue" combination therapy (erythromycin plus metoclopramide) in patients who failed to respond to either erythromycin or metoclopramide. In addition, the safety profile of erythromycin and metoclopramide during the treatment, especially in regard their impact on the hemodynamics, cardiac adverse effects and the development of diarrhoea and *Clostridium difficile* (CD) infection, was also examined.

11.2 THE EFFECTS OF ERYTHROMYCIN VERSUS METOCLOPRAMIDE ON THE SUCCESS OF FEEDS

11.2.1 INTRODUCTION

Metoclopramide and low dose erythromycin are the two most widely used prokinetic agents in critically ill patients. A single intravenous dose of metoclopramide has been reported in several studies to improve gastric emptying in critically ill patients (Jooste, *et al.* 1999; MacLaren, *et al.* 2000; MacLaren, *et al.* 2001), but its effect on the success of feeding is unknown. In contrast, 3 mg/kg of erythromycin is associated with both increased gastric emptying and improved feeding success in previously feed-intolerant critically ill patients (Dive, *et al.* 1995; Chapman, *et al.* 2000; Berne, *et al.* 2002; Reignier, *et al.* 2002). Many critical care units now initiate either metoclopramide or erythromycin to treat feed intolerance, and therapy is often continued until enteral feeding is ceased. If monotherapy fails a combined administration of erythromycin and metoclopramide may be effective. Other approaches include total parental nutrition and placement of a post-pyloric feeding tube. Combination therapy is the preferred treatment due to its ease of use; however its effectiveness in managing feed intolerance in critically ill patients has not been formally assessed. As there are limited data on the longer term effectiveness of erythromycin, metoclopramide or combination therapy in the management of feed intolerance in critically ill patients, the aims of the current study were: (i) to compare the effects of metoclopramide and erythromycin on the rate of successful feeding in critically ill patients who were feed intolerant, and (ii) to determine the effectiveness of rescue combination therapy in patients who failed to response to either erythromycin or metoclopramide or who relapsed during treatment.

11.2.2 METHODS

11.2.2.1 Subjects

One hundred and seven consecutive mechanically ventilated patients who failed NG feeding were enrolled into the study over a 12 month period (from August 2004 to August 2005). All patients shared common inclusion and exclusion criteria described in Chapter 6, and 'feed intolerance' was defined clinically by a 6 hourly gastric aspirate volume ≥ 250 mL at least 6 hours after commencing nasogastric feeds (Chapter 5 and Chapter 6). All patients received enteral feeds, via a 114cm x 14 French naso-gastric tube, according to the standardized feeding protocol described in Chapter 6 (Figure 6.1).

11.2.2.2 Protocol

The study was conducted as a 2 way randomised, double blind, parallel group study. After enrolment, patients received either metoclopramide (10 mg intravenous (IV) four times daily (qid)) or erythromycin (200 mg IV twice daily (bd), plus 2 placebo injections (0.9% normal saline) for blinding purposes). Study drugs were administered at 0400 h, 1000 h, 1600 h, and 2200 h. The randomisation of therapy was performed by the study pharmacist using a computer generated random number program. Allocation was concealed from the investigators. After enrolment, the assigned study drugs were prepared daily by the pharmacist, in 10 mL syringes and packaged in black plastic bags with the study number and time and date of drug administration clearly labelled on each syringe. Correct administration of study drugs was monitored by the candidate on daily basis.

The total gastric residual volume (GRV) aspirated via the NG tube over the previous 24 hours was documented. Patients were then given either erythromycin or metoclopramide in a

randomized, double blind fashion. After the first dose of study medication, NG feeding was recommenced at a rate of 40 mL/h. Manual aspiration of the gastric contents using a 60 mL syringe was performed 2 hours after administration of the first dose of the study drug, and then 6 hourly over the following 7 days. The aspirate volumes obtained were recorded. All patients were fed according to the feeding protocol described in Chapter 6.

All patients who failed to response to monotherapy and required further enteral feeding were given open-label "rescue" combination therapy of IV metoclopramide (10mg qid) and IV erythromycin (200mg bd). Combination therapy was planned to continue for at least 6 days and only ceased if enteral feeding was no longer required as judged by the treating Intensive Care Specialist, or patients continued to have high gastric aspirates despite combination therapy. In the later circumstances, all prokinetic agents were discontinued and a post-pyloric feeding tube was placed endoscopically for administration of enteral nutrition.

11.2.2.3 Data analysis

The following data were collected prospectively over the 7 days of treatment: 6 hourly GRVs, volume of daily prescribed feeds, volume of daily administered feeds, occurrence of vomiting, the need for post-pyloric tube insertion, length of hospital stay and hospital mortality. Potential side effects of therapy were also recorded. At all time points, successful feeding was defined as a gastric volume < 250mL with a feeding rate ≥ 40 mL/h. Failure with either erythromycin or metoclopramide was defined as: (i) two or more high aspirate volumes (i.e. ≥ 250 mL) within the first 24 hours; or (ii) any 6 hourly gastric residue ≥ 250mL thereafter. Both intention to treat (ITT) and per protocol (PP) analyses are reported. All enrolled patients (n=107) were included in the ITT analysis, whilst only patients who participated in the trial for 7 days (n=90) were included in the PP analysis.

11.2.2.3 Statistical analysis

The study code was not broken until the completion of the study. A priori, the number of patients enrolled was determined using power calculations to be able to show a 20% difference in the rate of successful feeding between the different arms of therapy, with an α–value of less than 0.05 and β value of 80%. Differences in the demographic characteristics between critically ill patients treated with erythromycin and metoclopramide were assessed using the Student's unpaired t-test. Differences in the success of feeding between the treatment groups over time were assessed using Kaplan Meier survival curves with a log rank test. Risk factors for poor response to prokinetic therapy were assessed by the Cox proportional hazards model.

11.2.3 RESULTS

Of 107 enrolled patients, 17 (9 on metoclopramide and 8 on erythromycin) were excluded from the analysis because their participation in the trial was less than 7 days. Reasons for withdrawal from the trial included early recovery and ability to have oral intake (n=8), death from withdrawal of medical therapy (n=7) and massive gastrointestinal bleeding (n=1). One patient with myasthenia gravis was withdrawn from the trial after the first dose, as erythromycin has been reported to precipitate myasthenic crises (May 1990).

Ninety patients completed the study, of whom 45 were treated with erythromycin (52 ± 2 yr; 31M) and 45 with metoclopramide (46 ± 2 yr; 35M). The demographic characteristics (APACHE II, duration and type of mechanical ventilation prior to study, GRV, sedation regimen and admission diagnosis) and mean blood glucose concentrations were similar between the two treatment groups (Table 11.2.1). The feeding rate achieved prior to the development of feed intolerance was also similar between the 2 groups (erythromycin: 47 ± 2 mL/h vs. metoclopramide: 43 ± 2 mL/h).

Table 11.2.1 Demographics and characteristics of critically ill patients who were treated with erythromycin or metoclopramide. Gastric residual volume is the total over the previous 24 h period.

	Metoclopramide (n=45)	**Erythromycin (n=45)**
Age (yrs)	46 ± 2	52 ± 2
Gender (M:F)	35:10	31:14
Body mass index (kg/m^2)	26.3 ± 0.4	27.4 ± 0.4
Days in ICU prior to study	6.1 ± 0.6	6.4 ± 0.7
APACHE II score		
Admission	24.3 ± 0.5	26.2 ± 0.6
Study day	21.4 ± 0.5	22.2 ± 0.7
Prior total GRV (mL)	722 ± 27	680 ± 22
DIAGNOSIS [a] (% (n))		
Sepsis	47% (21)	71% (32)
Respiratory failure	71% (32)	82% (37)
Trauma	38% (17)	18% (8)
Renal failure	24% (11)	29% (13)
Head injury	29% (13)	14% (6)
Burns	9% (4)	11% (5)
Diabetes mellitus	9% (4)	11% (5)
Blood glucose level (mmol/L)	7.3 ± 0.2	7.8 ± 0.2
Serum creatinine (mmol/L)	0.120 ± 0.01	0.110 ± 0.006
Medications (% (n))		
Opioid ± Benzodiazepine	71% (32)	84% (38)
Propofol	35% (16)	38% (17)
Inotropes	44% (20)	47% (21)
Insulin (actrapid infusion)	64% (29)	64% (29)
Mode of ventilation		
SIMV (% (n))	51% (23)	51% (23)
Pressure support (% (n))	49% (22)	49% (22)
Positive end expiratory pressure (cmH_2O)	8.1 ± 0.4	8.7 ± 0.4
Positive inspiratory pressure (cmH_2O)	20 ± 1	21 ± 1

[a] >1 diagnosis possible in any patient. SIMV= Synchronized, intermittent, mandatory ventilation

11.2.3.1 Effects of erythromycin and metoclopramide on the total 24h gastric residual volume (GRV) on Day 1

After 24 hours of treatment with either metoclopramide or erythromycin, the total GRV in both groups was significantly smaller than during the 24 hours prior to therapy (Figure 11.2.1; P<0.0001). Treatment with erythromycin produced a greater reduction in GRV than metoclopramide (erythromycin = 59 ± 4 % vs. metoclopramide = 35 ± 6 %, P<0.001; Figure 11.2.1).

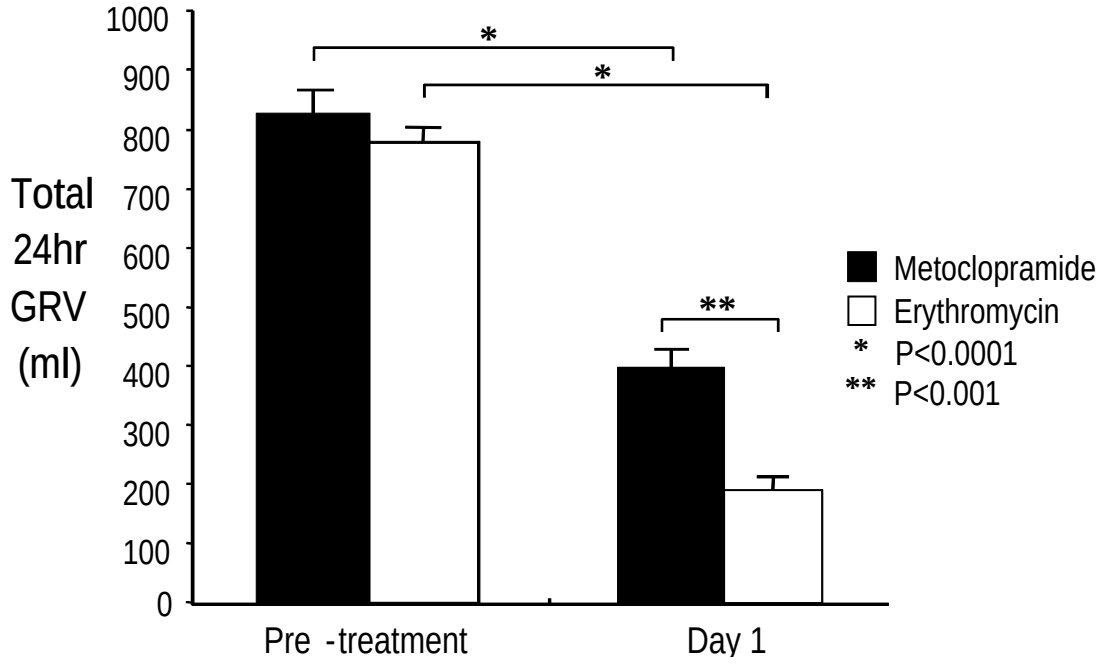


Figure 11.2.1 The effect of erythromycin and metoclopramide treatment on the total 24h gastric residual volume (GRV). * P<0·0001, ** P<0·001.

