STUDIES OF NORMAL AND DISORDERED GASTRIC MOTILITY IN HUMANS

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SUMMARY

This thesis presents studies relating to normal and disordered gastric motility and the role of the gastrointestinal tract in appetite regulation in humans. Three broad areas have been addressed: (i) methodological approaches to the evaluation of gastric motility, (ii) gastric emptying of oil in normal subjects and patients with pancreatic insufficiency and (iii) the prevalence, clinical significance and treatment of disordered gastric emptying in patients with insulin dependent (IDDM) and non-insulin (NIDDM) diabetes mellitus. All of the studies have been either published, accepted for publication or submitted for publication and are presented as complete manuscripts.

There are many techniques available to assess gastric motility, including manometry, which measures pressure changes caused by gastric contractions, and scintigraphy which can be used to quantify gastric emptying and antral contractile activity. Concurrent measurements of antral pressure waves by manometry and antral contractions by fast frame scintigraphy (2 sec) were performed in normal volunteers. The frequency of contractions was substantially greater than the number of lumen occlusive pressure waves detected by manometry. Manometric measurements, however, unlike scintigraphy, reflected events occurring with a 0.1 sec resolution. Complimentary information about gastric motility, therefore, arises from the simultaneous use of scintigraphy and manometry.

While most information about disordered gastric emptying has been derived from studies using scintigraphy, the technique is not always readily available and involves exposure to radiation. Concurrent scintigraphic and ultrasound measurements of gastric emptying of liquid were performed in normal volunteers. There was a close correlation between measurements of nutrient and non-nutrient

liquid meals between the two techniques, indicating that ultrasound can be used to quantify gastric emptying of liquids in normal subjects.

There is relatively little information about the mechanisms which control appetite in humans, although signals from the gastrointestinal tract are important. The relationship between appetite and antral area, measured with ultrasound, was evaluated in normal volunteers after a liquid meal. The score for fullness and the width of the antrum were related both before and after the drink, supporting the concept that antral distension is an important mechanism mediating postprandial satiation.

The effects of volume and posture on gastric emptying and intragastric distribution of a solid meal and appetite were evaluated in normal volunteers. Meal volume had a major effect on gastric emptying and intragastric distribution of a digestible solid meal; in particular the rate of solid emptying (kcal/min) was faster in the sitting than the left lateral position. In contrast posture had only a minor impact on intragastric meal distribution, and no effect on gastric emptying. These observations indicate that gastric emptying of digestible solids is load-dependent.

Studies which have evaluated gastric emptying in patients with upper gastrointestinal symptoms, have characteristically used bland test meals, however, such symptoms are often precipitated by fatty meals. The effect of posture on gastric emptying of a meal containing oil and aqueous components and the relationship between appetite and gastric emptying was evaluated in normal volunteers. Gastric emptying of the oil phase was initially faster in the lying than the sitting position, but, the overall rate of emptying of oil was similar in the two postures. In contrast, emptying of the aqueous phase was much faster in the

sitting position when compared to the lying position. Hunger was inversely related to gastric emptying of oil, ie subjects were less hungry when more oil emptied from the stomach. These observations suggest that the interaction of fat with small intestinal receptors plays a major role in the regulation of gastric emptying and appetite in normal volunteers.

To evaluate the hypothesis that fat must be digested to fatty acids in order to slow gastric emptying the effect of posture on gastric emptying of a meal containing oil and aqueous components was evaluated in patients with cystic fibrosis who had exocrine pancreatic insufficiency. Gastric emptying of oil was faster than normal in both positions and much faster in the lying than the sitting position. In contrast, hunger did not decrease after the meal. These observations indicate that gastric emptying of oil is accelerated in pancreatic insufficiency and that digestion of fat is required for supression of appetite.

Cisapride is arguably the optimum drug for the treatment of gastrointestinal symptoms in patients with gastroparesis. The effects of cisapride on gastric emptying of a meal containing oil and aqueous meal components and appetite were evaluated in a group of normal volunteers. Cisapride accelerated gastric emptying of oil by shortening the lag phase and did not affect the post-lag emptying rate. The retention of oil in the distal stomach was increased by cisapride. Preprandial hunger was greater, and postprandial fullness less on cisapride. These observations indicate that cisapride may inflence appetite in humans.

30-50% of patients with longstanding diabetes mellitus have delayed gastric emptying of solid or liquid meals and this may be associated with gastrointestinal symptoms, poor control of blood glucose concentrations and impaired oral drug

absorption. The prevalence of abnormal intragastric meal distribution was assessed in patients with longstanding diabetes mellitus. Intragastric meal distribution was often abnormal with increased retention of both solids and liquids in the proximal stomach but the relationships with the rate of emptying from the total stomach and gastrointestinal symptoms were poor.

The prevalence of abnormal gastric emptying in patients with recently diagnosed non insulin-dependent diabetes mellitus (NIDDM) and the relationship between postprandial blood glucose concentrations and gastric emptying in NIDDM are poorly defined. The prevalence of disordered gastric emptying of a nutrient liquid meal and the relationship between the rise in blood glucose concentration and gastric emptying of a 75g glucose load were assessed in patients with "early" NIDDM. There was no overall difference in gastric emptying between patients with "early" NIDDM and normal volunteers. There was a significant relationship between the magnitude of the increase in plasma glucose after the glucose load and the rate of gastric emptying. This study indicates that during hyperglycaemia gastric emptying of a nutrient liquid meal is similar in patients with "early" NIDDM to normal subjects and a significant determinant of the glycaemic response.

Gastrointestinal symptoms occur frequently in patients with diabetes mellitus, but the relationship with gastric emptying is weak, suggesting that other factors are important. Recent studies have suggested that the blood glucose concentration influences sensations arising from the gut. The relationships between gastric emptying, gastrointestinal symptoms and the blood glucose concentration were evaluated in patients with longstanding insulin dependent diabetes mellitus. There was a significant relationship between both pre- and postprandial fullness and the blood glucose concentration, consistent with the concept that the latter is a

significant determinant of gastrointestinal symptoms in patients with diabetes mellitus.

Postprandial hypotension is a major clinical problem in the elderly and in patients with autonomic failure; including patients with diabetes mellitus. The relationship between the postprandial fall in blood pressure and the rate of gastric emptying was evaluated in patients with "early" NIDDM and both young and older normal volunteers. In the NIDDM group the area under the change in mean blood pressure curve between was related to the rate of gastric emptying, accounting for approximately 45% of the variance. There was no significant relationship between the change in blood pressure and gastric emptying in the normal subjects. These observations suggest that the rate of gastric emptying has a significant impact on the change in blood pressure after a meal in patients with diabetes.

Recent studies have demonstrated that acute changes in the blood glucose concentration may effect gastrointestinal motor function. The effects of erythromycin (3mg/kg IV) on gastric emptying of a solid meal and, postprandial hunger and fullness were assessed in normal subjects during both hyperglycaemia (~15mmol/L) and euglycaemia. Hyperglycaemia markedly slowed gastric emptying after both saline and erythromycin administration. Erythromycin accelerated gastric emptying during euglycaemia, but had little effect during hyperglycaemia. Postprandial hunger was less during hyperglycaemia after administration of saline but not erythromycin. This study indicates that the prokinetic effect of erythromycin on gastric emptying of solids is attenuated during hyperglycaemia and that the hyperglycaemia-induced changes in gastrointestinal sensation may be altered by erythromycin.

STATEMENT OF ORIGINALITY

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

I give consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Signed:

Karen Louise Jones
November 1997

DEDICATION

To Michael,
My teacher, boss and friend. You showed me the world. For this, I will always be grateful.

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CHAPTER 1

GASTRIC MOTOR FUNCTION

1.1 INTRODUCTION

The factors responsible for the regulation of gastric emptying are still poorly understood, largely because of the limitations in the techniques which are available for measurement of gastrointestinal motor function in humans. In particular, there is no single technique which has the capacity to quantify gastric electrical activity, wall motion and lumen occlusion resulting from gastric muscular contractions, and transpyloric flow simultaneously.

The purpose of this chapter is to review current knowledge of gastric motor function, including the mechanics and patterns of gastric emptying in humans.

1.2 MOTOR FUNCTIONS OF DIFFERENT REGIONS OF THE STOMACH

The major functions of the stomach are to store ingested food, to mix food with gastric secretions and grind it into particles less than 1mm in size, and to deliver chyme into the small intestine at a rate which optimises the digestion and absorption of nutrients. Recent studies have demonstrated that gastric emptying is predominantly pulsatile, so that the majority of chyme enters the small intestine as a series of gushes, rather than continuously (King et al 1984, Malbert et al 1991, Hausken et al 1992, Malbert & Mathis 1994). The characteristics of these pulses (i.e. their volume and duration) vary on a second by second basis (Figure 1.1) and are dependent on the relationships between contractions generated by the fundus,

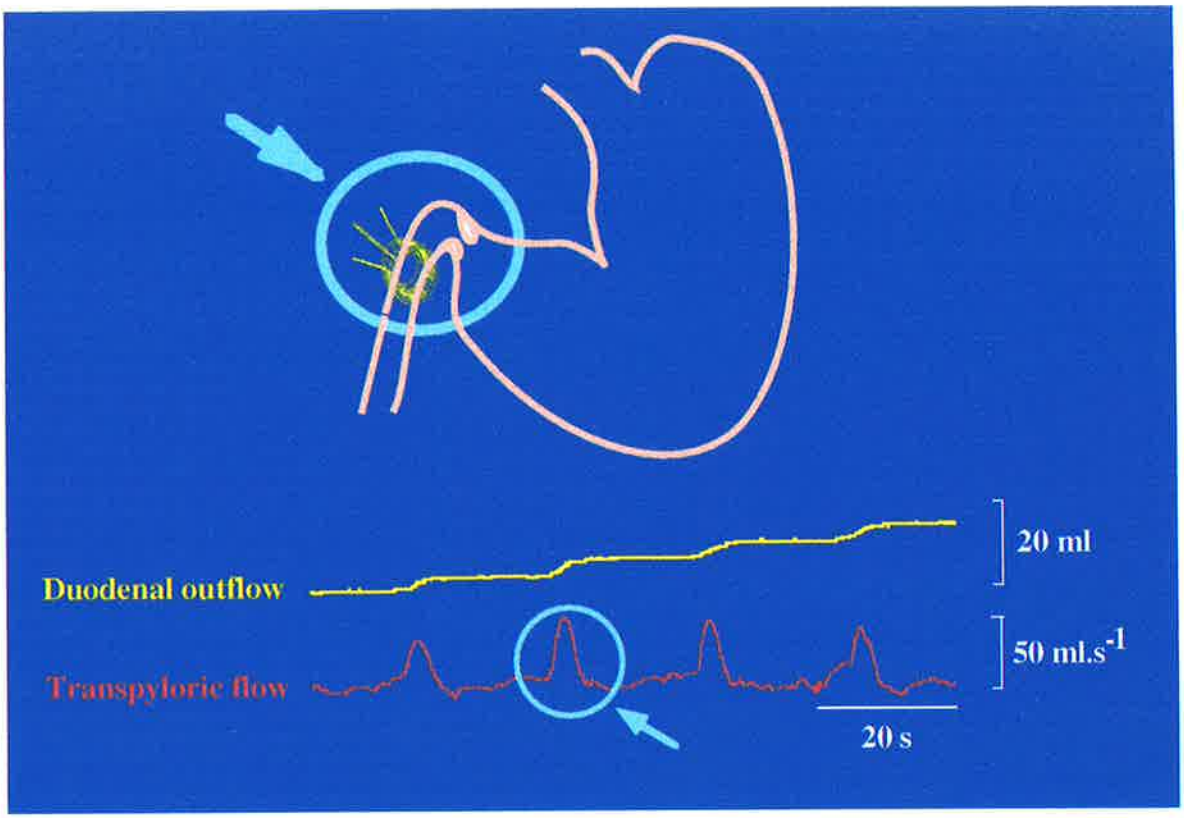

Figure 1.1: Recording of transpyloric flow in the pig using an electromagnetic flow meter probe implanted in the proximal duodenum. (Diagram provided by Professor C-H Malbert)

antrum, pylorus and proximal small intestine. It is also recognised that no single motor component should be considered to exert the dominant control over normal gastric emptying (Horowitz & Dent 1994) and that substantial changes in the characteristics of individual flow pulses may be associated with little, if any, modification in the overall rate of gastric emptying (Malbert & Mathis 1994).

Although the stomach can be divided into three anatomical regions: the fundus, the body and the antrum, it is usually considered to have two functionally distinct areas: the proximal one third, which acts mainly as a reservoir, and the distal stomach which grinds and mixes food (Meyer 1987). The pylorus, a band of muscular tissue distal to the antrum, also appears to play a major role in the regulation of gastric emptying (Horowitz & Dent 1994).