11.2.3.2 Effects of erythromycin and metoclopramide on the success of gastric feeding over 7 days

By 24 hours, successful enteral feeding was achieved in 87% of erythromycin treated patients and 62% of patients treated with metoclopramide. Thereafter, both treatments became

significantly less effective (erythromycin: Day 3 = 47% and Day 7 = 31%, P=0.02; and metoclopramide: Day 3 = 27% and Day 7 = 16%, P=0.02; Figure 11.2.2a). Erythromycin was associated with a greater success of feeding than metoclopramide at all time points (P=0.02), and patients treated with metoclopramide became feed-intolerant sooner than those treated with erythromycin (2.6 ± 0.2 days vs. 3.9 ± 0.3 days; respectively; P=0.01).

On an intention-to-treat analysis, erythromycin was also associated with more successful feeding than metoclopramide at all time points (P=0.005; Figure 11.2.2b). The factors that were associated with a poor response to monotherapy are summarised in Table 11.2.2. Taking into account treatment effects, only a high pre-treatment GRV was found to be a significant predictor of poor response to monotherapy (P=0.01; hazard ratio = 1.13 (CI: 1.03, 1.24)).

Table 11.2.2 Factors associated with a poor response to erythromycin or metoclopramide therapy.

	Global P-value	**Control for treatment effects** P-value; hazard ration (CI)
High pre-treatment GRV	0.006	0.01; 1.13(1.03-1.24)
On inotropic therapy	0.03	0.08; 1.53(0.94-2.51)
High blood glucose level	0.04	0.16; 0.9 (0.77-1.04)
On insulin therapy	0.04	0.12; 1.51(0.9-2.5)
Higher degree of hypoalbuminemia	0.02	0.08; 1.03(0.99-1.07)
High APACHE II score on admission	0.05	0.19; 1.03(0.99-1.07)

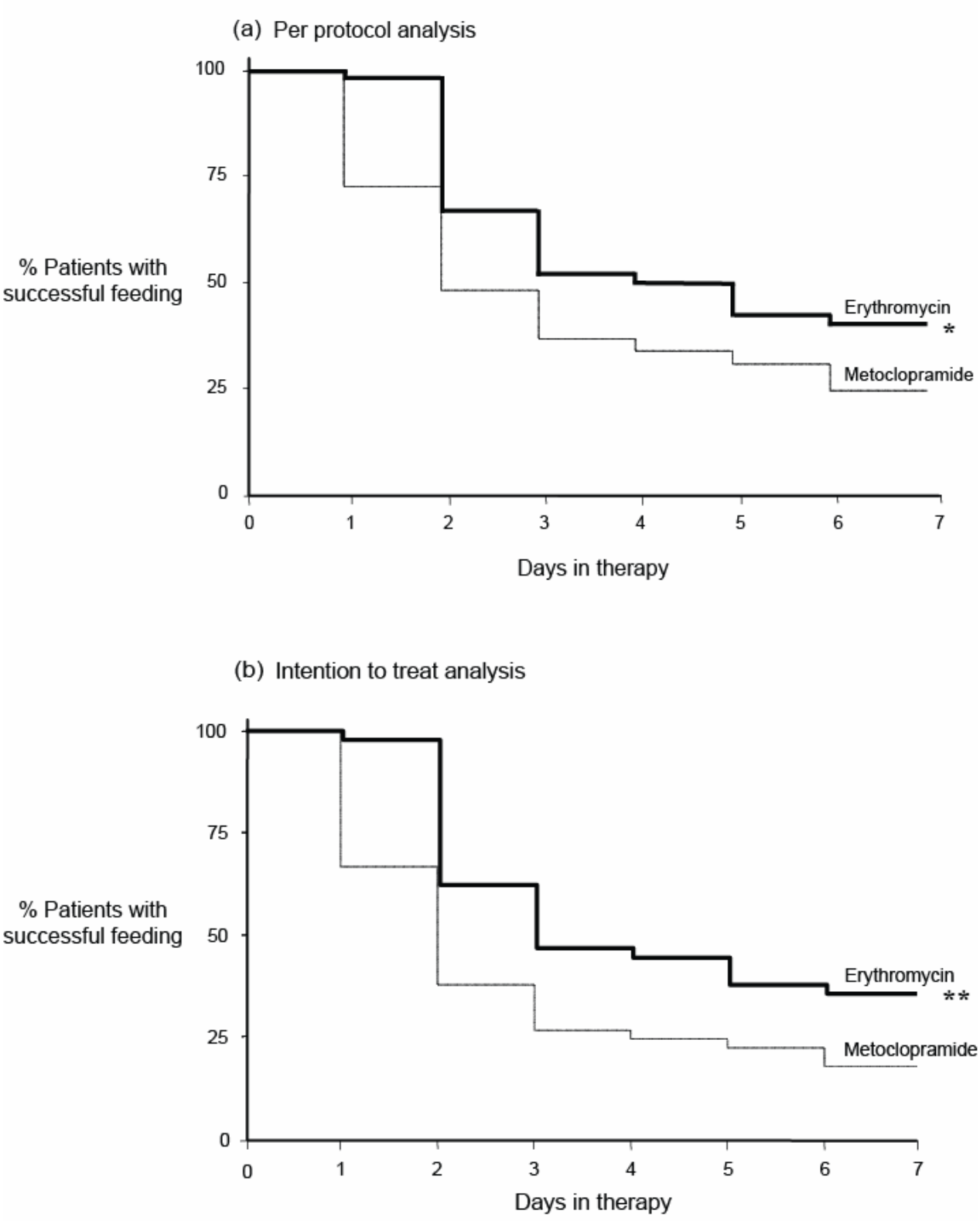


Figure 11.2.2 The effectiveness of erythromycin and metoclopramide on the success of feeding over the 7 days, based on (a) *per protocol* analysis and (b) *intention to treat* analysis. * P<0·05, ** P<0·01; vs. metoclopramide.

11.2.3.3 Effectiveness of combination therapy on the success of gastric feeding in patients who failed monotherapy

Fifty seven of the 67 patients who failed monotherapy were enrolled into open-label combination therapy. Six of these patients were excluded from the final analysis due to their short (< 48 hours) participation in this phase of the study (early recovery=4; death=2). The mean duration of combination therapy was 4.8 ± 0.2 days. The characteristics of patients who received rescue combination therapy are summarized in Table 11.2.3.

After 24 hours of combination therapy, enteral feeding was successful in 47 (92%) of the patients who had failed monotherapy. Patients continued to be fed successfully for the first 5 days (Day 3: 89%; and Day 5: 71%; P>0·05), but the therapy became less effective by Day 6 (67%, P=0.03; Figure 11.2.3). Overall, 10 of the 13 patients who failed monotherapy eventually required insertion of a post-pyloric feeding tube for ongoing nutritional support. There were no factors associated with a poor response to "rescue" combination therapy identified on Cox regression analysis.

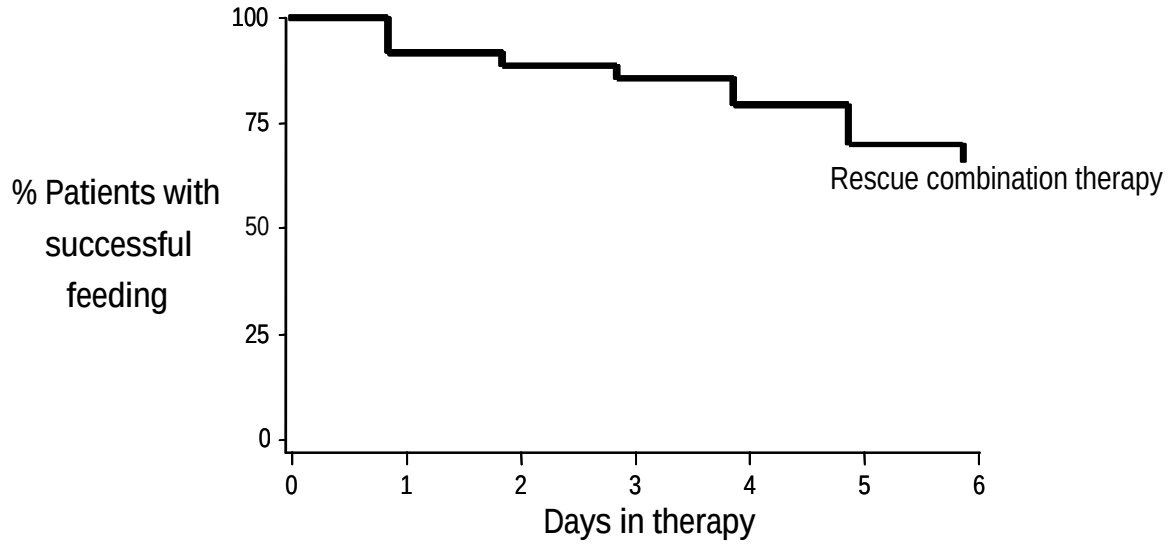


Figure 11.2.2 Effectiveness of rescue combination therapy on the success of feeding in patients who failed to respond to monotherapy.

Table 11.2.3 Demographic characteristics of critically ill patients who were treated with rescue combination therapy with erythromycin and metoclopramide.

	Rescue Combination Therapy (n=51)
Age (yr)	49 ± 3
Gender (M:F)	34:17
Body mass index (kg/m^2)	27.2 ± 0.5
Days in ICU prior to study	5.6 ± 0.7
APACHE II score	
Admission	25.0 ± 0.9
Study day	21.8 ± 0.9
Prior total GRV (mL)	723 ± 35
DIAGNOSIS [a] (% (n))	
Sepsis	51% (26)
Respiratory failure	80% (41)
Trauma	33% (17)
Renal failure	23% (12)
Head injury	23% (12)
Burns	12% (6)
Diabetes mellitus	12% (6)
Blood glucose level (mmol/L)	7.3 ± 0.2
Serum creatinine (mmol/L)	0.123 ± 0.01
Medications (% (n))	
Opioid ± Benzodiazepine	78% (40)
Propofol	35% (18)
Inotropes	57% (29)
Insulin (actrapid infusion)	69% (35)
Mode of ventilation	
SIMV (% (n))	51% (29)
Pressure support (% (n))	49% (22)
Positive end expiratory pressure (cmH_2O)	8.5 ± 0.6
Positive inspiratory pressure (cmH_2O)	21.7 ± 1.5

[a] More than one diagnosis possible in any patient. SIMV= Synchronized, intermittent, mandatory ventilation

11.2.4 DISCUSSION

This is the first prospective, double blind, randomised controlled trial comparing erythromycin and metoclopramide in the management of feed intolerance in critically ill patients. The results show that (i) erythromycin is significantly more effective than metoclopramide in the short term treatment of feed intolerance, (ii) tachyphylaxis develops rapidly with the use of both drugs, and (iii) combination therapy is highly effective in patients who have failed monotherapy. The current study demonstrates that metoclopramide is a relatively ineffective prokinetic agent, particularly after the first 48 hours of therapy. On the other hand, consistent with previous findings (Dive, *et al.* 1995; Jooste, *et al.* 1999; Chapman, *et al.* 2000; MacLaren, *et al.* 2000; MacLaren, *et al.* 2001; Reignier, *et al.* 2002), low dose erythromycin was highly effective as initial therapy for feed intolerance in critical illness. Furthermore, critically ill patients treated with erythromycin remained tolerant to NG feeding longer than patients who were treated with metoclopramide (4 versus 2 days). This greater efficacy of erythromycin has also been observed in diabetic patients with gastroparesis (Erbas, *et al.* 1993). The greater efficacy of erythromycin over metoclopramide in the current study suggests a revision of the current recommendation that metoclopramide should be the first line therapy for feed intolerance in critical illness (Booth, *et al.* 2002; Doherty and Winter 2003; Karamanolis and Tack 2006; Roberts, *et al.* 2006), and that erythromycin should be the preferred prokinetic agent in the treatment of feed intolerance.