1.2.1 *Proximal stomach*

The proximal stomach maintains a continuous state of partial contraction, or tone, and phasic contractions occur relatively infrequently. Gastric tone is modulated by neural and/or hormonal inputs to perform the functions of accommodation and storage, regulation or maintenance of intragastric pressure and propulsion of food into the distal stomach (Meyer 1987). Recent studies, using the barostat technique developed by Azpiroz and Malagelada, have provided substantial insights into proximal gastric motor function (Azpiroz 1997).

The ability of the proximal stomach to perform these functions is mediated by two neural reflexes: receptive relaxation and gastric accommodation. Receptive relaxation of the proximal stomach occurs within 10 seconds after swallowing. The reduction in tone is mediated by the release of vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) from nerves in the fundus (Fahrenkrug et al 1978,

Desai et al 1991). This reflex is blocked by vagotomy. Gastric accommodation is triggered by gastric distension and allows the intragastric pressure to remain relatively stable after meal ingestion; so that ingestion of up to 2L of fluid is associated with minimal increase in intragastric pressure (Weisbrodt 1984). Gastric accommodation is mediated by mechanoreceptors in the gastric wall and via vagal pathways. Truncal or proximal gastric vagotomy results in impaired gastric relaxation and increased intragastric pressure (Jahnberg 1977).

Stimuli arising from other areas of the gastrointestinal tract also modulate proximal gastric tone. For example, distension of the duodenum (Rouillon et al 1991) or colon (Sims et al 1995) and small intestinal infusion of hydrochloric acid, protein, glucose or fat (Azpiroz & Malagelada 1985) all reduce proximal gastric tone. These effects appear to be mediated by vagal nonadrenergic, noncholinergic nerves. In dogs, nitric oxide (NO) has been shown to play a role in proximal gastric relaxation triggered by small intestinal nutrient infusion (Meulemans & Schuurkes 1995); this is likely to also be the case in humans.

1.2.2 *Distal stomach*

In contrast to the proximal stomach, the distal stomach exhibits phasic contractions, which allow grinding and breakdown of food as well as the regulated delivery of chyme into the small intestine (Meyer 1987). The contractions of the distal stomach are generated by a pacemaker located in the greater curve (Hinder & Kelly 1977). The pacemaker discharges at a rate of approximately 3/min, however, not every discharge results in muscular contraction. Neurohumoral factors modulate the frequency, intensity and duration of phasic muscular contractions (Hasler 1995). The pacemaker potentials propagate both circumferentially and distally through the smooth muscle layers; because circumferential conduction is much faster than

longitudinal conduction (Publicover & Sanders 1985), contractions propagate distally in a well-defined ring, or band. Not all pacemaker potentials resulting in contractions start at the same region: contractions may start at the mid-corpus, but stop before reaching the antrum or alternatively, begin in the antrum with no contractions proximal to this. In humans, the velocity of contractions increases from proximal to distal stomach: in the mid-corpus contractions have a velocity of approximately 0.5cm/sec which increases to 4cm/sec in the terminal antrum (Hinder & Kelly 1977, Meyer 1987).

Patterns of contractions vary markedly from the fasting to the postprandial state. The migrating motor complex (MMC) acts as the stomach's "housekeeper", removing undigested food particles and sloughed epithelial cells. The MMC consists of three phases and is usually 80 to 120 minutes in duration (Rees et al 1982). Phase I is a period of gastric motor quiescence which lasts for approximately 40-60 min; phase II is characterised by a period of irregular, but increasing, contractions which lasts 20-40 min, and phase III is a much shorter period (5-10) min of intense contractions, beginning in the mid-corpus and propagating, without interruption, to the pylorus. During phase III almost every pacemaker potential results in a contraction so that antral contractions occur at a rate of about 3/min (Rees et al 1982). It is during phase III and "late" phase II that larger undigestible solids are emptied from the stomach. While the pathways responsible for regulating the MMC are poorly understood, however, both vagal and hormonal mechanisms are thought to be important (Sarna 1985).

After meal ingestion, the MMC is replaced by the "fed pattern" characterised by contractions of variable frequency, amplitude and duration. The onset of the fed motor pattern is within 5-10 min of meal ingestion and it continues until the stomach has emptied the majority of its contents. Fluoroscopic studies have

demonstrated that during this time, antral contractions propel the ingesta both forward and retrograde, serving to mix and grind food (Tougas et al 1992a). In the postprandial state the amplitude and frequency of antral contractions is dependent on the physical and chemical characteristics of the meal. For example, higher amplitude contractions are observed after a meal containing solid particles, when compared to the same meal given in a homogenised form (Rees et al 1979).

There is, very little information about the organisation, or space/time relationships of lumen-occlusive antral pressure waves resulting from antral contractions. While it has been traditionally assumed that patterns of lumen occlusion associated with antropyloric contractions waves would follow an aborad pattern similar to that of the pacemaker discharge, this seems not to be the case. A recent study in which the spatial patterning of antropyloric pressure waves both before and after a meal was evaluated using manometry (Sun et al 1997) demonstrated in normal healthy subjects that there was a wide diversity of pressure wave patterns with only a minority of pressure wave sequences conforming to an antegrade pattern of lumen occlusion. This observation is not surprising as there is, a major difference between pressure waves and contractions; in particular the time of onset of an antral contaction and time of onset of a lumen occlusive pressure wave may be quite different (Dent et al 1994). Furthermore, because not all contractions result in lumen occlusion, the term contraction should not be used in describing pressure waves. Therefore techniques which do not record lumen occlusion may be more useful than manometry in evaluating antral contractions, or at least provide additional information. This issue is addressed further in Chapters 3 and 6.

Like the proximal stomach, stimulation of other areas of the gastrointestinal tract may influence the function of the distal stomach. For example, distension of the fundus results in increased antral pressure waves, probably through a vagal

cholinergic pathway (Abrahamsson & Glise 1984). While distension of the duodenum (De Ponti et al 1987, Edelbroek et al 1994) and small intestinal infusion of fat, protein, carbohydrate or hydrochloric acid suppress antral pressure waves (Heddle et al 1988a, Fone et al 1990b, Fraser et al 1992).

1.2.3 *Pylorus*

The pylorus is comprised of two muscular loops, the proximal and distal, joined by a muscular torus on the lesser curvature; the distal muscular loop represents the sphincter, which consists mainly of circular smooth muscle, reinforced by longitudinal muscle from the antrum and connective tissue from the mucosa and smooth muscle layers (Meyer 1987). The zone of pyloric contraction is narrow; frequently being less than 4mm in width in humans (Heddle et al 1988b). The innervation of the pylorus is different to that of the antrum or the duodenum, with a much higher density of nerve fibres (Daniel et al 1989).

The pylorus exhibits both tonic and phasic contractions (Schulze-Delrieu et al 1984, Heddle et al 1988b) and characteristic patterns of motility are evident in both the fasting and postprandial periods. Studies in dogs have shown that during phase III of the MMC, the pylorus remains open to allow chyme to pass into the small intestine (Erhlein 1980). During the postprandial period, the pylorus acts in concert with the antrum, opening and closing periodically thereby influencing the mixing and grinding of food into small particles the delivery of chyme into the small intestine (Rhodes et al 1966).

The pathways responsible for pyloric stimulation include neural, and possibly humoral factors (Hasler 1995). Small intestinal infusion of fat, glucose, amino acids and hydrochloric acid and proximal duodenal distension all stimulate pyloric

tone, as well as phasic pressure waves isolated to the pylorus (so-called IPPW's) (Heddle et al 1988b, Fone et al 1989, Fraser et al 1992, Edelbroek et al 1994) and retard gastric emptying (Heddle et al 1989). The IPPW's induced by intraduodenal glucose are blocked by atropine suggesting that phasic pyloric motility is mediated, at least in part, by cholinergic neural pathways (Fone et al 1989). Exogenous administration of cholecystokinin octapeptide (CCK8) (Fraser et al 1993a) and hyperglycaemia (Fraser et al 1991) also stimulate pyloric motility in humans.

1.3 PATTERNS OF GASTRIC EMPTYING

As mentioned earlier, it has been established that gastric emptying is predominantly pulsatile (King et al 1984, Malbert et al 1991, Malbert & Mathis 1994). Patterns of gastric emptying are complex and highly dependent on a number of factors, including meal composition, volume, posture and temperature.

The components of a meal may be classified as: digestible solids, non-digestible solids, non-nutrient and nutrient liquids, and fat. There are substantial differences between these meal components in their rates and patterns of gastric emptying (Figure 1.2). Most studies have evaluated overall patterns of emptying and there is little information about the characteristics of individual flow pulses.

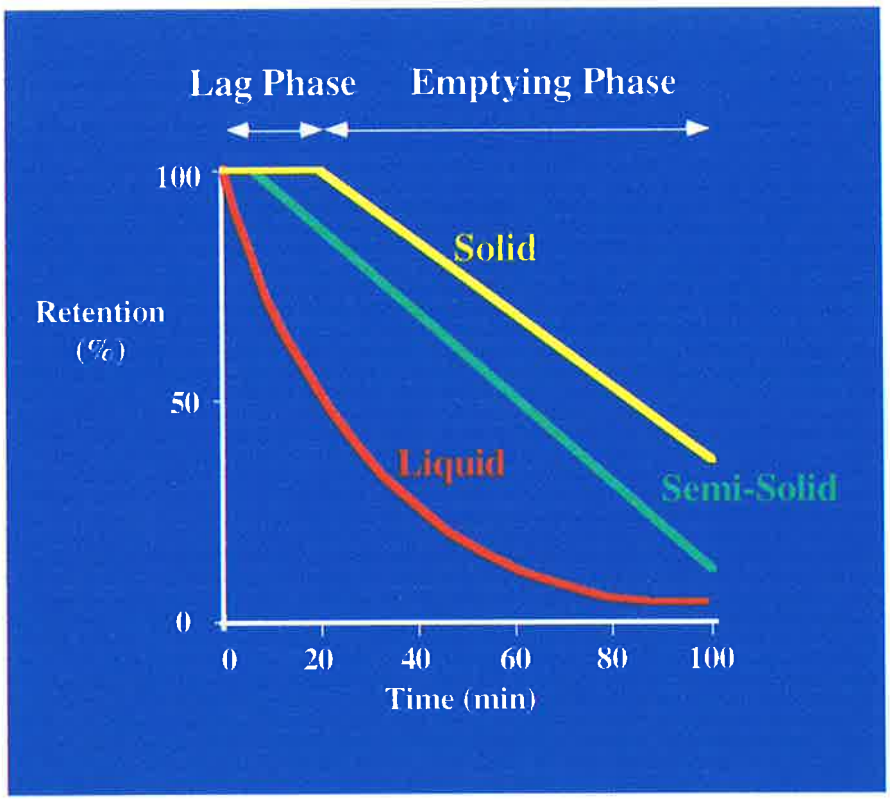

Figure 1.2: Gastric emptying curves for solid (pancake), semi-solid (porridge) and liquid (10% dextrose) represent percent retention in the total stomach over time. The overall pattern of gastric emptying of both solids and semi-solids is linear, following a lag phase which is longer for solids. In contrast, emptying of the low nutrient liquid is mono-exponential with minimal lag phase.

1.3.1 *Digestible solids*

There are usually two phases of gastric emptying of solid foods: a lag phase, followed by an emptying phase which approximates a linear pattern (Collins et al 1983). When the majority of a solid meal has emptied from the stomach, the emptying rate may be slower than previously (Siegel et al 1988).

During the lag phase solid food moves from the proximal stomach into the antrum where it is ground into small particles of <1mm (Meyer et al 1987). The intragastric distribution of a meal may therefore influence its rate of emptying. It has been suggested that the so called "mid-gastric band" observed on scintigraphic images as a region of decreased radioactivity, separating the proximal and distal stomach regions, may modulate intragstric meal distribution (Moore et al 1986). Since antral contractions play a major role in the grinding of solid food the emptying rate of solids, particularly the duration of the lag phase is critically dependent on antral motor activity and the size of ingested food particles (Houghton et al 1988, Urbain et al 1989). For example, egg or noodles empty much faster from the stomach than 10mm cubes of liver containing an equal number of calories (Weiner et al 1981, Siegel et al 1989). Similarly, homogenised egg empties much faster than 2.5mm or 5mm liver cubes (Urbain et al 1989). It has accordingly been suggested that the duration of the lag phase/time taken to grind solid food into small particles is a major rate limiting step in gastric emptying of solids (Lin et al 1992). In dogs, the density of solid particles has also been shown to influence their rate of emptying (Meyer et al 1985). There is little information about the effect of passive forces resulting from meal volume and posture on gastric emptying of solids in humans. In dogs with duodenal fistulae, Lin et al have reported that increasing meal volume of a solid meal does not significantly affect gastric emptying suggesting that solids may normally empty from the stomach at near maximum rates (Lin et al 1992). This issue is addressed further in Chapter 9.

While the grinding of a solid meal is primarily the result of the function of the antrum and pylorus (Meyer 1987), the proximal stomach and small intestine probably also play a role (Kroop et al 1979, Mayer et al 1984). For example, after antrectomy approximately 30% of chyme is delivered to the duodenum as particles greater than 1mm in size, indicating that 70% of the meal has been ground down into small particles which is certainly not completely attributable to chewing (Mayer et al 1984). Gastric emptying of a meal containing fat has been shown to slow gastric emptying of solids, presumably via small intestinal mechanisms, after antrectomy (Kroop et al 1979).

1.3.2 *Non-digestible solids*

Emptying of larger non-digestible solids occurs predominatly during phase III of the MMC. During phase III highly expulsive antral contractions clear the stomach of any remaining food particles left behind after postprandial gastric emptying has ceased (Sarna 1985, Husebye 1997).

1.3.3 *Nutrient and non-nutrient liquids*

In contrast to solids, gastric emptying of liquids commences almost immediately after meal ingestion, with a minimal lag phase. After a few minutes, the overall emptying of non-nutrient liquids approximates a monoexponential pattern whereas emptying of nutrient liquids approximates an overall linear rate of about 2-3 kcal/min (Brener et al 1983); at least for the majority of the emptying phase Schirra et al 1996). The intragastric distribution of liquids is also dependent of their nutrient content, so that the retention in the proximal stomach is greater for nutrient containing liquids (Horowitz et al 1993). The difference in emptying patterns between nutrient - and non-nutrient liquids can largely be explained by small

intestinal feedback. There are "specific" small intestinal receptors for a variety of nutrients, including glucose, fatty acids, amino acids and acid (Hunt & Knox 1968); the location and number of receptors varies substantially between nutrient classes. The extent of small intestinal feedback is dependent on the site of stimulation, as well as the length of small intestine which is exposed (Lin et al 1989, Lin et al 1990a, Lin et al 1990b). Patterns of prior nutrient intake also influence gastric emptying, probably by affecting small intestinal feedback. For example, in normal, healthy subjects gastric emptying of glucose and fructose are faster after dietary supplementation with glucose (Horowitz et al 1996a), an increase in fat intake is associated with more rapid gastric emptying of fat (Cunningham et al 1991a), while fasting slows gastric emptying of glucose (Corvillain et al 1995). Meal volume and gravity influence gastric emptying of non-nutrient liquids so that larger volumes and gravity increase the rate of gastric emptying (Burn-Murdoch et al 1980). Gastric emptying of non-nutrient liquids (volumes <200ml) is also influenced by the phase of fasting gastric motility which exists when the drink is ingested - emptying is faster during phase III than phase I (Oberle et al 1990). Because of the effect of small intestinal feedback, meal volume and posture have relatively little effect on gastric emptying of nutrient-dence liquids.

1.3.4 *Interaction between solids and liquids*

Most meals contain a mixture of solid and liquid components and there is relatively little information about the interaction between them. About 80% of the liquid components of a meal empty during the lag phase for solids (Horowitz et al 1989b); an increase in the nutrient content of the liquid is associated with prolongation of the lag phase (Collins et al 1991). In contrast, the presence of a solid meal also slows gastric emptying of liquids (Horowitz et al 1989b); the magnitude of this slowing is dependent on the volume of the solid meal (Collins et al 1996). Furthermore, an

increase in the volume of a solid meal, without changing the volume of liquid is associated with prolongation of the lag phase but acceleration of the post-lag emptying rate (Collins et al 1996).

1.3.5 *Fats*

The way in which the stomach handles fat is complex and should be considered separately from solids or liquids. An understanding of gastric emptying of fat is fundamental to the optimal use of pancreatic enzyme replacement in patients with exocrine pancreatic insufficiency and an understanding of the sequelae of gastric resection. Before meal ingestion, fat is often in a solid or semi-solid state, but when warmed to body temperature, extracellular fats are often converted to a liquid (oil) form. Despite its liquid nature, gastric emptying of oil resembles that of solids with a lag phase, followed by a linear pattern of emptying (Cunningham et al 1991d). Furthermore, after ingestion of an oil/aqueous meal in the sitting position oil does not start to empty until the majority of the aqueous phase has left the stomach (Edelbroek et al 1992b).

Gastric emptying of fat is potentially dependent on a number of factors including meal composition, posture and the availability of lipolytic enzymes. Extracellular fat tends to empty as an oil phase, in a similar fashion to a solid meal but considerably after an aqueous phase (Meyer et al 1986). In contrast, intracellular fat tends to empty within a solid food phase (Meyer et al 1986). It has been suggested that oil may "float" on top of a more dense aqueous and solid meal components (Edelbroek et al 1992b). Layering of fat on top of the aqueous phase may, however, also potentially reflect intragastric redistribution of fat from the distal into the proximal stomach (Heddle et al 1989) or the result of the "mid-gastric band". Studies examining the influence of posture on gastric emptying and

intragastric distribution of fat in normal subjects and patients with pancreatic insufficiency, may shed further light on these issues and are discussed in Chapters 10 and 11.

There is persuasive evidence that receptors in the small intestine play a major role on regulating gastric emptying of fat. As with other nutrients, the degree of inhibition of gastric emptying by small intestinal feedback is dependent on both the length and site of intestine exposed as well as the concentration of fat (Lin et al 1990b). It was suggested as early as 1968 that fat must be broken down into fatty acids in order to inhibit gastric emptying, with medium chain fatty acids containing between 12 and 20 carbon atoms being more potent than long or shorter fatty acids (Hunt & Knox 1968). For example, the nondigestible lipid, sucrose polyester, empties rapidly from the stomach without a significant lag phase (Cortot et al 1982). In dogs with pancreatic insufficiency, the rate of gastric emptying of fat is dependent on the availability of pancreatic enzymes so that gastric emptying of fat is influenced by the amount of lipase in the small intestine (Meyer et al 1994b, Meyer et al 1994c). In humans with pancreatic insufficiency, there is evidence that gastric emptying of fat is also more rapid, but prevous studies have substantial limitations (Long & Weiss 1974, Roillet et al 1980). In the canine model, in the absence of pancreatic lipase, gastric emptying of fat is load dependent (Meyer et al 1994a); emptying is more rapid with increased volume of ingested fat. Although it is unlikely that volume has a major effect on gastric emptying of oil in normal humans, due to the potent effect of small intestinal feedback mechanisms (Meyer et al 1994a, Hunt et al 1995), posture is likely to be a significant factor in circumstances where the latter has a major effect on intragastric distribution of fat. In patients with pancreatic insufficiency, the effects of posture may be even more marked if small intestinal feedback is reduced. This latter issue is addressed in the study reported in Chapter 11.

1.4 CONCLUSIONS

This chapter has briefly reviewed the literature pertaining to normal gastric motor function, including the mechanics and patterns of gastric emptying. A number of the issues raised are addressed in this thesis. In particular:

(1) In Chapter 6 a new radioisotopic technique designed to provide information about non-lumen occlusive antral contractions is evaluated.

(2) In Chapter 9 the effects of meal volume and posture on gastric emptying of a digestible solid meal in normal subjects are evaluated.

(3) The effects of pancreatic insufficiency and posture on gastric emptying of an oil/aqueous meal in both normal subjects and patients with exocrine pancreatic insufficiency, are discussed in Chapters 10 and 11 respectively.

CHAPTER 2

REGULATION OF APPETITE

2.1 INTRODUCTION

The factors which influence appetite and food intake in humans are poorly understood and much of our knowledge in this area has been derived from animal studies. The desire to eat is influenced by a variety of stimuli, including both psychosocial and physiological factors. However, in general terms, feeding is controlled by a central system, responsible for the initiation of eating, and a peripheral satiety system, activated by the presence of food in the gastrointestinal tract (Morley 1980, Morley et al 1990, Cook & Horowitz 1996) (Figure 2.1). The purpose of this chapter is to review current literature relating to the regulation of appetite, particularly the role of the gastrointestinal tract in mediating satiation.

2.2 CONTROL OF APPETITE

The urge to eat, the act of eating and the absorption of digested food, results in a series of responses which determine both the onset of satiation and the length of satiety; the so called "satiety cascade" (Blundell & Halford 1994). There are four main processes which regulate food intake: (i) sensory stimulation driven by the sight, smell and taste of food, (ii) cognitive responses ie beliefs about the food, (iii) pre absorptive responses prior to food ingestion, including gastric distension, and (iv) post absorptive responses which occur subsequent to the release of gastrointestinal hormones which trigger a variety of chemical and neural reactions.

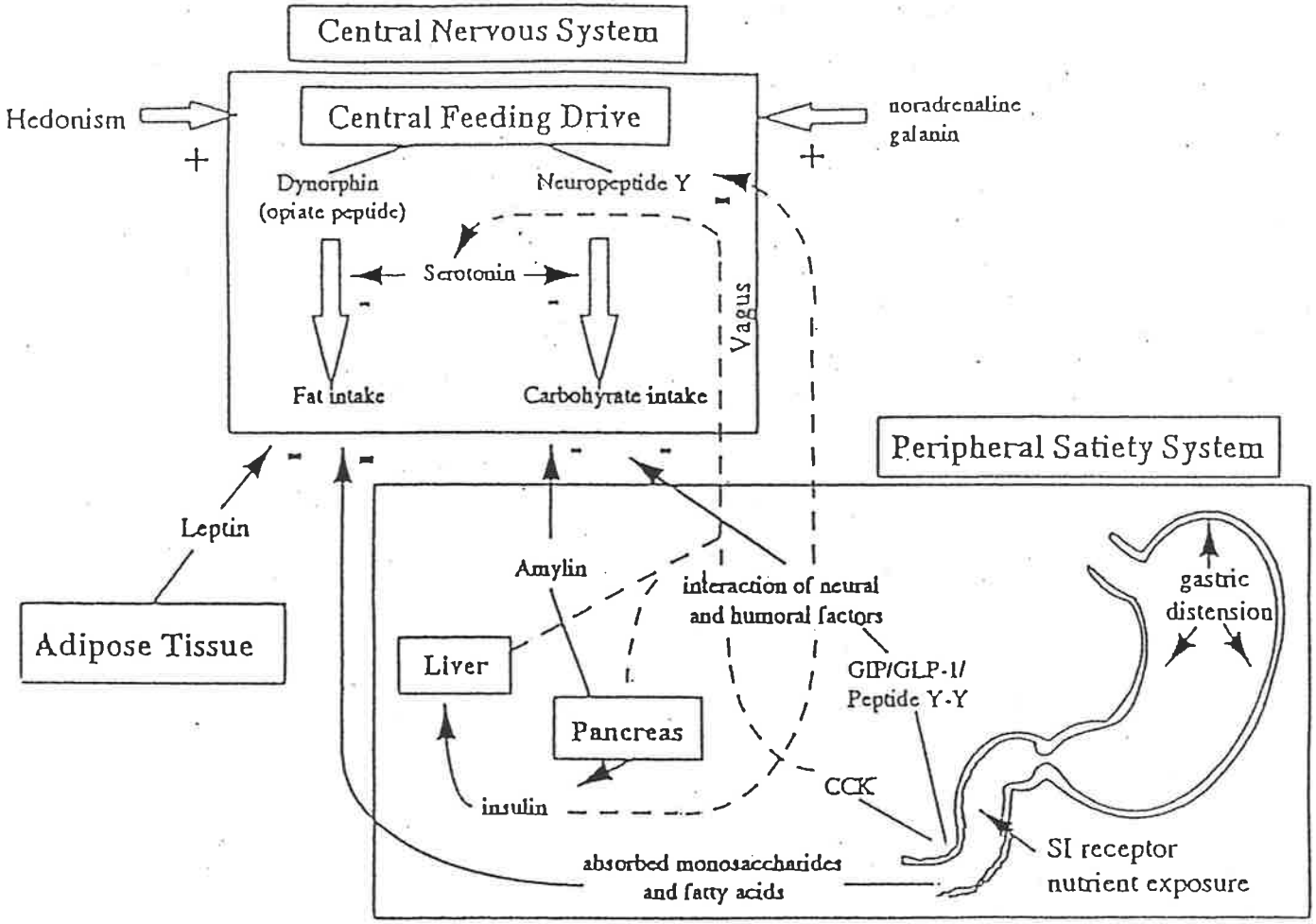

Figure 2.1: Overview of putative mechanisms involved in appetite regulation in humans (adapted from Morley 1987), Cook & Horowitz 1996.

The central feeding drive has traditionally been considered to comprise two distinct parts; a "feeding centre" regulated by the lateral hypothalamus and a "satiety centre" controlled by the ventromedial hypothalamus. However, there is now evidence that many areas within the central nervous system play a role in appetite regulation (Ballinger 1994). The central feeding drive involves a number of neurotransmitters. Those shown to increase food intake include endogenous opioids, neuropeptide-Y, noradrenaline and possibly, dopamine (Morley 1987, Read et al 1994). Serotonin, cholecystokinin, corticotrophin releasing hormone, glucagon-like-peptide-1 and vasopressin, inhibit food intake (Morley 1987, Read et al 1994).