There are a number of interesting findings in the current study, including the speed with which tachyphylaxis developed such that monotherapy with either drug became relatively ineffective after only 3 days of therapy, and the sustained effectiveness of treatment with combination therapy in patients who failed monotherapy. Failure of sustained gastrokinetic agents has

been reported in other clinical situation with these agents. Tachyphylaxis has been reported two weeks after commencing oral metoclopramide (Schade, *et al.* 1985), and similarly, after three weeks of oral erythromycin (Janssens, *et al.* 1990) for the treatment of diabetic gastroparesis. Although a decline in the effectiveness of erythromycin has been reported in critically ill patients (Boivin and Levy 2001; Reignier, *et al.* 2002), the rapid development of tachyphylaxis within the first three days of therapy in the current study was unexpected. The mechanisms underlying this rapid loss of effectiveness of erythromycin and metoclopramide are unclear, but may relate to the down-regulation, desensitization and endocytosis of neuro-humoral receptors (Thielemans, *et al.* 2005; Lamian, *et al.* 2006).

The sustained effect of combination therapy in patients who failed enteral feeding on two occasions was also unexpected. The control of gastric emptying is complex and highly regulated by multiple neuro-humoral pathways (Kellow 2003). The mechanisms underlying the diminished tachyphylaxis with combination therapy are not known, but may relate to the actions of the prokinetic agents on multiple pathways that involve in the regulation of gastric motility. A well recognised technique to prevent the development of drug resistance or tachyphylaxis in the treatment of infection and neoplasia is the use of a combination of drugs with different modes of actions (Kannan 2004; Komarova and Wodarz 2005). In the current study, the combination of metoclopramide and erythromycin was highly successful in preventing tachyphylaxis. Although the treatment was open-label, the highly sustained response to combination therapy suggests this approach should be considered for feed-intolerant patients who fail monotherapy. The findings suggest a potential role for combination therapy as the first line therapy for feed intolerance in critical illness, which

should be further investigated. Furthermore, they may indicate a strategy for developing pharmaco-therapeutic agents in the future.

Factors associated with poor response to prokinetic therapy from the current study are consistent with the previous findings (Bech, *et al.* 1984; Valenzuela and Dooley 1984; Heyland, *et al.* 1995; MacLaren 2000; Mentec, *et al.* 2001; Mutlu, *et al.* 2001). The severity of patient's critical illness, as reflected by high APACHE II score and the requirement of inotropic support, has been reported to correlate with the severity of disturbed gastrointestinal motility and feed intolerance (Bech, *et al.* 1984; Valenzuela and Dooley 1984; Heyland, *et al.* 1995; MacLaren 2000; Mentec, *et al.* 2001; Mutlu, *et al.* 2001). Inotropic medications are also well recognised to inhibit gastric motility and emptying (Bech, *et al.* 1984; Mentec, *et al.* 2001). In this study, high pre-treatment GRV was a significant predictor of poor response and may potentially reflecting the severity of gastric dysmotility in these patients. The finding that patients who had high blood glucose concentrations responded poorly to prokinetic therapy is consistent with previous report (Bech, *et al.* 1984; Jones, *et al.* 1999; Rayner, *et al.* 2000; Mentec, *et al.* 2001), which demonstrated that hyperglycemia attenuate the pro-motility effects of erythromycin.

In conclusion, although erythromycin is more effective than metoclopramide in the treatment of feed intolerance in critical illness, the effectiveness of both drugs diminishes rapidly over time. In patients who fail to respond to these agents, combination therapy is highly effective, and its efficacy is sustained for at least five days. The role of combination therapy as a first line therapy should be further investigated.

11.3 THE EFFECTS OF COMBINATION OF ERYTHROMYCIN AND METOCLOPRAMIDE ON THE SUCCESS OF FEEDS

11.3.1 INTRODUCTION

There are no previous data on the role of combining prokinetic agents in the management of feed intolerance in critically ill patients. In particularly, the efficacy of combining the currently available prokinetic agents, erythromycin and metoclopramide, as first line therapy has not been evaluated. The high rate of success in feeding with combined erythromycin and metoclopramide in patients who previously failed monotherapy supports the hypothesis that combination therapy may be a more effective first line approach (Chapter 11.2). The aims of the current study, therefore, were to: (i) compare the effectiveness of combination therapy, as a first line therapy, against erythromycin alone for feed intolerance of critical illness, and (ii) determine factors associated with resistance to treatment in this group of patients.

11.3.2 METHODS

11.3.2.1 Subjects

Seventy five consecutive, mechanically ventilated patients who failed NG feeding were enrolled into the study between October 2005 and June 2006. The definition of 'failure of feeding', the type of enteral nutrition, feeding protocol and exclusion criteria in the current study were identical as that outline in Chapter 6 and Chapter 11.2.

11.3.2.2 Protocol

The study was conducted as a 2 way randomised, double blind, parallel group study comparing the 7 day effectiveness of combination therapy with metoclopramide (10 mg IV qid) and erythromycin (200 mg IV bd) against erythromycin alone (200 mg IV bd, plus 4 placebo injections (0.9% normal saline) for blinding purposes) in improving the success of NG feeding in feed-intolerant, critically ill patients. The study drugs were administered at 0400 h, 1000 h, 1600 h, and 2200 h.

The protocols on drug randomization, preparation, administration, enteral feeding, and technique of monitoring gastric residual volumes were identical to those in Chapter 11.2. After patients received the first dose of either combination therapy or erythromycin alone, NG feeding was recommenced at an initial rate of 40 mL/hr, and subsequently adjusted as described in Chapter 6 and Chapter 11.2.

11.3.2.3 Data analysis

As in the previous study, the following data were collected prospectively over the 7 days of treatment: 6 hourly GRVs, amount of daily prescribed feeds, amount of daily administered feeds, occurrence of vomiting, the need for post-pyloric tube insertion and feeding, length of hospital stay and hospital mortality. Potential side effects of therapy were also noted. The definitions of "successful" and "failure" feeding were identical to those in Chapter 11.2. Both intention to treat (ITT) and per protocol (PP) analyses are reported. All enrolled patients (n=75) were included in the ITT analysis, whilst only patients who participated in the trial for 7 days (n=61) were included in the PP analysis.

11.3.2.4 Statistical analysis

Based on the results in Chapter 11.2, the difference in the rate of successful feeding between combination therapy and erythromycin alone was estimated to be approximately 40% (PP analysis). A *priori* power calculations based on this difference, indicated that at least 60 patients (30 patients in each arm) would be required in the PP analysis (ie. patients who completed 7 day study) in order to demonstrate a statistically significant difference with an α–value of less than 0.05 and β value of 80%. In addition, as it was expected that not all enrolled patients would complete the 7 day study, patients were recruited until at least 60 patients were included in the per-protocol analysis. The study code was not broken until the completion of the study. Similar statistical tests to those reported in Chapter 11.2 were used to assess the differences between the groups.

11.3.3 RESULTS

In the ITT analysis, 37 were randomised to combination therapy and 38 to erythromycin alone therapy. The demographic characteristics and admission diagnoses are summarised in Table 11.3.1.

In PP analysis, 14 patients (combination therapy (n=7) and erythromycin therapy (n=7)) were excluded because their participation in the trial was $\leq$ 48 hours. The reasons for early withdrawal of enteral feeding included (i) recovery and ability to tolerate oral feeds (combination therapy=5, erythromycin alone=4) and (ii) death after withdrawal of medical therapy (combination therapy =2, erythromycin alone=3). Of the 61 patients who completed the 7 days, 30 received combination therapy and 31 patients received erythromycin alone. Patient's demographics and characteristics were similar between the two groups (Table 11.3.2).

Table 11.3.1 Demographics and characteristics of critically ill patients included in *intention-to-treat* analysis.

	Combination therapy (n=37)	**Erythromycin alone (n=38)**
Age (yr)	50.9 ± 3.4	52.1 ± 4.1
Gender (M:F)	29 : 8	24 : 14
BMI (kg/m^2)	27.2 ± 0.8	26.9 ± 1.0
Days in ICU prior to study	6.8 ± 1.2	5.0 ± 0.7
APACHE II score		
Admission	26.5 ± 1.0	26.2 ± 1.0
Study day	23.0 ± 0.9	22.6 ± 1.2
Enteral feeding rate before study (mL/hr)	47 ± 3	44 ± 3
Days to intolerance	3.9±0.8	3.0±0.7
Diagnosis [a] (% (n))		
Sepsis	47% (18)	55% (21)
Respiratory failure	70% (26)	63% (24)
Trauma	29% (11)	38% (10)
Renal failure	8% (3)	18% (7)
Head injury	24% (9)	42% (16)
Burn	8% (3)	0% (0)
Diabetes mellitus	8% (3)	5% (2)
Blood glucose level on study day (mmol/L)	8.4 ± 0.3	8.5 ± 0.3
Serum creatinine on study day (mmol/L)	0.098 ± 0.01	0.110 ± 0.02
Admission serum albumin (mmol/L)	23.9 ±0.9	23.7± 1.0
Medications (% (n))		
Opioid ± Benzodiazepine	75% (28)	74% (28)
Propofol	41% (15)	50% (19)
Inotropes	56% (21)	63% (24)
Insulin (actrapid infusion)	70% (26)	55% (29)
Method of ventilation		
SIMV (% (n))	38% (14)	47% (18)
Pressure support (% (n))	62% (23)	52% (20)
Positive end expiratory pressure (cmH2O)	8.6 ± 0.5	8.0 ± 0.7
Positive inspiratory pressure (cmH_2O)	22.9 ± 1.4	23.3 ± 1.3

[a] More than one diagnosis possible in any patient

Table 11.3.2 Demographics and characteristics of critically ill patients included in *per-protocol* analysis.