2.3 ROLE OF THE GASTROINTESTINAL TRACT IN APPETITE REGULATION

Ingestion of a meal results in gastric distension, the interaction of chyme with the small intestine and the release of gastrointestinal hormones; these interrelated mechanisms all appear to play a role in triggering satiation.

2.3.1 *Gastric distension*

The results of animal studies indicate that gastric distension is a potent stimulus for satiation (Carlson 1912, Cannon & Washburn 1912, Janowitz & Grossman 1949). For example, in sham-fed dogs with oesophageal fistulae, food intake is inhibited by balloon distension in the stomach (Janowitz & Grossman 1949). The effects of gastric distension on food intake may be mediated by vagal mechanisms (Paintal 1954, Grundy et al 1981). In humans it has been suggested that the stomach must be distended by at least 20% to induce satiety signals (Morley 1990) and that obesity is associated with reduced perception of gastric distension

(Geliebter et al 1988). Gastric distension acutely reduces food intake by up to 30% in young adults (Geliebter 1988). A deficiency of these studies relates to methodology employed to distend the stomach. With the availability of the barostat technique, both isobaric and isovolumetric distensions can be performed (Azpiroz 1997). Using balloon distension, it has been demonstrated that gastric distension alone probably does not induce satiation, but rather an unpleasant sensation of bloating (Khan & Read 1992). Both the site of gastric distension and the intragastric distribution of food may be important in triggering sensation (Dozois et al 1971, Houghton et al 1992). While in previous studies the site of gastric distension was not usually standardised, there is evidence that antral distension is particularly effective in inducing fullness and satiation (Benini et al 1994). Furthermore, in patients with non-ulcer dyspepsia (Hausken & Berstad 1992) and diabetes mellitus (Undeland et al 1996), postprandial antral area is increased. Delayed gastric emptying increases the retention of the food and fluid in the stomach and may potentially induce satiation by increasing and prolonging gastric distension (Read et al 1994). Some of these issues are addressed in the studies reported in Chapters 7 and 8.

2.3.2 *Small intestinal mechanisms*

The small intestine is an important regulator of satiation. This effect is probably mediated via a number of mechanisms, including slowing of gastric emptying and the release of hormones such as cholecystokinin (Read et al 1994). In healthy humans small intestinal (intrajejunal and intraileal) infusion of nutrients suppresses appetite and subsequent food intake much more than intravenous infusions of the same nutrients (Welch et al 1995, Welch et al 1988, Lavin et al 1996). Similarly in rats, intravenous lipid infusion does not influence eating behaviour, whereas intraduodenal infusion of fat suppresses food intake

(Greenberg et al 1989). These effects may not necessarily be dependent on gastric distension; small intestinal infusion of nutrients inhibits feeding in animals with gastric or oesophageal fistulae (Liebling et al 1975, Gibbs et al 1981). There is little information about the effects of different nutrient classes on appetite, although in a recent study in normal young men, intraduodenal lipid infusion suppressed sensations of hunger and subsequent food intake to a greater extent than an equicaloric intraduodenal glucose load (Cook et al 1997). Studies in humans have also demonstrated that the site of small intestinal nutrient stimulation may also be important in the regulation of appetite. For example, while both ileal and jejunal infusion with lipid, reduce subsequent food intake and period of consumption, only jejunal infusion is associated with a reduction in preprandial hunger (Welch et al 1988). As discussed in Chapter 11, there is evidence that fat must be digested to fatty acids in order to slow gastric emptying (Meyer et al 1994a). It has not been established whether a similar process is required for stimulation of satiation. This issue is addressed in the study reported in Chapter 11.

2.3.3 *Interaction between gastric and small intestinal mechanisms*

There is substantial evidence that gastric and small intestinal mechanisms may act synergistically to suppress food intake (Khan & Read 1992, Feinle et al 1995, Feinle et al 1996). For example, when nutrients are present in the small intestine, gastric distension induces a "meal-like" sensation of satiety (Khan & Read 1992). It has been demonstrated in normal subjects that when guar gum is added to both high and low fat soups, gastric emptying is slowed and fullness increased (French & Read 1994). After ingestion of the low nutrient soup and guar gum, the increase in fullness and reduction in hunger are transient and related to the rate of gastric emptying, indicating that gastric distension/intragastric volume is

important in regulating short-term appetite. In contrast, after the high fat soup and guar gum, the greater suppression of appetite does not relate to the rate of gastric emptying (French & Read 1994), suggesting that greater exposure of the small intestine to nutrients is more important in this situation. Current evidence therefore suggests that when a meal contains few nutrients, gastric distension is the major factor triggering satiation, whereas with a high-nutrient meal, the interaction of nutrients with receptors in the small intestine may be more important (French & Read 1994). These concepts, however, require additional clarification. In Chapters 10, 11 and 12 the author has evaluated the relationships between sensations of hunger and fullness and gastric emptying after ingestion of a test meal containing 60ml olive oil 290ml low nutrient beef soup (in normal subjects and patients with cystic fibrosis). Since most of the nutrients are contained in the oil, the demonstration of a direct relationship between the rate of gastric emptying of oil and the suppression of appetite would favour the role of small intestinal receptors in regulating satiety. In contrast, the soup contains few calories, but accounts for the majority of the volume of the meal; an inverse relationship between gastric emptying of soup and the suppression of appetite would therefore be indicative of a role for gastric distension. As discussed in Chapter 9, meal volume and posture may affect gastric emptying and intragastric meal distribution (Burn-Murdoch et al 1980, Hunt et al 1985), and hence both gastric distension and the exposure of the small intestine to nutrients. Accordingly, in the studies reported in Chapters 9, 10 and 11, which evaluated the effects of posture and volume on gastric emptying of a solid meal (Chapter 9) and the effects of posture on gastric emptying of an oil/aqueous meal (Chapters 10 and 11), effects on sensations of hunger and fullness were also quantified.

As discussed in Chapter 4, the use of prokinetic drugs forms the mainstay of treatment in patients with symptomatic gastroparesis. There is evidence that these

drugs may improve symptoms by effects unrelated to changes in gastric emptying (Piessevaux et al 1997, Tack et al 1997). The effects of both cisapride and erythromycin on appetite have not previously been assessed and are discussed in Chapters 12 and 17, respectively.

2.3.4 *Gastrointestinal hormones*

Gastrointestinal hormones released after a meal are important modulators of food intake. Several gastrointestinal hormones have been implicated as satiety factors (Morley 1990, Read et al 1994), of which the best characterised is cholecystokinin (CCK). This was established by the elegant experiments by Davis and co-workers in cross-perfused rats (Davis et al 1969). A number of other gastrointestinal hormones including insulin, bombesin, gastric inhibitory polypeptide (GIP), glucagon-like-peptide-1 (GLP-1), peptide YY and amylin (Morley 1990, Read et al 1994), may also play a role in appetite regulation. There is, however, limited information about the physiological role of most gastrointestinal hormones, in the absence of few specific antagonists for them.

CCK is released from the small intestine in multiple forms after ingestion of fat or protein and has been shown to slow gastric emptying and influence satiety in humans and animals (McHugh & Moran 1986, Meyer et al 1989, Fried et al 1991). There is evidence that fat must be digested in order to stimulate the secretion of CCK (Masclee et al 1989). In animal studies, exogenous administration of CCK produces satiety and CCK receptor antagonists increase food intake (Gibbs et al 1973, Kissileff et al 1981, McHugh & Moran 1985). CCK administration results in dose-related reductions in food intake in humans, probably, at least in part, by slowing gastric emptying (Feinle et al 1996); the satiating effects of CCK are enhanced in the presence of gastric distension

(Melton et al 1992). Although CCK receptor antagonists have to date not been shown to increase food intake in humans, the CCK antagonist, loxiglumide reduces the sensation of fullness induced by intraduodenal lipid infusion and gastric distension (Feinle et al 1996). These latter observations support the concept that the release of CCK in response to a meal affects appetite in humans, via CCK-A receptors (Feinle et al 1996).

While CCK has been the focus of attention, it is clear that other gastrointestinal hormones are important in appetite regulation. For example, in normal volunteers intraduodenal glucose infusion (which is a minimal stimulus to CCK release) suppresses appetite; an effect blocked by octreotide (a long acting somatostatin analogue) which inhibits the release of most gastrointestinal hormones (Lavin et al 1996). There is at present, substantial interest in the role of incretion hormones, particularly glucagon-like-peptide-1 (GLP-1) which reduces food intake in rats (Turton et al 1996).

As discussed in Chapter 5, there is evidence that the blood glucose concentration may modulate sensations arising from the gastrointestinal tract in normal subjects (Hebbard et al 1996a). Although there is evidence that physiological changes in blood glucose have minimal, if any effect on appetite (Lavin et al 1996), patients with diabetes mellitus often experience marked hyperglycaemia. In these patients there is known to be a high prevalence of gastrointestinal symptoms including fullness or bloating (Schvarcz et al 1996), particularly in those patients with poor glycaemic control (Schvarcz et al 1996). There have been no studies which have evaluated the effect of blood glucose concentrations on appetite and other gastrointestinal sensations in patients with diabetes mellitus. This issue is addressed in Chapters 14, 15 and 17.

2.4 CONCLUSIONS

While the factors influencing appetite are complex, it appears that gastric distension, small intestinal mechanisms and the release of gastrointestinal hormones are all likely to play a role. In this thesis the relationships between sensations of hunger and fullness ("appetite") and gastric emptying were evaluated in a number of studies, specifically:

(1) the relationships between postprandial fullness and antral area (Chapters 7 and 8).

(2) the effects of meal volume and posture on appetite (Chapter 9).

(3) the effects of posture on appetite after a meal containing oil and soup components in both normal subjects (Chapter 10) and patients with cystic fibrosis (Chapter 11).

(4) The effect of the prokinetic agent cisapride on appetite after ingestion of a meal containing oil and soup components (Chapter 12).

(5) the relationship between appetite and both gastric emptying and glycaemic control in patients with both non-insulin (Chapter 14) and insulin (Chapter 15) dependent diabetes mellitus.

(6) the effects of hyperglycaemia and the prokinetic drug, erythromycin, on appetite in normal subjects (Chapter 17).

CHAPTER 3

ASSESSMENT OF GASTRIC MOTOR FUNCTION

3.1 INTRODUCTION

Several techniques may be used to assess gastric motor function in humans and these can be broadly divided into three categories: (i) measurement of gastric emptying, (ii) measurement of gastric intraluminal pressures or contractions and (iii) measurement of gastric electrical activity (Table 3.1).

For a comprehensive evaluation of the mechanics of gastric emptying, transpyloric flow and both wall motion and patterns of luminal closure (resulting from gastric contractions) should be evaluated concurrently, with a temporal resolution of only a few seconds (Horowitz et al 1994). Studies in animals, using electromagnetic flow meter monitoring (Malbert et al 1991, Malbert et al 1994) and humans, using Doppler ultrasound (King et al 1984), have shown that gastric emptying is predominantly pulsatile, rather than continuous, so that most chyme enters the duodenum in gushes or pulses (Chapter 1). No single technique provides quantitative information about transpyloric flow on a second by second basis in a way that is comparable to the electromagnetic flow meter (Malbert et al 1991, Malbert et al 1994). Most information about both normal and disordered gastric motor physiology is therefore obtained by simultaneous application of several techniques.

Table 3.1:

Methods to assess gastric motor function
(i) Measurement of gastric emptying Scintigraphy Ultrasound Radiology - liquid barium sulphate - radio-opaque markers Radioisotopic breath tests Magnetic resonance imaging Applied potential tomography/epigastric impedance Pharmacokinetics of oral drug absorption Intubation/aspiration of gastric contents
(ii) Manometry
(iii) Electrogastrography

The major purpose of this chapter is to describe the methodology that is currently available for measurement of gastric motor function in humans and to discuss the advantages and disadvantages inherent in each of these techniques. Particular emphasis will be given to two methods: (i) ultrasound measurement of gastric emptying and (ii) scintigraphic measurement of gastric emptying and antral wall motion "antral curves", as these methods were employed extensively by the author.

3.2 MEASUREMENT OF GASTRIC EMPTYING

A considerable amount of information about both normal and disordered gastric physiology has been obtained from measurements of gastric emptying. There are a number of techniques which have been used to assess gastric emptying and these are summarised below.

3.2.1 *Scintigraphy*

Scintigraphy has become the gold standard for the evaluation of gastric emptying and quantifies the rate at which the stomach empties radiolabelled food. The technique is non-invasive and provides a physiological means to assess gastric emptying. Images are acquired on computer, usually for 2-3 hours, via a gamma camera which detects the radioactivity in the meal (Collins et al 1983, Collins et al 1988). Regions-of-interest (ROI's) can be drawn around the image of the stomach on the computer. By dividing ROI's for the total stomach into proximal and distal stomach regions, intragastric meal distribution can also be evaluated (Collins et al 1988). Assessment of intragastric meal distribution may provide important information, particularly in patients who have gastrointestinal symptoms but normal rates of emptying from the total stomach (Troncon et al 1994). Counts plotted over time represent the emptying rate from each region. Images should be acquired at

frequent intervals, usually every 1-3 minutes, so that the lag phase (the time before any solid food enters the proximal small intestine), can be calculated precisely (Collins et al 1983, Collins et al 1988, Ziessman et al 1996). Standard parameters such as the lag phase, retention of the solid at a given time (eg. 100 min) and the 50% emptying time (T50) of the liquid phase, are commonly used to define normal ranges (Horowitz et al 1991).

The test meal should be of a standard size and caloric content, which can be consumed within a short period of time. Meal temperature influences gastric emptying such that meals hotter or cooler than body temperature (Sun et al 1988), empty more slowly. Gravity may also affect the rate at which the stomach empties food, particularly low nutrient liquids (Burn-Murdoch et al 1980, Moore et al 1988). Both meal temperature and posture should therefore be standardised when performing a gastric emptying test. The blood glucose concentration has been shown to influence gastric emptying, (Chapter 4, Chaper 5). This issue is particularly relevant to patients with diabetes mellitus. The blood glucose concentration should be measured in these patients, both before and during the gastric emptying study and should be taken into consideration when reporting the results (Fraser et al 1990).

During a dual isotope study, the patient is exposed to a small amount of radiation (approximately 1-2mSv), which is often less than that obtained from an abdominal x-ray. This radiation exposure, however limits the number of studies which can be performed over a period of time in any one subject. A futher deficiency of radioisotopic gastric emptying tests is that both solid and liquid markers are diluted progressively by an unknown quantity of gastric secretion.

The most frequently used radioisotope to label meal components is ^{99m}Tc. ^{99m}Tc has a half life of 6 hours and a gamma ray energy of 140keV, making the isotope ideal for imaging. When more than one meal component, eg. solids and liquids, is to be measured, another isotope such as ^{111}In or ^{67}Ga may be used in conjunction with ^{99m}Tc. ^{67}Ga has a half life of 78 hours and three gamma energy windows (90keV, 185keV, 296keV) and ^{111}In a half life of 67 hours and two gamma energies (170keV and 250keV). Since there is a poor correlation between gastric emptying of solid and liquid meal components (Horowitz et al 1991), particularly after gastric surgery, simultaneous measurement of gastric emptying of both solids and liquids by a dual isotope study, is the preferred method (Horowitz et al 1991). There are, however a number of technical difficulties associated with dual isotope studies. In particular, because both ^{67}Ga and ^{111}In have energies greater than ^{99m}Tc, downscatter into the ^{99m}Tc window occurs (when gamma rays derived from ^{67}Ga or ^{111}In traverse tissue, some lose energy, resulting in gamma rays of 140keV which are recognised by the ^{99m}Tc energy window), causing a spurious increase in counts recorded. In contrast, the ^{67}Ga or ^{111}In gamma rays which have lost energy will not be recorded in their specific energy window.

Another problem inherent in scintigraphic measurement techniques is tissue attenuation. The amount and type of tissue between the gamma ray source and the gamma camera, determines the number of gamma rays that are recorded (ie. increasing depth and density of tissue, is associated with a proportionately smaller number of gamma rays detected in the energy window for that particular isotope). Correction for tissue attenuation can be done using several methods. A left lateral image obtained at the end of the study can be used to derive correction factors according to differences in depth between the stomach and the back of the subject (Collins et al 1983), and this technique was used by the author. Alternatively a geometric mean technique can be used, whereby the square root of anterior x

posterior counts is plotted over time (Tothill et al 1978, Christian et al 1980). This latter method represents the gold standard, but the requirement for a double-headed gamma camera, which has the capacity to measure both anterior and posterior counts simultaneously, limits its use. Images acquired in the left anterior oblique position may reduce attenuation effects (Maurer et al 1991, Ford et al 1992), but as the position of the stomach in the body is highly variable, this is not the method of choice.

Correction for isotope decay must also be performed, particularly for isotopes such as ^{99m}Tc which has a relatively short half life.

Radiopharmaceuticals are now available to label all of the components of a normal meal - digestible solid, nondigestible solid, liquid and oil (Madsen et al 1989, Horowitz et al 1991, Cunningham et al 1991d). ^{99m}Tc is generally used as a solid marker in the form of ^{99m}Tc-sulphur colloid. After intravenous injection, ^{99m}Tc-sulphur-colloid binds to the Kupfer cells in the liver. To obtain a solid marker, ^{99m}Tc-sulphur-colloid is injected into the wing vein of a live chicken, the chicken is then sacrificed and the labelled liver extracted (Meyer et al 1976). The labelling efficiency of this technique is of the order of 97-99%. The labelled liver can then be minced and mixed into the test meal, eg. minced beef (Collins et al 1983). While this labelling technique represents the gold standard it is not always practical in the clinical setting and alternative methods, such as labelling egg white or yolk mixed in the solid with slightly less labelling efficiency, are frequently preferred (Meyer et al 1976).

Liquids are usually bound to non-absorbable chelates such as diethylenetriamine penta-acetic acid (DTPA) or ethylenediamine tetra-acetic acid (EDTA). ^{99m}Tc is frequently used to label liquids (Horowitz et al 1993) in single isotope studies of

liquid gastric emptying. In dual isotope studies, ^{111}In or ^{67}Ga is often used as the liquid marker with ^{99m}Tc as the solid marker so that the different meal components can be differentiated (Fisher et al 1982, Bellen et al 1995).

Studies measuring gastric emptying of fat have recently been performed. ^{75}Se glycerol triether incorporated into butter (Jian et al 1982) and ^{123}I labelled corn oil (Meyer et al 1994a) have both been used as markers to evaluate gastric emptying of fatty meals. A marker of olive oil developed at the Royal Adelaide Hospital, ^{99m}Tc-thiocyanate, has superior imaging properties to either ^{75}Se or ^{123}I and exposes the patient to much less radiation (Cunningham et al 1991d).

3.2.2 *Ultrasound*

High resolution ultrasound has been used to measure gastric emptying in normal subjects (Bolondi et al 1985, Holt et al 1986) and in patients with functional dyspepsia (Hausken et al 1992, Hausken et al 1994). It is a non-invasive technique, which is now readily available, and does not expose the patient to radiation, allowing it to be used on many occasions. Gastric emptying can be measured with ultrasound using a variety of techniques (Scarpignato 1990). The most common method is to image a standardised parasagittal area of the antrum (Figure 3.1) with both the aorta and the superior mesenteric vein in the field of view (Bolondi et al 1985). Using a built in measurement program, found on most modern ultrasound machines, the circumference of the antrum can be outlined and the area calculated. The area recorded during the fasting state is subtracted from subsequent measurements made after the meal. Gastric emptying is expressed at any time as: $A_{c(t)} = 100 - ((A_{(t)}/A_{max}) \times 100)$, where $A_{c(t)}$ = corrected antral area at a time point, $A_{(t)}$ = area measured at the given time and A_{max} = maximum antral area recorded after meal ingestion (Hveem et al 1994). Due to technical limitations,

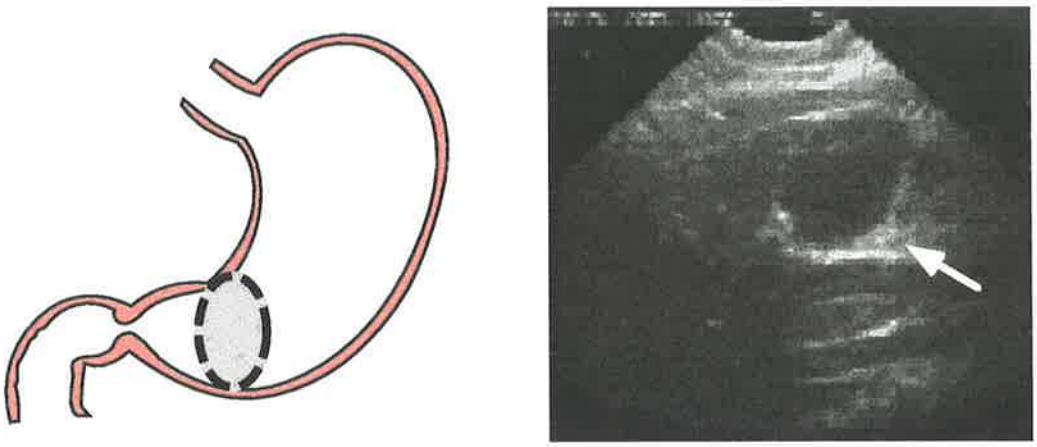

Figure 3.1: Parasagittal ultrasound image of the antrum (indicated by the arrow).

images of the cross-section of the antrum are more readily available than the fundus, although studies which have imaged both regions have been performed (Bateman et al 1982, Holt et al 1986, Gilja et al 1996). The technique is operator dependent, technically demanding in the obese or in subjects with large amounts of bowel gas and can only be used to measure gastric emptying of meals of specific composition, mainly liquids. Even so, due to its widespread availability and the absence of radiation, ultrasound represents a promising technique which is likely to become more frequently used in the future. Other studies using Doppler techniques, have also been utilised to assess the velocity of flow within the stomach (Hausken et al 1992). To evaluate the precision of ultrasound, ultrasonic measurements of gastric emptying have been compared to scintigraphic measurements of total stomach emptying (Bolondi et al 1986, Holt et al 1986, Marzio et al 1989, Wedmann et al 1990). These studies, however have substantial limitations. Furthermore, since the ultrasound technique measures changes in antral area there may be a closer correlation with scintigraphic measurements of the content of the distal stomach but this issue has hitherto not been examined. In Chapter 7, the author reports a study in which simultaneous measurements of gastric emptying using ultrasound techniques and scintigraphic recordings of both the total and distal stomach have been performed.

3.2.3 *Radiological measurement*

Radiological studies, using contrast media to assess gastric emptying, are limited primarily by the radiation exposure and inability to quantify the rate of gastric emptying and intragastric meal distribution (Feldman et al 1984). X-rays taken after ingestion of radiopaque markers (usually plastic tubing) have been used as a measure to assess gastric emptying of non-digestible solids (Feldman et al 1984). The correlation between gastric emptying of solids measured scintigraphically and

radiological measurement of radiopaque markers was recently reported (Chang et al 1996). In this study that there was no correlation between the techniques (Chang et al 1996) possibly because emptying of the radiopaque markers occurred during phase III of the MMC, some time after gastric emptying of the solid meal had presumably already taken place. The use of radioopaque markers is therefore not recommended for assessment of gastric emptying.

3.2.4 *Radioisotopic breath tests*

Measurement of gastric emptying of meals labelled with ^{14}C-octanoic acid and ^{13}C-glycine, by detection of excreted CO_2 has recently been reported (Ghoos et al 1993, Maes et al 1994a, Maes et al 1994b). Maes et al (1994a) described the first dual carbon-labelled breath test for simultaneous measurement of gastric emptying of liquids and solids and it appears that this technique has a precision similar to that of scintigraphy. While radioisotopic breath tests do not provide information about intragastric meal distribution, the method has several advantages over scintigraphy. It is non-invasive, relatively easy to perform and involves exposure of the patient to much less ionising radiation than scintigraphy, allowing multiple measurements in a short period of time. In addition, costly equipment such as a gamma camera is not required. Measurements can be made at the bedside or outside of the hospital and, if appropriate, analysed later. The method is, however dependent on absorption of the test meal to enable the radioactivity to be recorded. Spurious results may therefore be seen in patients with small intestinal malabsorption or increased small bowel transit. Nevertheless, with all of the advantages associated with radioisotopic breath testing, it is likely that this method will be used more widely in the future as a screening test for disordered gastric emptying.

3.2.5 *Magnetic Resonance Imaging (MRI)*

Magnetic resonance imaging (MRI) has recently been used to measure gastric emptying (Schwizer et al 1992). This technique has advantages over scintigraphy in that it can assess the volume of gastric secretion, is non-invasive and does not expose the patient to radiation. MRI is, however extremely expensive, not readily available, and requires the subject to be lying in the supine position. The value of MRI as a diagnostic tool is yet to be established.