	Combination therapy (n=30)	**Erythromycin alone (n=31)**
Age (yr)	52.1 ± 2.1	49.9 ± 2.5
Gender (M:F)	22 : 8	21 : 10
BMI (kg/m^2)	27.5 ± 0.6	27.4 ± 0.7
Days in ICU prior to study	7.3 ± 1.0	5.0 ± 0.5
APACHE II score		
Admission	26.9 ± 0.7	26.1 ± 0.7
Study day	22.8 ± 0.5	22.7 ± 0.7
Enteral feeding rate before study (mL/hr)	45 ± 2	43 ± 3
Days to intolerance	3.7 ± 0.9	3.2 ± 0.8
Diagnosis [a] (% (n))		
Sepsis	53% (16)	48% (15)
Respiratory failure	70% (21)	61% (19)
Trauma	26% (8)	26% (8)
Renal failure	10% (3)	19% (6)
Head injury	23% (7)	42% (13)
Diabetes mellitus	10% (3)	6% (2)
Blood glucose level (mmol/L)	8.3 ± 0.3	8.5 ± 0.2
Serum creatinine (mmol/L)	0.092 ± 0.01	0.107 ± 0.01
Admission serum albumin (mmol/L)	23.2 ± 0.9	23.7 ± 0.8
Medications (% (n))		
Opioid ± Benzodiazepine	73% (22)	72% (22)
Propofol	41% (13)	40% (13)
Inotropes	60% (18)	58% (17)
Insulin (actrapid infusion)	66% (20)	71% (22)
Method of ventilation		
SIMV (% (n))	46% (14)	48% (15)
Pressure support (% (n))	54% (16)	52% (16)
Positive end expiratory pressure (cmH2O)	8.7 ± 0.4	8.3 ± 0.5
Positive inspiratory pressure (cmH2O)	26.1 ± 1.0	24.2 ± 0.8

[a] More than one diagnosis possible in any patient

11.3.3.1 Gastric residual volumes (GRVs) before and after 24h of treatment

On both ITT and PP analyses, GRVs decreased significantly after 24 hours of treatment with both regimens (ITT & PP: P<0.0001) (Figure 11.3.1). The GRVs in patients treated with combination therapy were significantly smaller than those treated with erythromycin alone (ITT: P=0.034; PP: P=0.02).

11.3.3.2 Success of gastric feeding over the 7 days

On both ITT and PP analyses, combination therapy was associated with significantly greater success of feeding than erythromycin alone, at all time points (Figure 11.3.2). Successful enteral feeding was achieved in almost all patients after 24 hours of therapy. Over time, both treatments became less effective, with a marked reduction in the rate of successful feeding by day 7. Failure of therapy occurred earlier in patients treated with erythromycin alone (4.5 ± 0.5 days), compared to those treated with combination therapy (6.5 ± 0.5 days; P=0.003).

11.3.3.3 Factors associated with poor response

After controlling for treatment effects, only sedation with opioid and/or benzodiapines (RR=3.3, CI: 1.3-8.2; P=0.01), high pre-treatment GRV (RR=1.20, CI: 1.09-1.30; P=0.02) and degree of hypo-albuminemia (RR=1.10, CI: 1.03-1.19; P=0.01) were significant predictors of a poor response to prokinetic therapy. Higher APACHE II scores were associated with a poor response on uni-variate analysis (P=0.01), but not after controlling for treatment effects (P=0.18).

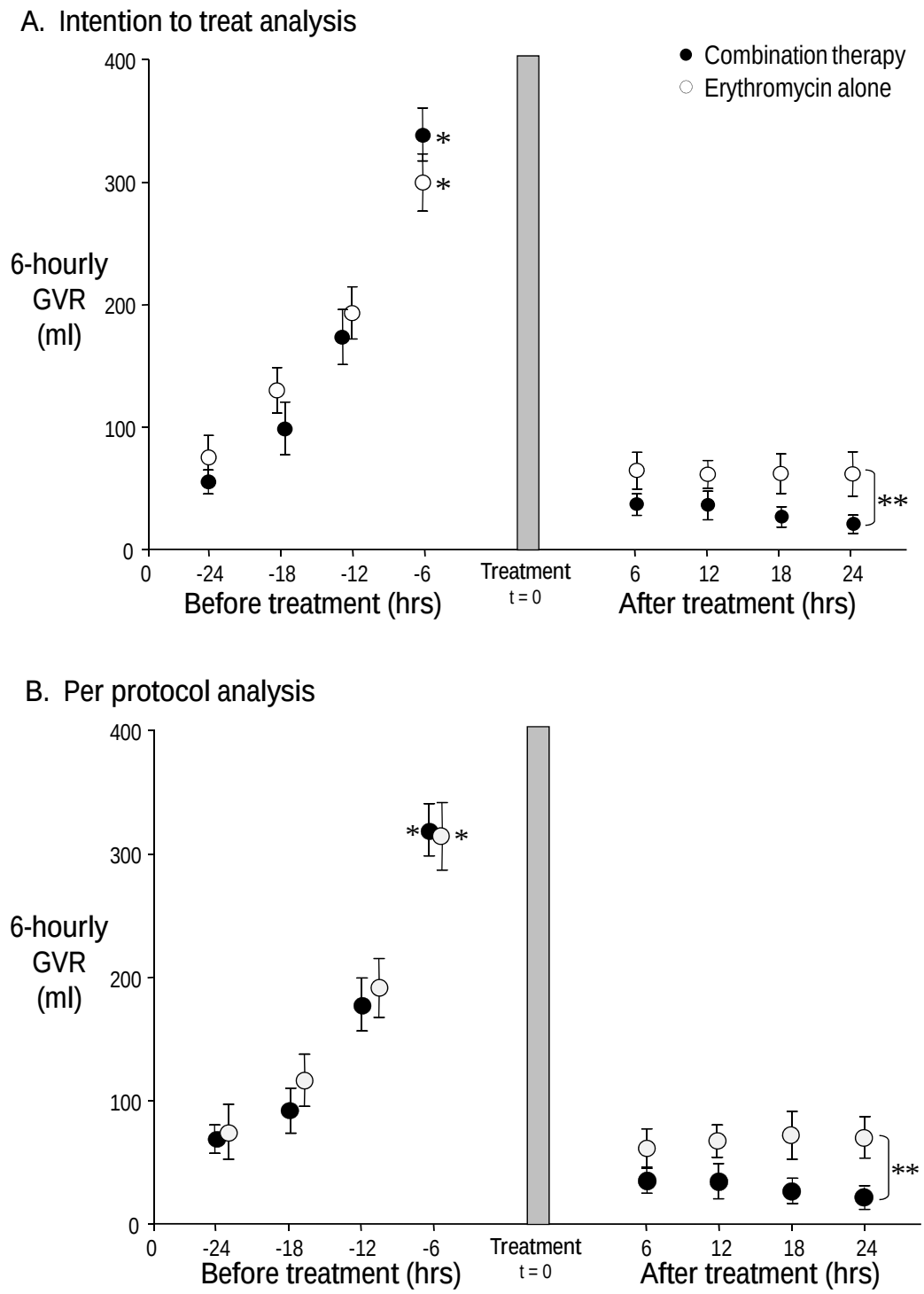


Figure 11.3.1 Six hourly gastric residual volumes (GRVs) during the 24 hours immediately before (pre-treatment) and after the commencement of either (i) combination therapy or (ii) erythromycin alone, based on intention to treat (A) and per protocol analyses (B). * P<0.0001, GRVs 24 hrs before versus after treatment of either combination or erythromycin alone therapy; ** P<0.05, erythromycin vs. combination therapy 24 hrs after treatment.

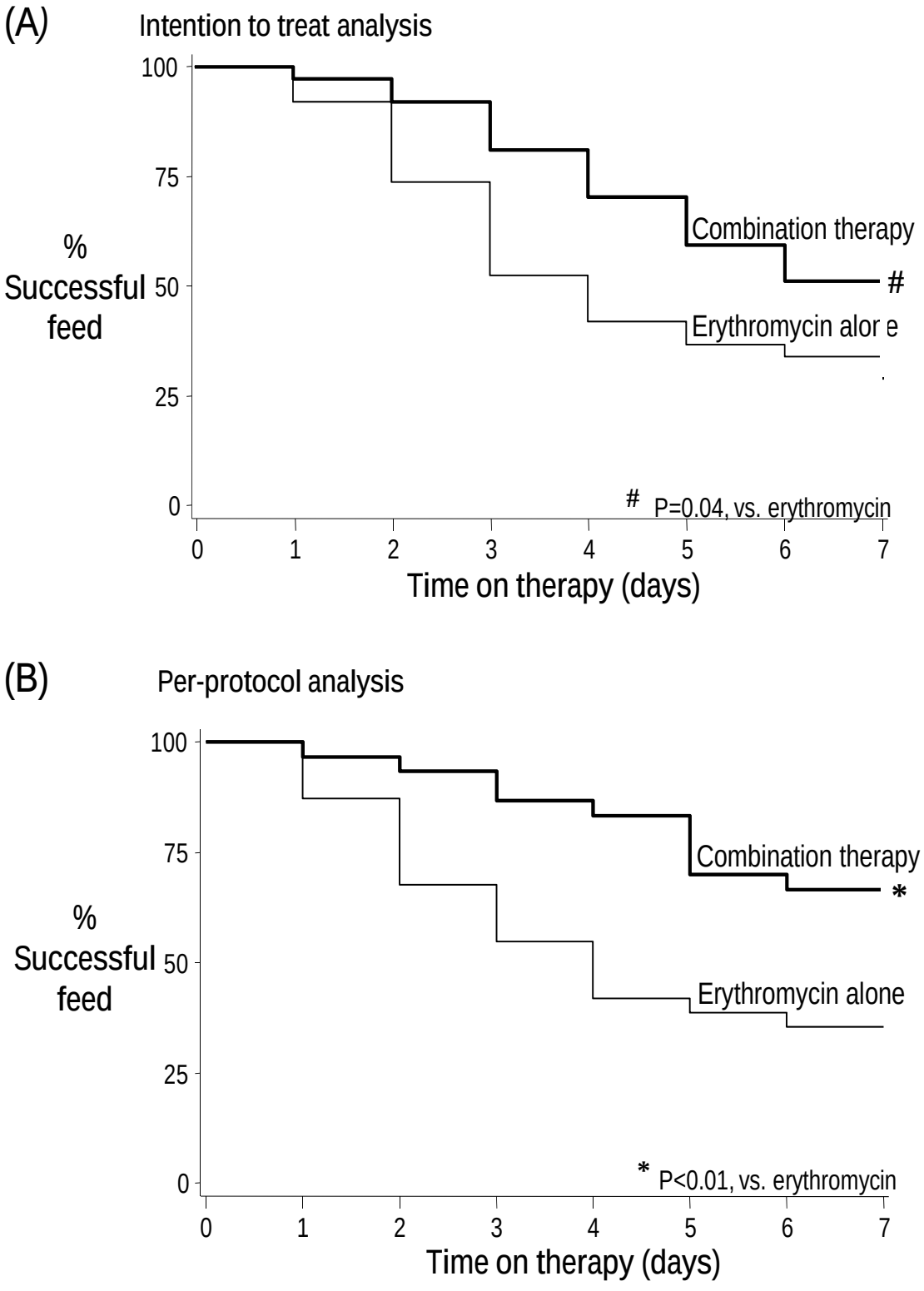


Figure 11.3.2 Kaplan-Meier plots of the effectiveness of combination and erythromycin alone therapy on the success of feeding over the 7 days, based on intention to treat (A) and per protocol analyses (B).

11.3.3.4 Adequacy of caloric intake over 7 days

Over the 24 hours prior to treatment, feed-intolerant patients received only one quarter of their prescribed calories. Both therapies significantly increased the amount of calories delivered to the patients, an effect which was most pronounced in the first 3 days of therapy (Figure 11.3.3). Thereafter, however, the amount of calories delivered to the patients gradually reduced, particularly in those patients treated with erythromycin alone. Overall, patients treated with combination therapy received a significantly greater proportion of their prescribed calories than those treated with erythromycin alone, on both ITT (P=0.02) and PP (P<0.001) analyses.

11.3.3.5 Secondary outcomes

On both ITT and PP analyses, patients treated with combination therapy were less likely to require post-pyloric tube insertion for ongoing enteral nutritional support, compared to those treated with erythromycin alone (Table 11.3.3). However, there were no differences in the rate of vomiting, length of stay in hospital, or death in hospital between the groups.

Table 11.3.3 The impact of combination therapy and erythromycin alone on secondary outcomes, based on both ITT and PP analyses.

	***Intention to treat* analysis**		***Per protocol* analysis**	
	Combination (n=37)	**Erythromycin (n=38)**	**Combination (n=30)**	**Erythromycin (n=31)**
Post-pyloric feeds (% (n))	5% (2)	21% (8) *	7% (2)	25% (8) *
Vomiting (% (n))	5% (2)	13% (5)	7% (2)	12% (4)
LOS in hospital (days)	53.0 ± 6.1	47.8 ± 9.1	57.2 ± 5.7	49.3 ± 8.6
Death in hospital (% (n))	22% (8)	26% (10)	20% (6)	22% (7)

* P<0.05, vs. combination therapy. LOS – length of stay

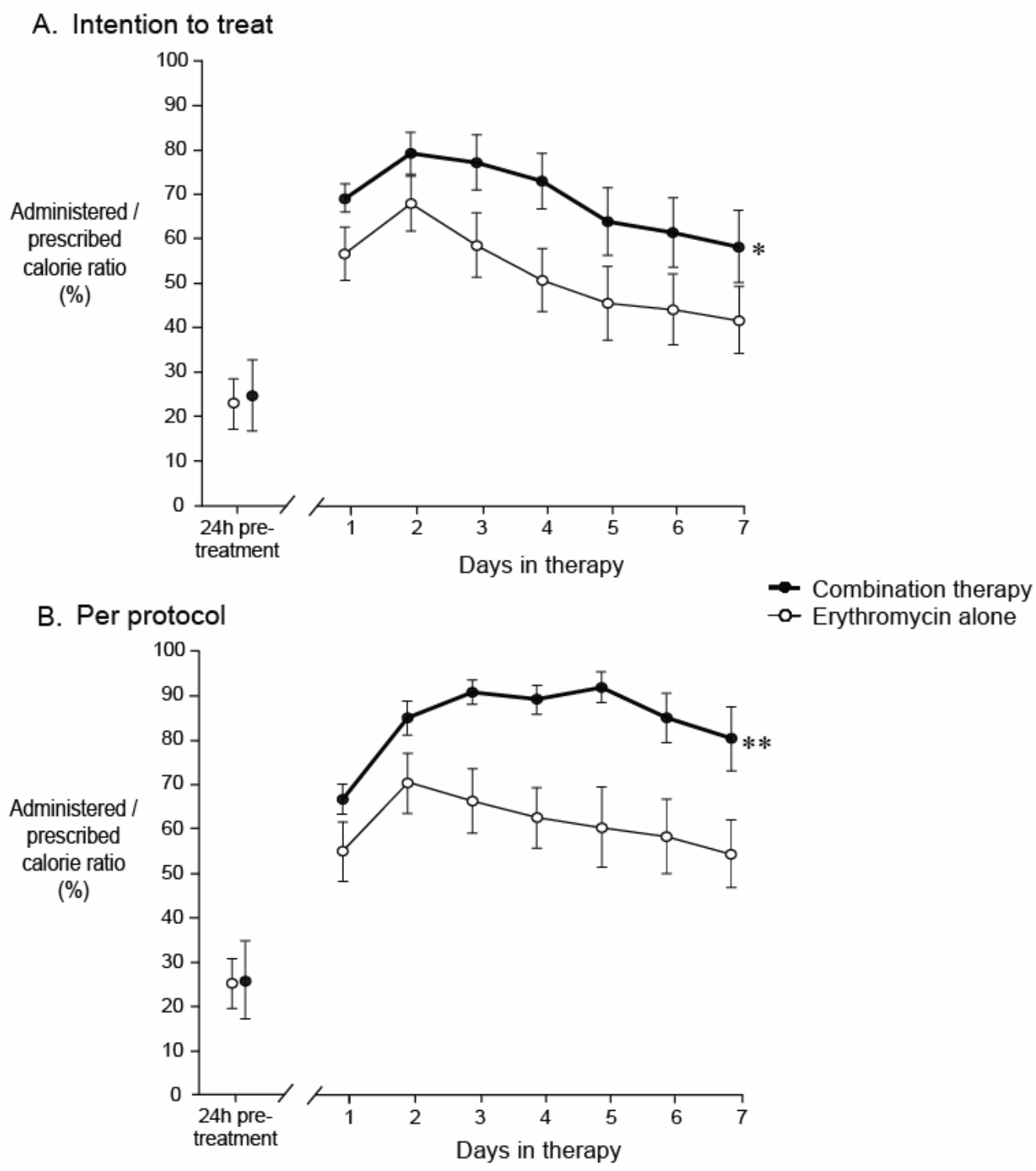


Figure 11.3.3 The effect of combination therapy and erythromycin alone on the percentage of administered/prescribed calorie over the 7 days, based on (A) intention to treat and (B) per protocol analyses. * P= 0.02 vs. erythromycin; ** P<0.001 vs. erythromycin

11.3.4 DISCUSSION

The current study is the first prospective, double blind, randomised controlled trial to examine the impact of combination therapy with erythromycin and metoclopramide as the first line treatment on the outcomes of critically ill patients intolerant of enteral feeding. The major findings were that, compared to erythromycin alone, combination therapy was (i) significantly more effective in improving the success of feeding, with a lesser degree of tachyphylaxis, (ii) associated with the delivery of a significantly greater percentage of prescribed feed to the patients during treatment, (iii) associated with a reduced need for post-pyloric feeding, and (iii) not associated with major adverse effects. Together, these findings demonstrate that combination therapy is more effective in improving the outcomes of enteral feeding than those of erythromycin alone, and suggest it should be considered as primary therapy for feed intolerance in critical illness.

In the current study, the reasons for the enhanced gastric emptying seen with the combination of metoclopramide and erythromycin are unclear, but may relate to complex interactions between the multiple mechanisms of the two prokinetic agents (Kellow, *et al.* 2006). The two agents are likely to modulate gastric motor function by a number of neuro-humoral pathways including dopaminergic, cholinergic pathway, and serotonergic pathways, as well as motilin receptors on vagus nerve and gastric smooth muscle (Chapter 4). It is also conceivable that these interactions between multiple regulatory mechanisms may lessen the degree of tachyphylaxis and thereby, improve the effectiveness of the combination therapy overtime compared to erythromycin alone. As previously observed with the long-term use of oral erythromycin (Janssens, *et al.* 1990; Erbas, *et al.* 1993), the effectiveness of intravenous erythromycin as a single agent reduces rapidly over time (Chapter 11.2), a phenomenon that

may involve down regulation, desensitization and endocytosis of neuro-humoral receptors in response to ongoing exposure of erythromycin (Thielemans, *et al.* 2005). Furthermore, the complementary actions of the two prokinetic agents may also play a role in the enhanced gastric emptying as well as the lesser degree of tachyphylaxis (Buchheit, *et al.* 1985; Sanger and King 1988; Kellow, *et al.* 1999; Curry, *et al.* 2001). This concept is consistent with pharmacological treatment of infection and neoplasia, where the use of a combination of drugs with different modes of action is a well recognised approach to prevent development of drug resistance (Kannan 2004; Komarova and Wodarz 2005).

The factors associated with a poor response to prokinetic therapy that were identified in the current study are also consistent with previous findings (Chapter 11.2) (Heyland, *et al.* 1996; MacLaren 2000; Mutlu, *et al.* 2001). Sedation with opiates or benzodiazepines severely inhibits gastric motility and emptying (Heyland, *et al.* 1996; MacLaren 2000; Mutlu, *et al.* 2001). In the absence of specific antagonists, these agents are likely to antagonize the beneficial effect of prokinetic therapy. It is also possible that poor response seen with high pre-treatment gastric residual volumes reflect the severity of motor dysfunction in these patients. The association between hypo-albuminemia and a poor response to prokinetic therapy also suggests the importance of illness severity, as reflected by APACHE II scores in the pathogenesis of gastrointestinal dysmotility and feed intolerance (Heyland, *et al.* 1996; MacLaren 2000; Mutlu, *et al.* 2001).

In the current study, the most important clinical finding was the positive translation of the higher rate of successful feeding during combination therapy to a greater delivery of nutrients to patients. However, there was no improvement in survival or length of hospital stay.

Previous data suggest that adequate delivery of enteral nutrients in critically ill patients is associated with a lesser degree of mucosal atrophy and permeability, leading to a better mucosal barrier and a lesser risk of bacterial translocation and infection (Frost, *et al.* 1997; Hernandez, *et al.* 1999; Kompan, *et al.* 1999; De-Souza and Greene 2005). The reason for the lack of improvement in survival or length of hospital stay between the groups is unclear. It is, however, likely that a larger study would be necessary to show such an effect in light of the many other variables which impact on these outcomes.

Until now, the optimal dosage for IV erythromycin as a prokinetic agent remains unclear and has varied from 200 mg IV twice daily to 250 mg IV four times daily (Dive, *et al.* 1995; Chapman, *et al.* 2000; Berne, *et al.* 2002; Reignier, *et al.* 2002). In the current study, 200 mg IV twice daily was chosen because positive pro-motility effects have been demonstrated at such dosage (Chapter 11.2) (Chapman, *et al.* 2000)and to minimise the development of drug tachyphylaxis. Although erythromycin has a half life of only 1.5 hours, it increases antral motility for more than 5 hours (Dive, *et al.* 1995) and improves the success of feeding for up to 24 hours in critically ill patients (Chapman, *et al.* 2000).

Although the weaknesses of the practice of monitoring GRVs as an indirect measure of slow gastric emptying are acknowledged (McClave, *et al.* 2005), this technique remains a simple, convenience and inexpensive method to guide the delivery of enteral feeds (Heyland, *et al.* 2003). Especially, the current study used the 250 mL threshold GRV as an indication for therapy for feed intolerance rather than cessation of enteral feeds, and this volume has been used previously by many studies that have examined the effectiveness of various therapies in

the treatment of feed intolerance in critically ill patients (Chapman, *et al.* 2000; Yavagal, *et al.* 2000; Mentec, *et al.* 2001; Berne, *et al.* 2002).

In conclusion, combination therapy with erythromycin and metoclopramide is more effective than erythromycin alone in improving the provision of enteral nutrition, and should be considered as first line therapy in the treatment of feed intolerance in critical illness. Tachyphylaxis, however, remains a problem with this regime and further drug development is required to ensure successful feeding in all patients.