3.2.6 *Applied potential tomography and epigastric impedance*

Applied potential tomography and impedance epigastrography are methods which assess gastric emptying by evaluating changes in electrical resistivity or impedance in the abdomen (Sutton et al 1983, Mangnall et al 1987, Mangnall et al 1988). These techniques are non-invasive and do not expose the patient to radiation, however, they are limited by the ability to only measure gastric emptying of one meal component ie. solids (Mangnall et al 1991) or liquids (Mangnall et al 1987). Gastric acid secretion results in a spuriously rapid rate of emptying by increasing the conductivity of gastric contents and thereby reducing impedance. For this reason gastric acid must be inhibited pharmacologically (Mangnall et al 1988) prior to the test. When this is done measurements correlate resonably well with scintigraphy (Mangnall et al 1988). Epigastric impedance has several other limitations. In particular, measurements are influenced by body movement, electrode position, small intestinal transit and gallbladder emptying (Mangnall et al 1988). Applied potential tomography appears to be a more reliable technique than epigastric impedance, although neither method is considered to be an optimal test for measurement of gastric emptying (Scarpignato 1990).

3.2.7 *Pharmacokinetics of oral drug absorption*

Absorption of oral drugs occurs mostly in the small intestine with only minimal absorption from the stomach. The rate of gastric emptying can therefore be determined indirectly by quantifying the plasma concentrations after oral ingestion of a drug. Measurements of blood or salivary concentrations of paracetamol, alcohol and glucose (Nimmo 1976, Holt et al 1980b, Horowitz et al 1989b), have been used to assess gastric emptying. The technique, however lacks precision, even in the assessment of gastric emptying of liquids. The method is therefore infrequently used.

3.2.8 *Intubation/aspiration techniques*

Prior to the widespread availability of scintigraphy, substantial information about gastric emptying was obtained by techniques requiring gastric intubation and aspiration techniques (Ewald et al 1885, Dubois 1979). Such techniques have been used to measure gastric emptying of both solids (Ewald et al 1885) and liquids (Malagelada et al 1976) but cannot provide information about intragastric meal distribution. The method is invasive, as it necessitates the intubation of a nasogastric tube, which may itself influence gastric motility (Fone et al 1991).

3.3 MEASUREMENT OF INTRALUMINAL PRESSURES AND CONTRACTIONS

A great deal of information about gastric physiology has also been obtained from measurement of intragastric pressure or gastric contractions. In this section the current methodology for assessment of intragastric pressure and contractions is reviewed.

3.3.1 *Manometry*

Gastric manometry is a technique used to measure intragastric pressure (Houghton et al 1988). Both solid state and water - perfused pressure manometric catheters can be used. With the technique used by the author in Chapter 6 the subject was intubated with a multi-lumen catheter perfused with water through sideholes spaced along the tube. By incorporating sideholes at many points along the catheter, (Figure 3.2), antral, pyloric and duodenal pressures could be recorded simultaneously on a second by second basis (Heddle et al 1988a). Because it is impossible to accurately position a recording sidehole inside the pylorus, which is a mobile and narrow structure (Heddle et al 1988b), pyloric pressure was recorded by a sleeve sensor (Dent 1976) 4.5 cm in length (Figure 3.2). For accurate measurements, it is essential that the position of the manometric catheter is maintained accurately. This was done by monitoring the transmucosal potential difference (TMPD) between the stomach and duodenum (Heddle et al 1988a, Heddle et al 1988b). Antral and duodenal TMPD sensors were positioned at either side of the sleeve sensor so that the position of the sleeve across the pylorus could be maintained. Manometry accurately records those contractions which result in occlusion of the lumen. Such contractions are likely to be mechanically important ie. when the lumen is occluded, neither orad or aborad movements of ingesta is feasible. However, contractions which indent, but do not occlude the lumen may also be important. It is clear that many gastric contractions do not completely occlude the lumen (Fone et al 1990a), particularly in the proximal stomach. Such contractions will therefore not be detected precisely using manometry (Fone et al 1990a). The combination of manometry with other methods to record gastric wall motion may provide additional information.

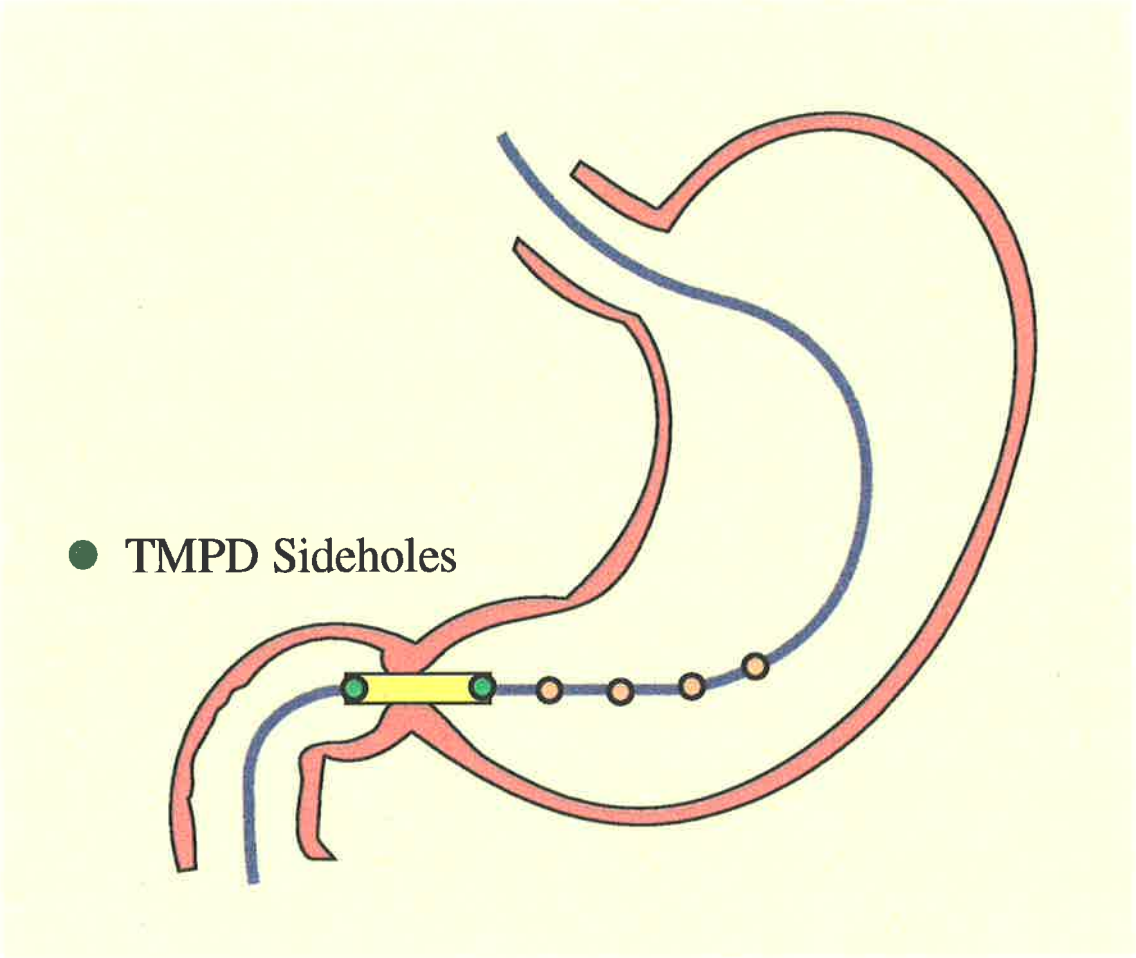

Figure 3.2: Schematic representation of manometric catheter with antral sideholes spaced at 1.5 cm intervals, sleeve sensor and transmucosal potential difference (TMPD) sideholes placed either side of sleeve.

3.3.2 *Barostat*

Because phasic gastric contractions do not occur in the proximal stomach, manometry cannot be used to assess pressure changes in this region. Proximal gastric tone can be measured using a barostat (Azpiroz et al 1987). The barostat incorporates a thin-walled bag attached to an air pump via a plastic tube. When placed in the proximal stomach, with the pressure in the bag made constant, changes in intrabag volume reflect proximal gastric tone. The barostat method is technically demanding, quite invasive and may result in more rapid gastric emptying (Moragas et al 1993).

3.3.3 *Scintigraphy*

Recent studies have shown that scintigraphy can be used to measure both the frequency and amplitude of antral contractions (Akkermans et al 1980, Urbain et al 1990a, Urbain et al 1993). After ingestion of a radiolabelled meal, small regions of interest are drawn over the antrum and activity in these regions quantified ("antral curves"). Data must be acquired at frequent intervals, (approximately 1-2 sec) and for this reason the dose of radioactivity is three to five times more than that required for a standard gastric emptying study (Urbain et al 1990a). Thus far, the antral curve technique has only been used to evaluate antral contractions after ingestion of solid, and semi-solid, but not liquid (Akkermans et al 1980, Urbain et al 1990a, Urbain et al 1993) meals. The advantage of this technique is that it can provide information about both the frequency and amplitude of antral contractions as well as the rate of gastric emptying simultaneously. It has not been established whether the "antral curve" technique has the capacity to determine which contractions result in lumen occlusion. The results of a study comparing scintigraphic and manometric measurements of antral motility is presented in Chapter 6.

3.3.4 *Ultrasound*

Ultrasound techniques can also be used to evaluate the frequency and amplitude of antral contractions by imaging a coronal segment of the antrum. A recent study evaluated the relationship between antral pressure waves measured by intraluminal manometry and antral contractions using ultrasound (Hveem et al 1995) and demonstrated a close correlation between the two techniques. The number of antral contractions measured by ultrasound however, was much greater than the number of pressure waves measured by manometry, as the former technique does not require the contraction to occlude the lumen in order to be detected. Ultrasound techniques show great promise for evaluation of antral motility in humans.

3.3.5 *Radiological measurement*

Fluoroscopy offers qualitative data about distension of the stomach when it is filled with contrast and provides only limited information about gastric contractions and direction of intragastric or transpyloric flow. The examination is not very physiological and involves a high radiation dose, limiting its use (Feldman et al 1984).

3.3.6 *Magnetic Resonance Imaging (MRI)*

Apart from measuring gastric emptying, MRI can be used to evaluate gastric wall motion and record antral contractions with very good temporal resolution after a liquid meal (Schwizer et al 1994). Coronal scans, demonstrating the proximal and distal stomach, can be imaged approximately every 1.2 seconds (Schwizer et al 1994), providing information about the frequency and amplitude of both lumen and non-lumen occlusive contractions. At present MRI is used solely a research tool, primarily because of the substantial cost.

3.4 MEASUREMENT OF GASTRIC ELECTRICAL ACTIVITY

As discussed in Chapter 1, antral contractions are controlled by a gastric pacemaker, located in the greater curve of the proximal stomach, which discharges at a rate of above 3/minute. The electrical activity of the stomach can be measured either in vivo or using external electrodes.

3.4.1 *Serosal electrogastrography*

By placing electrodes either directly on the serosa or the mucosa of the stomach, changes in electrical potentials can be measured (Hamilton et al 1986). This technique is generally limited to animal studies because of its invasive nature.

3.4.2 *External electrogastrography*

External electrogastrography is a non-invasive technique which can be used to examine the electrical activity of the stomach by placing surface electrodes on the skin (Smout et al 1980). An increased prevalence of both bradygastria (decreased number of slow waves) and tachygastria (increased number of slow waves) have been related to abnormal gastric motor function and disordered gastric emptying (Cucchiara et al 1992). The technique requires specialised equipment, experienced personnel and subject movement must be limited throughout the procedure. Electrogastrography is currently used primarily as a research tool.

3.5 CONCLUSION

While there are a number of techniques available to assess gastric motor function in humans, at this time no single technique has the capacity to provide information

about gastric emptying, wall motion, intraluminal pressure and transpyloric flow simultaneously.

Scintigraphy has the potential to measure both gastric emptying and gastric contractions simultaneously. Studies comparing the scintigraphic "antral curve" technique to manometry are required to establish its precision. This issue is addressed in Chapter 6. Ultrasound is also a promising technique which has the capacity to concurrently measure both gastric emptying, transpyloric flow and wall motion, without any radiation exposure. Further studies, however are essential to ensure the accuracy of the ultrasound technique by comparing ultrasonic measurements of gastric emptying with scintigraphic measurements from both the total and distal stomach. This matter is discussed in the study reported in Chapter 7.

CHAPTER 4

CLINICAL MANIFESTATIONS OF DISORDERED GASTRIC EMPTYING

4.1 INTRODUCTION

Disordered gastric emptying may be associated with upper gastrointestinal symptoms, poor glycaemic control and delayed oral drug absorption (Horowitz & Dent 1991, Lin & Hasler 1995). Gastrointestinal symptoms occur frequently in patients with disordered gastric motor function, including patients with diabetes mellitus (Schvarcz et al 1996). Although postprandial hypotension is now recognised as an important clinical problem (Mathias et al 1991), no studies have evaluated whether the magnitude of the fall in blood pressure after a meal is dependent on the rate of gastric emptying.

In this chapter, current knowledge of the pathogenesis and treatment of the clinical consequences of disordered gastric emptying is reviewed briefly.

4.2 GASTROINTESTINAL SYMPTOMS

Gastrointestinal symptoms, including nausea, vomiting, abdominal pain, early satiety and bloating, represent the most common indication for treatment in patients with disordered gastric emptying. Anecdotal evidence suggests that symptoms are often exacerbated by ingestion of food, particulary fatty meals, and are most severe postprandially. Vomiting may occur many hours after food ingestion, and in such cases the presence of recognisable old food is strongly suggestive of gastroparesis.

The mechanisms mediating upper gastrointestinal symptoms in patients with disordered gastric emptying are poorly understood. In particular, it is now recognised that there is a poor correlation between the severity of gastrointestinal symptoms and the rate of gastric emptying (Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991, Stangellini et al 1996), so that some patients with a marked delay in gastric emptying may have none or few symptoms, whereas others with severe unexplained symptoms may have normal gastric emptying. Furthermore, delayed and more rapid gastric emptying may be associated with similar symptoms (Smout et al 1987). Rapid gastric emptying of liquids eg. after a gastric drainage procedure such as Billroth II gastrectomy, may result in the symptom complex known as the: "dumping syndrome" (Lin & Hasler 1995). Symptoms of dumping may be both alimentary (abdominal pain, diarrhoea, bloating and nausea), and vasomotor symptoms (palpitations, lightheadedness, tachycardia and syncope) and can be divided into into the "early" dumping syndrome, occurring within the first 30-60 minutes postprandially and the "late" dumping syndrome, occurring 90-240 minutes after a meal (Lin & Hasler 1995). The rapid delivery of hyperosmolar nutrients into the lumen of the small intestine results in fluid shifts, which may be important in the aetiology of both alimentary and vasomotor symptoms of the "early" dumping syndrome (Smout et al 1987, Lin & Hasler 1995). Modifications in the release of a number of gastrointestinal hormones may also play a role in vasomotor symptoms (Lin & Hasler 1995). Symptoms of the "late" dumping syndrome (palpitations, hunger, confusion, weakness, syncope) are likely to result primarily from reactive hypoglycaemia, induced by a supraphysiological release of insulin (Lin & Hasler 1995).

Gastrointestinal symptoms may reflect abnormal oesophageal, small intestinal or colonic motility (Camilleri et al 1986b), which frequently coexist with disordered gastric motility (Horowitz et al 1991). In some cases psychiatric abnormalities may

be important (Clouse and Lustman 1989). Abnormal gastric myoelectrical activity, which is not always associated with delay in gastric emptying (Dubois 1979, Abell et al 1987, Koch et al 1989), may also be important in the aetiology of symptoms.

4.2.1 *Treatment of gastrointestinal symptoms in patients with gastroparesis*

In patients with gastroparesis, treatment of gastrointestinal symptoms is based mainly on the use of prokinetic drugs, including metoclopramide (McCallum 1985), domperidone (Brodgen et al 1982, Horowitz et al 1985a), erythromycin (Janssens et al 1990, Moswecz et al 1990, Urbain et al 1990b) and cisapride (Camilleri et al 1986, Horowitz et al 1987, McCallum et al 1988). Dietary modifications appear to have relatively little value (Lin & Hasler 1995). Short-term administration of all of the above-mentioned drugs has been shown to increase the rate of gastric emptying, but in all cases there is a poor correlation between the magnitude of symptomatic improvement and changes in gastric emptying. Although the motor mechanisms by which prokinetic drugs increase the rate of gastric emptying are poorly defined, all of these drugs stimulate antral contractions and affect the organisation of antropyloroduodenal motility (Sun et al 1997).

Acute (single) doses of metoclopramide, when given intravenously or orally, improve both gastrointestinal symptoms and gastric emptying of solids and liquids (Schade et al 1985). Metoclopramide can, however, reduce symptoms without accelerating gastric emptying, suggesting that both local and central effects of the drug are important (Horowitz & Dent 1991). Metoclopramide acts as a dopamine antagonist (Peringer et al 1976), displacing dopamine from neural receptor sites and stimulating the release of acetylcholine from the myenteric plexus (Hay & Man 1979). One of the diasadvantages of metoclopramide is that it causes neurological

side effects in up to 20% of patients (Hay & Man 1979, Horowitz & Dent 1991). There is also some evidence that the gastrokinetic effect of metoclopramide may not be sustained during chronic administration (Schade et al 1985).

Domperidone, like metoclopramide, acts as a dopamine antagonist, but lacks cholinergic activity. Because domperidone penetrates the blood brain barrier poorly, neurological side effects are rarely seen (Horowitz et al 1985a, Brogden et al 1982). Acute doses of domperidone have been shown to increase gastric emptying of both solids and liquids, the most marked increase evident in patients with the greatest delay in gastric emptying (Horowitz et al 1985a), and improve upper gastrointestinal symptoms in pateints with gastroparesis (Brogden et al 1982). Like metoclopramide, its gastrokinetic efficacy may diminish with time (Horowitz et al 1985a).

Erythromycin stimulates gastric emptying by acting as an agonist of the gastrointestinal peptide, motilin. The interaction with motilin receptors, which are located in the antrum and proximal small intestine, causes acetylcholine release (Horowitz & Dent 1991, Peeters 1993). Erythromycin has been shown to increase gastric emptying of solids and liquids in both normal subjects and patients with gastroparesis (Ramirez et al 1994, Mearin & Malagelada 1995, Urbain et al 1990b, Mozwecz et al 1990, Edelbroek et al 1993) When given intravenously to patients with gastroparesis, erythromycin may increase gastric emptying of solids and liquids to rates faster than normal (Janssens et al 1990, Urbain et al 1990b, Ramirez et al 1994). After chronic oral administration, erythromycin also improves gastric emptying, although it is not clear whether this effect is sustained in the long term (Urbain et al 1990b, Richards et al 1993). The dramatic acceleration of gastric emptying by intravenous erythromycin is associated with emptying of larger particles of food into the small intestine (Otterson and Sarna 1990), so that

erythromycin interferes with the normal sieving function of the stomach (Lin et al 1994).

Cisapride stimulates the release of acetylcholine from the myenteric plexus by binding to 5-hydroxytryptamine ($5HT_4$) receptors, and is devoid of antidopaminergic and antiemetic effects (McCallum et al 1988). Both acute and chronic administration of cisapride improves gastric emptying in patients with gastroparesis, including those with diabetes mellitus (Feldman & Smith 1987, Horowitz et al 1987, McCullum et al 1988). When given orally in therapeutic doses, cisapride has few side apart from abdominal cramps and increased bowel frequency. Intravenous cisapride may be associated with more serious side effects including cardiac arrhythmias, and for this reason an intravenous formulation is not available (Farrington 1996).

Prokinetic drugs have been shown to improve gastrointestinal symptoms, although as discussed in previous studies, the observed relationship between the magnitude of improvement of symptoms and change in gastric emptying is weak (Horowitz et al 1987, Reynolds 1989). The latter observation may potentially reflect the test meals that have been used, as in most studies the effect of prokinetic drugs on gastric emptying of relatively bland test meals, rather than meals that are high in volume and nutrient density, has been evaluated. For example, the effect of prokinetic drugs on gastric emptying of fat has hitherto not been evaluated and this issue forms the focus of the study reported in Chapter 12. It is also possible that symptomatic improvement is unrelated to the effects on gastric emptying or gastric motor function. More recent studies indicate that prokinetic drugs may influence gastrointestinal sensation (Piessevaux et al 1997, Tack et al 1997). The effects of cisapride (Chapter 12) and erythromycin (Chapter 17) on appetite in normal subjects are addressed in this thesis.

4.2.2 *Treatment of symptoms associated with more rapid gastric emptying*

In patients with rapid gastric emptying symptoms of the "early" dumping syndrome usually improve over time. Patients should be advised to modify their diet so that they eat small, solid, meals frequently and not drink soon after eating (Horowitz & Dent 1991). Postural adjustments may also be beneficial. Ingestion of guar gum, a soluble fibre may also improve symptoms, possibly by slowing the rate of gastric emptying (Harju & Makela 1984). Acute administration of somatostatin and its long acting analogue, octreotide, have been shown to improve symptoms probably by slowing gastric emptying and inhibiting release of gastrointestinal hormones (Hopman et al 1988, Tulassay et al 1988).

4.3 GLYCAEMIC CONTROL

In normal subjects, the rate of gastric emptying is a major factor in blood glucose homeostasis by controlling the delivery of carbohydrate to the small intestine so that the rate of gastric emptying accounts for about 36% of the variance in the rise in blood glucose after an oral glucose load of 50-75g (Horowitz et al 1993, Schwartz et al 1995). Gastric emptying of glucose is influenced by previous dietary intake of glucose, indicating that there are adaptive changes in the mechanisms that regulate gastric emptying (Cunningham et al 1991b, Horowitz et al 1996a). Hepatic glucose metabolism is also an important determinant of postprandial blood glucose concentrations (Frank et al 1995). Studies in which glucose absorption is measured directly are therefore required to clarify the relative contributions of gastric emptying and hepatic glucose metabolism to postprandial blood glucose concentrations in both normal subjects and patients with diabetes mellitus.

The relationship between postprandial blood glucose control and gastric emptying in both IDDM and NIDDM is likely to be complex, particularly as the blood glucose concentration is also a determinant of the rate of gastric emptying in patients with diabetes mellitus (discussed in Chapter 14). If the rate of gastric emptying is established as a major determinant of postprandial blood glucose concentrations, as appears probable, this has considerable relevance to the optimisation of blood glucose control in patients with diabetes mellitus. In patients with IDDM, delayed gastric emptying, may, at least theoretically, lead to poor glycaemic control by causing a mismatch in onset of insulin action and delivery of nutrients to the small intestine (Horowitz & Fraser 1994). Although it has been established in IDDM patients that both postprandial insulin requirement and blood glucose concentrations are initially reduced when gastric emptying is slower (Ishii et al 1994, Kong et al 1996), there is relatively little information about the relationship between postprandial blood glucose concentrations and gastric emptying in IDDM (Chapter 13). In contrast to IDDM, in NIDDM patients slowing of gastric emptying, by dietary or pharmacological means has clearly been shown to improve short term glycaemic control (Phillips et al 1993, Schwartz et al 1994), probably because the slower absorption of carbohydrate minimises the impact of the delay in insulin release characteristic of this disorder. However, no studies have evaluated the relationship between the rise in postprandial blood glucose concentrations and the rate of gastric emptying in patients with NIDDM. This latter issue is addressed in the study reported in Chapter 14.

4.4 ORAL DRUG ABSORPTION

Most drugs are absorbed predominantly in the small intestine, with only minimal absorption taking place in the stomach. The rate of gastric emptying is therefore, potentially an important determinant of oral drug absorption (Nimmo et al 1976,

Horowitz et al 1989b, Hebbard et al 1995). This has important implications in patients with gastroparesis as to whether medication should be administered either with or after a meal. For example, in patients with NIDDM who are taking oral hypoglycaemic agents absorption of these drugs may be delayed, especially during hyperglycaemia (Groop et al 1989, Horowitz et al 1991). Patients with symptoms of "early" dumping syndrome and rapid gastric emptying should also be aware that the latter may lead to an accelerated rate of absorption of drugs, including alcohol (Horowitz et al 1989b). As discussed, this effect may be minimised by consuming solid foods with liquids.

4.5 POSTPRANDIAL HYPOTENSION

Postprandial hypotension is an important clinical problem, particularly in the elderly and in patients with autonomic failure (Jansen et al 1991, Mathias et al 1991) resulting in syncope, dizziness, blurred vision and falls. The mechanisms responsible for postprandial hypotension are poorly understood, however, impaired regulation of splanchnic blood flow, and the release of gastrointestinal hormones appear to be important (Jansen et al 1991, Mathias et al 1991, Jansen et al 1995). The fall in blood pressure occurs soon after meal ingestion and with the maximum increase occurring at 30-60 min (Jansen et al 1995), and is most marked with meals with a high glucose content, suggesting a relationship to the rate of delivery of nutrients to the small intestine. The relationship between the postprandial blood pressure response to a meal and the rate of gastric emptying has, surprisingly, not been evaluated and this issue is addressed in the study reported in Chapter 16. If such a relationship was established, slowing gastric emptying, either pharmacologically or by dietary means, may potentially result in a reduction in the hypotensive effect of a meal.

4.6 CONCLUSIONS

This chapter raises a number of issues which are addressed by the author in this thesis. Studies were designed to evaluate the following:

(1) The effect of hyperglycaemia and erythromycin on gastric emptying and sensations of hunger and fullness (Chapter 17).

(2) The effects of cisapride on (i) gastric emptying of an oil/aqueous meal and (ii) appetite in normal subjects (Chapter 12).