11.4 THE ADVERSE EFFECTS OF PROKINETIC THERAPY FOR FEED INTOLERANCE IN CRITICALLY ILL PATIENTS.

11.4.1 INTRODUCTION

Together with previous studies (Dive, *et al.* 1995; Chapman, *et al.* 2000; Boivin and Levy 2001; Berne, *et al.* 2002), the data in Chapter 11.2 and 11.3 clearly demonstrate that low dose erythromycin, particularly in combination with metoclopramide, is effective in the treatment of feed intolerance. However, before recommending erythromycin for routine clinical use, either as a single agent or in combination, the efficacy must be balanced against the adverse effects of the drugs. Thus, although a number of theoretical or potential problems have been raised, to date, the side effects of these prokinetic regimens have not been well characterised in critically ill patients when used for a prolonged period.

In addition to the cardiac adverse effect, low dose of erythromycin has been recently reported to associate with a reduction of 10mmHg in systolic blood pressure in healthy volunteers (Mangoni, *et al.* 2004). The hypotensive effect was thought to be mediated by motilin induce endothelial relaxation and a transient reduction in blood pressure. Although of minor concern in health, such reduction in systolic blood pressure may be clinically relevant in critically ill patients whose cardiovascular function is already compromised. To date, the effect of low dose erythromycin on the hemodynamics of the critically ill has not been examined.

Routine use of erythromycin as a prokinetic therapy in critical illness has also been cautioned because of concerns of *Clostridium difficile* (CD) diarrhoea (Dall'Antonia, *et al.* 2006) and

development of bacterial resistance (Guerin and Leibinger 2002; Dall'Antonia, *et al.* 2006; Hawkyard and Koerner 2007). Erythromycin induced CD diarrhoea is a particularly important concern because this complication carries significant consequences for morbidity (Kelly, *et al.* 1983; Grube, *et al.* 1987; Kelly, *et al.* 1994; Wilcox 2003), with a more prolonged stay in ICU and hospital. Despite these concerns, the impact of low dose erythromycin on either CD infection, diarrhoea or both has not been evaluated previously. The aims of current study was, therefore, to describe the adverse effects seen during the 7 day treatment with erythromycin, metoclopramide, and combination therapy for feed intolerance in critically ill patients, particularly the effects on the hemodynamics and the developments of CD diarrhoea.

11.4.2 METHODS

11.4.2.1 Subjects

This analysis incorporated the 183 mechanically ventilated, critically medical ill patients enrolled in studies described in Chapter 11.2 and 11.3. Three patients were excluded from analysis as they had received prokinetic therapy for less than 2 days. Of 180 feed-intolerant patients included in the final analysis, 53 received erythromycin alone, 37 metoclopramide alone and 90 combined erythromycin and metoclopramide therapy. The demographic characteristics, feeding rate, serum albumin, admission diagnosis, antibiotic and inotropic therapy and the mode mechanical ventilation were similar amongst the three therapeutic groups and are summarised in Table 11.4.1.

Table 11.4.1 Demographic characteristics and outcomes of feed intolerant, critically ill patients who were treated with (i) erythromycin (E) alone, (ii) metoclopramide (M) alone and (iii) combination (E&M) prokinetic therapy.

	METOCLOPRAMIDE (N=37)	**ERYTHROMYCIN (N=53)**	**COMBINED E&M (N=90)**
Age (yr)	48.9 ± 1.3	50.9 ± 1.5	50.0 ± 1.5
Gender (M:F)	25:12	33:20	64:26
Body mass index (kg/m^2)	27.0 ± 0.3	26.4 ± 0.4	271 ± 0.3
Admission APACHE II score	25.6 ± 0.4	25.6 ± 0.4	25.7 ± 0.4
Admission blood glucose (mmol/L)	7.7 ± 0.2	8.2 ± 0.1	7.8 ± 0.2
Admission serum albumin (g/L)	21.7 ± 0.5	23.4 ± 0.4	23.7 ± 0.5
Admission diagnosis § (% (n))			
Sepsis	65% (24)	57% (30)	51% (46)
Respiratory failure	73% (27)	60% (42)	76% (48)
Renal failure	19% (7)	15% (8)	17% (15)
MVA	14% (5)	28% (15)	31% (28)
Head injury	19% (7)	36% (19)	22% (20)
Burn	8% (3)	0% (0)	9% (8)
Multi-organ failure	19% (7)	11% (6)	14% (13)
Medications (% (n))			
Full strength antibiotics	73% (27)	70% (37)	79% (71)
- Treating infection : prophylaxis	17 : 10	23 : 14	42 : 29
Inotropic therapy	46% (17)	49% (26)	57% (51)
Opiates/Benzodiazepines	81% (30)	70% (37)	76% (68)
Propofol	46% (17)	43% (23)	37% (33)
Acid suppression therapy ¶	84% (31)	77% (41)	89% (80)
Mechanical ventilation			
SIMV mode (% (n))	49% (18)	42% (22)	51% (46)
Pressure support mode (% (n))	51% (19)	58% (31)	49% (44)
PEEP(mmHg)	8.5 ± 0.2	8.0 ± 0.3	8.7 ± 0.3
Ventilation rate (per min)	21.6 ± 0.6	22.9 ± 0.6	22.0 ± 0.5

§ A number of patients had more than 1 diagnosis; * $P<0.05$, vs. erythromycin and combination therapy ** $P<0.05$, vs. combination therapy; † $P=0.08$, vs. combination therapy. ¶ included either a proton pump inhibitor or a histamine receptor 2 antagonist.

11.4.2.2 Assessment of general adverse side effects

The development of all adverse effects related to the use of prokinetic therapy in the 180 patients was collected prospectively. In particular, the occurrence of injection reactions, dystonic or dyskinetic movements, tremors, hypotension or cardiac arrhythmia related to prolonged QT interval was recorded and confirmed from the case records and intensive care charts. The QT interval of all patients was determined from a 6-lead ECG performed on a daily basis.

11.4.2.3 Assessment of associated hemodynamic changes

A subgroup of 19 patients who did not receive inotropic therapy (52 ± 18 yr, 10M, APACHE II score: 21 ± 6, LOS ICU: 10 ± 9 days) but was with erythromycin alone for feed intolerance were selected to examine the acute effects of a single intravenous infusion of erythromycin on blood pressure (BP) and heart rate (HR). In a randomised, double blind, cross-over fashion, each patient received either erythromycin (IV 200 mg) or placebo (IV normal saline) 12 hours apart. Continuous lying BP (systolic (SBP) and diastolic (DBP)) and HR were measured, via an arterial line, at 15 minute intervals for 60 minutes prior to and 180 minutes after drug administration using an automatic device (TRAM-RAC 4A, General Electrical, Milwakee, USA). A reduction in blood pressure of more than 10% from baseline was defined as clinically significant.

11.4.2.4 Assessment of diarrhoea and CD infection

The development of clinically relevant diarrhoea within 1 month of the start of prokinetic therapy was determined. Diarrhoea was defined as frequent (≥ 3 times per day) loose, liquid stool with an estimated total daily volume of more than 250 mL (Chapter 6). The duration of diarrhoea, the time to develop diarrhoea after the start of therapy, the number of specimens

sent for laboratory investigation, the outcomes of microbial examinations and any required treatment were recorded. In all patients with diarrhoea, stool specimens were evaluated for blood, white cells, bacteria and parasites by microscopy, culture and special stains. In addition, all specimens were tested for CD toxins (both A and B) using combination enzyme immunoassays.

11.4.2.5 Statistical analysis

Categorical data were compared by Chi-square test with Yates' correction and continuous data by Student's t-test. The effects of erythromycin on BP and HR were analysed using a linear mixed effects model fitted to the data. In this model, group status (erythromycin or placebo) and time were treated as fixed effects, while the subject was treated as a random effect.

11.4.3 RESULTS

11.4.3.1 General adverse effects

There were no reports of injection reactions in any patient during the 7 day treatment period. In patients who received metoclopramide, either alone or in combination with erythromycin, no dystonia, dyskinetic movements or tremors were observed. There were no cardiac arrhythmias related to prolonged QT interval amongst any of the treatment groups.

11.4.3.2 Impact of erythromycin on hemodynamic status

There were no differences between erythromycin- and placebo-treated groups in baseline systolic (SBP: 132 ± 30 vs. 125 ± 18 mmHg, P=0.44), or diastolic (DBP: 62 ± 12 vs. 61 ± 10 mmHg, P=0.72) blood pressure or heart rate (HR: 93 ± 14 vs. 92 ± 14 bpm, P=0.70). There

was no changes in SBP (P=0.61), DBP (P=0.45), and HR (P=0.42) after either erythromycin or placebo throughout the 3 hours after the injection (Figure 11.4.1). The percentage change in blood pressure and heart rate from baseline in the erythromycin group was minimal (SBP= - 2.1%; DBP= - 1.6%; and HR= + 1.5%) and was similar to placebo.

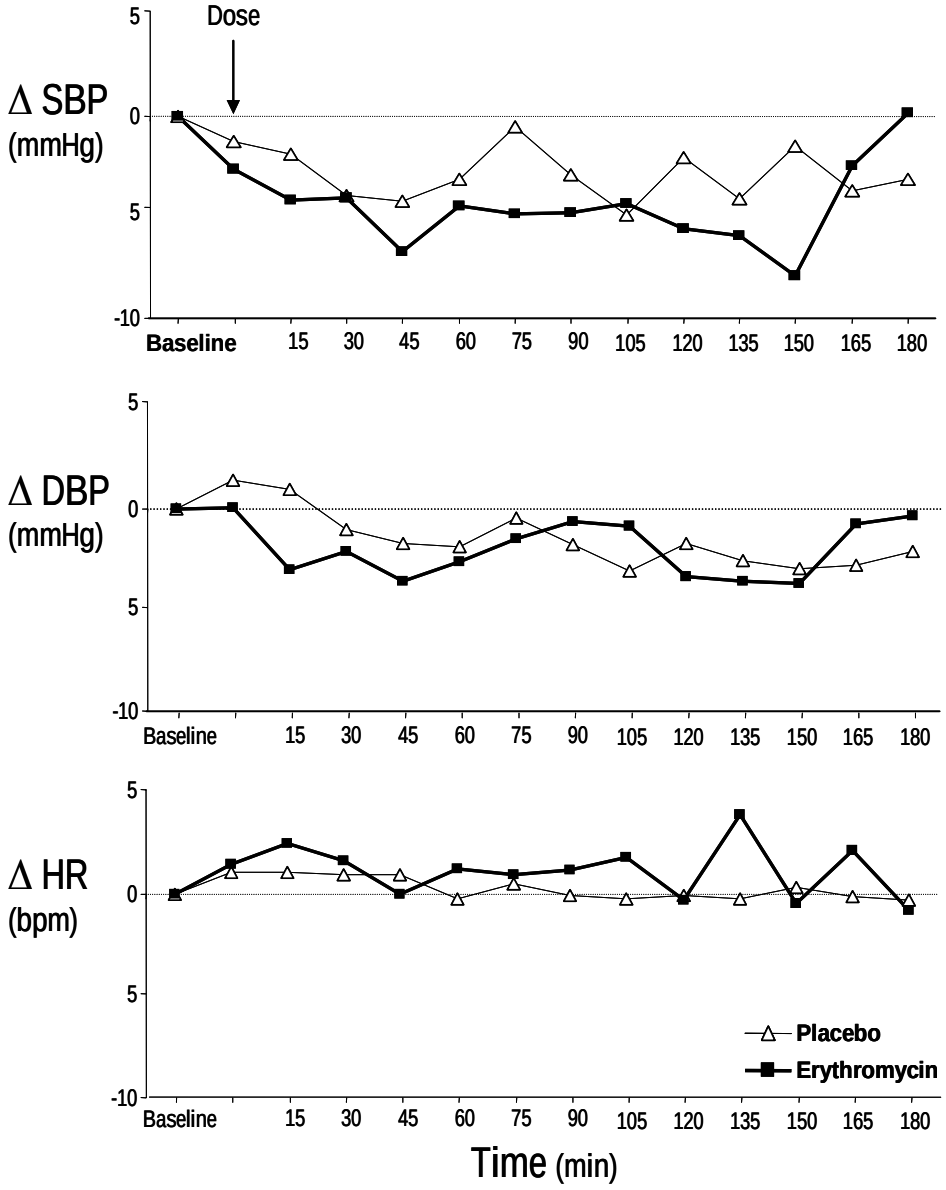


Figure 11.4.1 Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) after a single IV dose of erythromycin (200mg) and placebo (normal saline) in feed-intolerant, critically ill patients

11.4.3.3 Diarrhoea and Clostridium difficile infection

Diarrhoea developed in 40% (n=72) patients, at a mean of 9.9 ± 0.8 days after the commencement of prokinetic therapy. In patients who developed diarrhoea, 1.9 ± 0.4 stool specimens per patient were sent to the laboratory for microbial examination. None of the faecal specimens from these patients were positive for CD toxin, had leukocytes on microscopy or grew bacterial pathogens. Infections with *Blastocystic hominis* (n=2), *Dientamoeba fragilis* (n=1) and *Strongyloides stercoralis* (n=1) were found in 4 patients, who came from an area endemic for parasitic infection.

Diarrhoea was more common in patients treated with combination prokinetic therapy (49%) than in those treated with either erythromycin (30%) or metoclopramide alone (32%) (Table 11.4.2). This difference persisted even after excluding patients who received full strength antibiotic therapy for infection or prophylactically during admission (combination= 44% (8/18) vs. monotherapy= 19% (5/27); P=0.06). The incidence of diarrhoea was similar between patients who received single agent treatment with erythromycin or metoclopramide. Patients with watery diarrhoea were also more likely to have: (i) higher PEEP and ventilatory rate, (ii) significant burns, and (iii) significantly more enteral feeds during the course of prokinetic therapy. There was no association between use of acid suppressive therapy (either proton pump inhibitors or histamine 2 receptor antagonists) and diarrhoea. Age, gender, BMI and APACHE II score (either on admission or during therapy) also had no impact on the development of diarrhoea.

The mean duration of diarrhea was 3.6 ± 1.2 days and in most instances, the diarrhea resolved shortly after the cessation of the prokinetic therapy. The length of stay in ICU was significantly longer in patients who: (i) developed diarrhoea (19.8 ± 1.2 vs. 12.6 ± 0.5 days, P<0.001), and (ii) received combination therapy (17.0 ± 0.7 vs. 13.5 ± 0.9 vs. 14.0 ± 1.2 days; P<0.05) (Table 11.4.2). Interestingly, there was no correlation between the length of ICU stay and admission APACHE II score (P=0.51).

Table 11.4.2 Comparison in the development of diarrhea, length of stay in the ICU, and the volume of administered enteral feeds between the treatment groups.

	Metoclopramide (n=37)	**Erythromycin (n=53)**	**Combined E&M (n=90)**
Diarrhea			
- Frequency (n)	32% (12) †	30% (16) **	49% (44)
- Days after treatment	10.5 ± 0.8	9.3 ± 0.6	12.0 ± 0.9
- % of CD infection	0%	0%	0%
- Other infection detected (n)	Blastocystis hominis (1)	Strongyloides stercoralis(1); Blastocystis hominis (1)	Dientamoeba fragilis (1)
Length of stay in ICU (days)	14.0±1.2 **	13.5±0.9 **	17.0±0.7
Feeds delivered over 24 hrs (mL)			
Day 1	980 ± 49 *	1121 ± 45	1101 ± 36
Day 2	1119 ± 84 *	1370 ± 62	1435 ± 42
Day 3	1116 ± 97 *	1389 ± 70	1419 ± 51
Day 4	1100 ± 115 *	1371 ± 73	1409 ± 53
Day 5	1298 ± 98 *	1367 ± 92	1410 ± 57
Day 6	1327 ± 109	1340 ± 86	1458 ± 53
Day 7	1357 ± 116	1401 ± 86	1419 ± 69

** P<0.05, vs. combination therapy † P=0.08, vs. combination therapy

E&M – erythromycin and metoclopramide; CD – *Clostridium difficile*

11.4.4 DISCUSSION

Clinically, the use of erythromycin as a routine prokinetic agent has been applied cautiously, predominantly due to potential side effects and the concerns about CD infection and bacterial resistance (Kelly, *et al.* 1983; Tonini, *et al.* 1999; Guerin and Leibinger 2002; Dall'Antonia, *et al.* 2006). The current study indicates that the use of erythromycin and metoclopramide in the treatment of feed intolerance is relatively safe, with no major cardiac or lethal adverse effects. Although diarrhea was the most frequently observed side effect, it was not associated with CD infection. As the incidence of diarrhea was highest in patients who received combination therapy, the underlying cause of diarrhea in these patients may relate to the pro-motility effects of the therapies and the associated osmotic effects of increasing feed volumes reaching the distal small and large intestine. Contrary to recent findings in healthy volunteers (Mangoni, *et al.* 2004), low dose erythromycin has no impact on blood pressure and heart rate in critically ill patients. Thus, in view of the current limitation in the availability of prokinetic agents, these findings provide reassurance that it is reasonable to use erythromycin for feed intolerance in critically ill patients. The development of diarrhea in these patients, however, is an indication that prokinetics should be ceased and volume of feeds may need to be reduced.

In contrast to the effects of erythromycin on blood pressure and heart rate in healthy volunteers (Mangoni, *et al.* 2004), the current study was unable to detect any impact of erythromycin in critically ill patients. There are a number of reasons that may explain this apparent discrepancy. During fasting, the transient reduction in central blood pressure by erythromycin is believed to be related to its splanchnic vasodilatation effects (Berry, *et al.* 2003). In the current study, the hemodynamic effects of erythromycin were examined during continuous enteral feeding instead of fasting (Mangoni, *et al.* 2004). It is likely that nutrient

induced splanchnic vasodilatation was already present in these patients, and hence, erythromycin was unable to induce any further vasodilatation. The differences in posture (lying vs. erect) and route of administration of erythromycin (IV vs. oral) between the 2 studies may also have contributed to the differences in the results. Finally, whilst the possibility of a type 2 error exists, as the number of patients included in the analysis was small, the minimal effect on both absolute and percentage blood pressure relative to baseline indicate that any potential effect is unlikely to have a clinical importance.

Whilst the incidence of diarrhea in the current study is consistent with previous reports (Kelly, *et al.* 1983; Dobb 1986; Smith, *et al.* 1990; Wilcox 2003; Wiesen, *et al.* 2006), the proportion of diarrhea related to CD was lower than that of previous studies. Current data suggest that diarrhea occurs in between 12% and 25% of unselected enterally fed patients, and 10% of these cases are related to CD infection (Kelly, *et al.* 1983; Dobb 1986; Smith, *et al.* 1990; Wilcox 2003; Wiesen, *et al.* 2006). The reason for the lack of CD infection in the current study is unclear but may relate to the increased transit through the gastrointestinal tract caused by prokinetic therapy (Landry, *et al.* 1995), which may prevent colonization and growth of significant pathogens related to the use of antibiotics (Smith, *et al.* 1990; Ringel, *et al.* 1995). It is unlikely that CD infection was missed through insufficient testing as each patient with diarrhoea had at least 2 specimens sent, and the sensitivity of the CD cytotoxin immunoassays was high (87-90%) (Kelly, *et al.* 1983; Smith, *et al.* 1990; Ringel, *et al.* 1995). There were no patients who received sucrafate, an agent which is known to interfere with CD cytotoxin-B assays (Kelly, *et al.* 1983; Smith, *et al.* 1990; Jensen, *et al.* 1994; Kelly, *et al.* 1994; Ringel, *et al.* 1995).

In the context of reduced intestinal absorption (Smith, *et al.* 1990; McClave, *et al.* 1992; Ringel, *et al.* 1995; Hernandez, *et al.* 1999), reduced carbohydrate fermentation from altered bowel flora (Ringel, *et al.* 1995; Mutlu, *et al.* 2001) and the hyperosmolar effects of feeds (Ringel, *et al.* 1995; Mutlu, *et al.* 2001), the increased the rate of transit of feeds following prokinetic therapy (Landry, *et al.* 1995) in the critically ill patients may induce osmotic effects and cause diarrhea (Kelly, *et al.* 1983; Smith, *et al.* 1990; Ringel, *et al.* 1995; Mutlu, *et al.* 2001). Indeed, diarrhea is more frequent when enteral feeding rate is > 50 mL/hr (Smith, *et al.* 1990) and improves when the feeding rate is reduced (Kelly, *et al.* 1983; Ringel, *et al.* 1995). The current supports this concept as diarrhea was more prevalent in patients who received a greater volume of feeds. Finding that combination therapy was associated with a higher rate of diarrhea is consistent with the role of rapid transit and suggests the contribution of pro-motility agents, at least in part, in the etiology of diarrhea in these patients.

Other risk factors for diarrhea such as respiratory failure, hypo-albuminemia, and burns injury are also consistent with previous reports (Kelly, *et al.* 1983; Smith, *et al.* 1990; Ringel, *et al.* 1995; Mutlu, *et al.* 2001). Patients with burns were particularly at risk of developing diarrhea. This may relate to hypo-albuminemia, antibiotic use, and respiratory injury (Kelly, *et al.* 1983). In contrast to previous studies (Kelly, *et al.* 1983; Smith, *et al.* 1990; Cunningham, *et al.* 1991; Ringel, *et al.* 1995), the use of acid suppression in the current study was not associated with either CD infection or an increased incidence of diarrhea in the critically ill patients. The reason for the discordance with previous data is unclear, but may relate to the increased gastric and intestinal transit effect of prokinetic therapy, thereby preventing colonization of significant pathogens.

Consistent with previous reports (Kelly, *et al.* 1983; Smith, *et al.* 1990; Ringel, *et al.* 1995), diarrhoea in critically ill patients was associated with prolonged length of ICU stay. It seems unlikely that this is a direct consequence of the diarrhoea as the duration of diarrhoea in the patients was much shorter than the increase in length of stay. It is possible that the prolonged ICU stay in these patients is a reflection of a greater illness severity, as indicated by the higher incidence of respiratory failure, requiring ventilation with higher PEEP and ventilatory rate, in the diarrhoea group.

The findings in the current study have a number of clinical implications. First, the onset of diarrhea in these patients is an indication that prokinetics should be ceased and volume of feeds may need to be reduced. Second, given the incidence of diarrhea related to the "strength" of prokinetic effects, the role of reduced dosage or increased dosing interval of these prokinetic agents warranted further evaluation. Whilst recent data suggest that a single dose of 70 mg of erythromycin may be as effective as 200 mg in improving gastric emptying (Ritz, *et al.* 2005), its effectiveness and side effect profiles over longer term usage has not been investigated.

In summary, prokinetic therapy for treatment of feed intolerance is relatively safe in critically ill patients. Even with erythromycin, there are no major cardiac or hemodynamic adverse effects over the 7 day duration. Although watery diarrhea is the most common side effects of the treatment, it was not associated with CD infection but seems to relate to the pro-motility effects of the treatment. Prokinetic therapy, therefore, should be stopped at the onset of diarrhea and prophylactic use should be strictly avoided.

11.4 SUMMARY AND CONCLUSIONS

The clinical use of erythromycin as a routine prokinetic agent has been restricted currently due to both a lack of data on its effectiveness compared to other available prokinetic agents, and concerns regarding potential side effects (Kelly, *et al.* 1983; Grube, *et al.* 1987; Guenter, *et al.* 1991; Jensen, *et al.* 1994; Grundfest-Broniatowski, *et al.* 1996; Wilcox 2003; Wiesen, *et al.* 2006) and bacterial resistance (Burgess 1999; Guerin and Leibinger 2002; Dall'Antonia, *et al.* 2006). The findings in the current chapter clearly demonstrate that erythromycin is a more effective prokinetic agent for the clinical management of feed intolerance during critical illness, with no major adverse side effects. Whilst diarrhoea is a common side effect of both erythromycin and metoclopramide, it was not associated with CD infection and settled quickly after the cessation of the prokinetic therapy.

The possibility of combining erythromycin with metoclopramide, either as first line or rescue therapy for feed intolerance, was also examined in the current chapter. In feed intolerant patients who failed to response to either erythromycin or metoclopramide, rescue combination therapy was highly effective. The role of combination therapy as a first line therapy, however, is less clear. Although combination therapy is clearly more effective than either erythromycin or metoclopramide and has less tachyphylaxis, it is associated with a higher incidence of diarrhoea and a prolonged length of stay in ICU. On the other hand, the lesser effective monotherapy resulted in a greater incidence of feed intolerance, and delivered only a quarter of the daily nutritional requirement to the patients each time. The morbidity and mortality benefits associated with adequate nutritional support (Heyland 1998; Heyland, *et al.* 2003; Doig and Simpson 2005), would appear to outweigh the associated diarrhoea. In these patients, however, the development of diarrhoea usually results in cessation of prokinetic

therapy and possibly, a temporary reduction in the feeding rate. The data suggest that prokinetic drugs should be used in symptomatic patients and prophylactic use to prevent feed intolerance should be avoided.

Currently, effective and safe prokinetic agents that are available for treatment of feed intolerance are limited. If erythromycin is unavailable due to concerns of developing bacterial resistance (Guerin and Leibinger 2002; Dall'Antonia, *et al.* 2006), the only available therapy for feed intolerance presently is metoclopramide, which is a relatively ineffective prokinetic agent. Although cisapride has been reported to be effective, it is largely unavailable due to cardiac toxicity (Walker, *et al.* 1999). Motilin derivatives specifically developed to avoid bacterial resistance have poor effectiveness due to rapid development of tachyphylaxis (Netzer, *et al.* 2002). Agents such as tegaserod (Banh, *et al.* 2005) and loxiglumide (Chua, *et al.* 1994; Cremonini, *et al.* 2005) have been demonstrated to accelerate gastric emptying in humans, but the role of these agents in the treatment of feed intolerance in critical illness requires further investigation. Preliminary data suggested tegaserod to be an effective prokinetic agent for feed intolerance in critically ill patients (Stephens, *et al.* 2007). However, it is no longer available due to cardiovascular adverse effects (Thompson 2007). Although the development of novel prokinetic agent are in progress, the lack of suitable prokinetic agents suggests that short term use of low dose erythromycin (alone or in combination) is a reasonable approach for feed intolerance as the benefits appear to outweigh the risks. Furthermore, despite the ongoing concern of 'sub-lethal' concentrations of antibiotics exerting selective pressure for the development of bacterial resistance (Burgess 1999), there are no direct data in the current literature to support this hypothesis, especially with the use of short course of low dose erythromycin (Hawkyard and Koerner 2007).

CHAPTER 12: CONCLUSIONS AND FUTURE DIRECTION

The work described in this thesis has significantly enhanced the current understanding in the nature, pathogenesis, risk factors and treatment of disturbed gastric motor function in critically ill patients. Both the magnitude and the adverse impacts of delayed gastric emptying or the consequent intolerance to enteral feeding are of major important. These findings identify strategies for optimizing the management of feed intolerance and should also stimulate further research into the mechanisms responsible for the impaired gastric motility.

The work described in Chapter 7 has provided substantial insights into the nature of gastric motor disturbances in critically ill patients. In addition to previously reported antro-pyloro-duodenal abnormalities, both the motor activities of the proximal stomach and the integration of fundo-antral motor activity are significantly disturbed in these patients. In particular, compared to healthy volunteers, duodenal nutrient induces a more prolonged proximal gastric relaxation and a greater reduction in fundic waves, suggesting that the entero-gastric inhibition feedback to the proximal stomach was enhanced. This phenomenon is similar to that observed in the antro-pyloro-duodenum region. Together, these findings indicate that the widespread impairment of gastric motility during critical illness is potentially mediated by increased entero-gastric feedback in response to small intestinal nutrients. There are a number of implications from this work. Firstly, given the widespread motor impairment, effective therapy needs not only to address the motor disturbances in each gastric region but also to improve the motor integration between the proximal and distal stomach. In particular, the impact of current prokinetic agents, erythromycin and metoclopramide, on the proximal

gastric motility as well as the proximal-distal gastric integration warrants further evaluation in these patients. Secondly, the gastric region that is primarily responsible for delayed gastric emptying should be identified by examination of the contribution of disturbed motor activity in each gastric region and the regional integration to the overall gastric emptying. This information would be therapeutically valuable for the selection or design of therapies that target the most relevant gastric region responsible for delayed emptying. Thirdly, the underlying mechanisms responsible for the increased entero-gastric inhibition feedback in response to nutrients should be further evaluated.

The work presented in Chapter 8 explored the potential role of humoral mechanisms responsible in the enhancement of entero-gastric feedback as well as their relationship to gastric emptying. The activity of two major humoral mediators of the entero-gastric feedback, CCK and PYY, is markedly disturbed during critical illness. Compared to healthy volunteers, both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations are significantly elevated in critically ill patients, and are highest in patients with delayed gastric emptying or feed intolerance. Overall, there is an inverse relationship between the rate of gastric emptying and both fasting and postprandial plasma CCK and PYY concentrations after a nutrient liquid meal, suggesting the involvement of these hormones in the slowing of gastric emptying during critical illness. In order to determine whether this relationship is causal, further evaluation with specific antagonists is, however, required. Given the limitations of current prokinetic therapy, studies which assess the humoral mediation of disturbed gastric motility may provide alternative treatments for feed intolerance in critically ill patients.

Factors that involved in the pathogenesis of disturbed gastrointestinal motility and increased the risk of feed intolerance during critical illness remain poorly defined. The findings described in Chapter 9 identified patients who are "at risk" of delayed gastric emptying and feed intolerance based on the nature of the admission diagnosis, type of sedation, and blood glucose control. In addition, this work also refuted the hypothesis that delaying enteral feeding in critically ill patients slows gastric emptying. Early identification of "at risk" patients on admission allows the treating physician to monitor these patients closely for signs of feed intolerance and, thus, institute early therapy. The impact of this strategy on clinical outcomes, however, requires further evaluation. Similarly, the agents used for sedation have an important effect on feeding which needs to be taken into account when these drugs are chosen. Whilst the data suggest that sedation with morphine and/or midazolam should be minimized in the "at-risk" patients and propofol may be a preferred sedative, other factors such as analgesia and the potential adverse effects also need consideration. The findings do, however, need confirmation by a randomised, controlled study. The relationship between blood glucose control and feed intolerance in these patients also require further study to examine the impact of an intensive insulin protocol on the development of feed intolerance. Finally, although delaying enteral feeding for 4 days has little impact on gastric motor function, the increased duration of ventilation and ICU stay suggest that enteral nutrition should be commenced as early as possible in patients who have no contraindications to enteral feeding.

Contrary to the popular belief, the work performed in Chapter 10 has demonstrated that critically ill patients with a pre-existing diagnosis of type 2 diabetes mellitus have only a minor disturbance in the proximal gastric motility, relatively normal gastric emptying and are

at no higher risk of feed intolerance compared to non-diabetic patients. Hence, the presence of pre-existing type 2 diabetes mellitus in critically ill patients should not influence the standard practice of gastric feeding and, in the absence of contraindications, enteral feeding should be commenced as early as possible. In addition, proximal gastric motor responses to nutrients in these patients suggest a potential role for bolus cyclical enteral feeds as this may be more physiological than continuous feeds and could also minimize interruption of feeds due to procedures and clinical care. These issues are, therefore, warranted further evaluation.

The management of feed intolerance has always been challenging due to the current limitations of prokinetic drugs, the technical difficulty of post-pyloric placement and the morbidities associated with parenteral nutrition. The work performed in Chapter 11 provides a substantial increase in knowledge about the currently available prokinetic drugs, such as erythromycin and metoclopramide, in the treatment of feed intolerance during critical illness. Although short-term treatment with erythromycin is more effective than metoclopramide in improving the success of feeds, drug tachyphylaxis develops rapidly with both drugs and leads to recurrence of feed intolerance in approximately two third of patients. In these patients, treatment with the combination of erythromycin and metoclopramide is, however, highly effective. Furthermore, the use of combination therapy as a first line treatment is a promising strategy as it is both more effective than erythromycin alone and associated with a lower rate of drug tachyphylaxis, such that patients can be successfully fed and receive adequate nutritional support during their admission. The use of either erythromycin or metoclopramide or combination treatment was not associated with cardiac or hemodynamic adverse effect, although treatment with combination therapy is associated with a higher incidence of non-infective diarrhoea, which settled quickly after the cessation of the prokinetic drugs. The data

presented in Chapter 11, therefore, support the use of combination therapy as a first line treatment for feed intolerance in critically ill patients, provided that these agents to be ceased as soon as diarrhoea developed. As recent data suggest that 70 mg of erythromycin is as effective as 200 mg, the impact of combining the smaller doses of erythromycin with metoclopramide on the success of feeds and the development of diarrhoea should be further evaluated.

In conclusion, the studies described in this thesis have substantially increased knowledge about the relationship between the disturbed gastric motor function and enteral nutrition in critical illness. The results have important therapeutic implications, and suggest novel approaches to optimize enteral feeding in these patients. In addition, the work also highlights areas for further research into both the mechanisms and treatments of feed intolerance, which are likely to result in better strategies to manage this important clinical condition.

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