(3) The relationship between the fall in blood pressure after a meal and the rate of gastric emptying of an oral glucose load in patients with NIDDM and young and older normal subjects (Chapter 16).

CHAPTER 5

GASTRIC MOTOR FUNCTION IN DIABETES MELLITUS

5.1 INTRODUCTION

It is now recognised that abnormal gastric motor function, associated with disordered (particularly delayed) gastric emptying, is likely to have a major impact on the management of patients with insulin dependent (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). The concept that abnormal gastric emptying may contribute to, as well as result from, poor control of blood glucose concentrations has been supported by the demonstration that: (i) there is a high prevalence of delayed gastric emptying in patients with longstanding diabetes mellitus, (ii) the blood glucose response to oral carbohydrate and gastric emptying are related in both normal subjects and patients with IDDM and NIDDM, and (iii) acute changes in the blood glucose concentration (even within the physiological range) affect gastric emptying and motility. Recent studies also provide evidence that the blood glucose concentration may modulate the perception of sensations arising from the gastrointestinal tract.

The purpose of this chapter is to review current knowledge of gastric motor function in patients with diabetes mellitus with particular emphasis on the: (i) prevalence of abnormal gastric emptying and motor function, and (ii) effects of the blood glucose concentration on gastric emptying, gastric motor function and perception of gastrointestinal sensations. The content of this chapter is complimentary to that included in Chapters 1 and 4, in which the pathophysiology and clinical consequences of disordered gastric emptying is reviewed.

5.2 PREVALENCE OF DISORDERED GASTRIC EMPTYING IN DIABETES MELLITUS

There is unequivocal evidence that 30%-50% of randomly selected patients with longstanding diabetes mellitus have delayed gastric emptying of solid and/or nutrient liquid meals (Keshavarzian et al 1987, Horowitz et al 1989a, Wegener et al 1990, Horowitz et al 1991) (Figure 5.1). Evidence of a delay in the emptying of water is less consistent; possibly because the effects of hyperglycaemia on gastric emptying may be greater for nutrients than non-nutrients, and water does not stimulate mechanisms which retard gastric emptying (MacGregor et al 1976). It is recognised, particularly of nutrient liquids, that gastric emptying is accelerated in a minority of patients with longstanding IDDM (Keshavarzian et al 1987, Horowitz et al 1991). The reduced rate of gastric emptying observed in IDDM is often associated with an abnormal distribution of food within the stomach (Urbain et al 1993), but it has not been established whether evaluation of intragastric meal distribution increases the diagnostic sensitivity of measurement of gastric emptying in patients with diabetes. This issue is addressed in the study reported in Chapter 13. It has been suggested that in patients with non-ulcer dyspepsia, abnormal intragastric meal distribution may account for symptoms (Troncon et al 1994). It has been assumed that in most patients with diabetes there will be a close correlation between gastric emptying of solid and nutrient liquid meal components, but this is not the case (Wegener et al 1990, Horowitz et al 1991) (Figure 5.2). Furthermore, there is little evidence that measurement of emptying of solids is more sensitive than a high nutrient liquid (as opposed to water) in detecting disordered gastric emptying in patients with diabetes mellitus (Horowitz et al 1991). The prevalence of disordered gastric emptying during euglycaemia, and in patients with 'brittle' diabetes mellitus, have not been assessed. The prevalence of abnormal gastric emptying in patients with recently diagnosed IDDM has also not been evaluated.

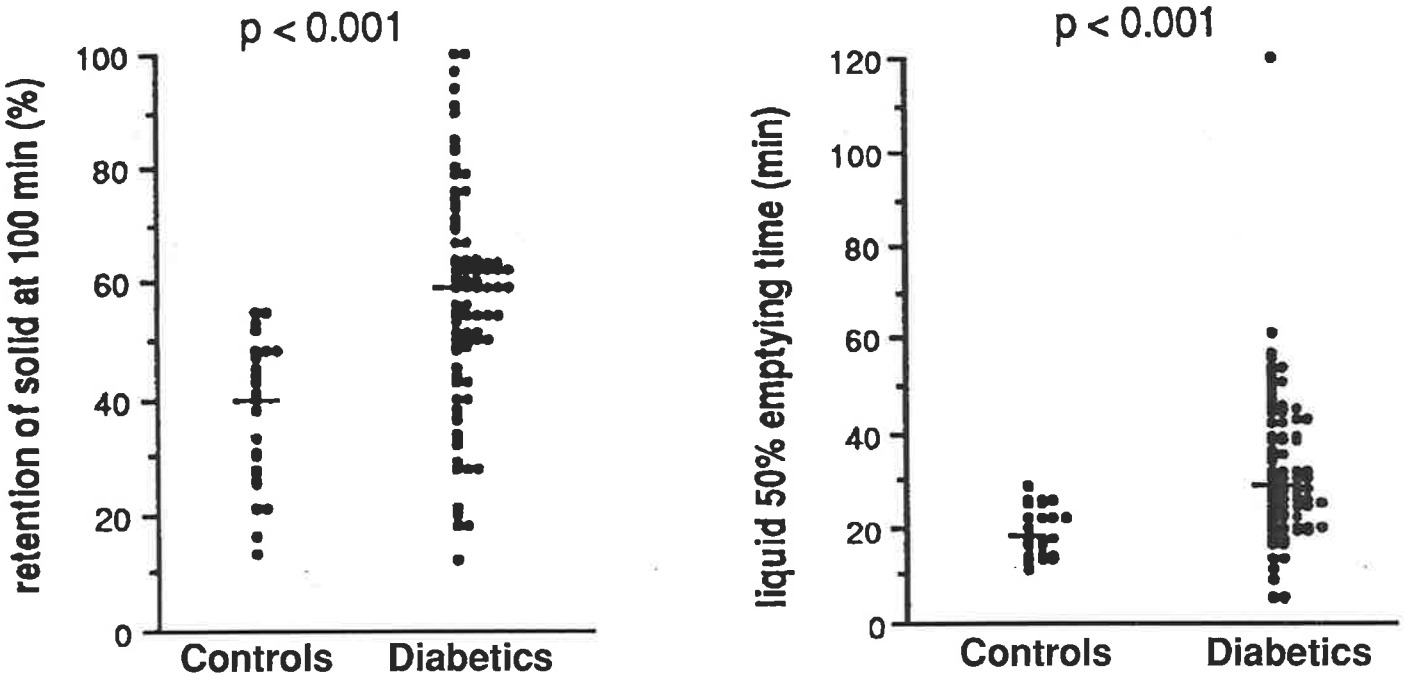

Fig 5.1: Gastric emptying of both solid (100g minced beef) and liquid (10% dextrose) in both normal subjects and patients with diabetes mellitus. Horizontal lines represent median values. (Horowitz et al 1991)

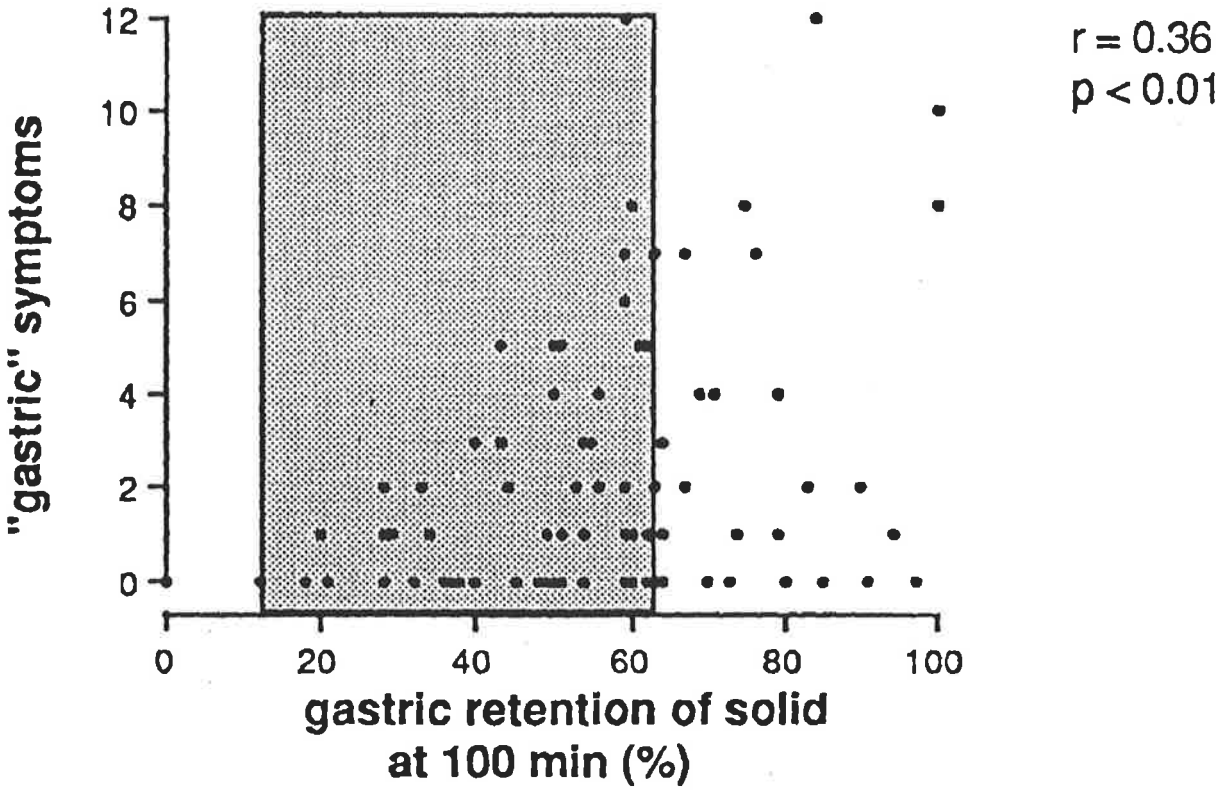

Fig 5.2: Relationship between the score for "gastric" symptoms and the percentage of solid remaining in the stomach at 100 min. The range for normal solid emptying is illustrated by the shaded area. (Horowitz et al 1991).

In most patients with NIDDM, fasting hyperglycaemia is present for a number of years before diagnosis (Harris et al 1992) and it is therefore impossible in most cases to define the onset of NIDDM. In contrast to longstanding NIDDM, where the prevalence of gastroparesis is similar to that in IDDM (Horowitz et al 1991), there is relatively little information about the prevalence of disordered gastric emptying in patients with "early" NIDDM. Phillips et al (1992) reported that gastric emptying of a 50g glucose load is more rapid than normal in such patients and suggested that this may predispose to the development of. There were, however, differences in racial distribution between the diabetic subjects, who were predominantly Hispanic, and the control subjects who were non-Hispanic, which may have contributed to their findings, particularly as the same group has reported that gastric emptying is more rapid in non-diabetic, Hispanic subjects compared to non-diabetic, non-Hispanic subjects (Schwartz et al 1995). More recently, gastric emptying of a solid (pancake) meal has been reported to be faster in patients with "early" NIDDM <2 years, compared with an appropriate control group, but the observed differences in gastric emptying were relatively modest (Phillips et al 1996). Additional studies are therefore required to resolve this issue (see Chapter 14). If it established that gastric emptying is more rapid in NIDDM, this observation would potentially have major implications for the management of glycaemic control in these patients.

5.3 GASTRIC MOTILITY IN DIABETES MELLITUS

In patients with diabetes there have been few measurements of the function of any motor component other than the antrum. Most studies have been performed without blood glucose monitoring in symptomatic patients with IDDM who were assumed to have gastroparesis (Camilleri et al 1984, Kim et al 1991). It is, however, clear that even during euglycaemia disordered fasting and postprandial

motility occur frequently and that the motor dysfunctions are complex and variable (Fraser et al 1993c, Samsom et al 1995, Samsom et al 1996). Their heterogeneous nature has important implications for targeting therapy and better definition of these is essential. In some patients there is a reduction in the number of antral waves which are temporally associated with duodenal pressure waves (Fraser et al 1994), while in others, the compliance of the proximal stomach is increased (Samsom et al 1995). Disordered proximal small intestinal motility also occurs frequently. Increased pyloric resistance is unlikely to be a major factor contributing to retardation of transpyloric flow, at least during euglycaemia (Fraser et al 1993c, Fraser et al 1994). In most patients gastric pacemaker activity is normal during euglycaemia (Jebbink et al 1994).

5.4 GASTROINTESTINAL SYMPTOMS IN DIABETES MELLITUS

There is a high prevalence of upper gastrointestinal symptoms in patients with insulin dependent diabetes mellitus (IDDM) particularly females (Schvarcz et al 1996). Although there is a poor correlation between the severity of symptoms and the rate of gastric emptying, symptoms have usually been assessed in the fasted state rather than postprandially (Keshavarzian et al 1987, Horowitz et al 1989a, Wegener et al 1990, Horowitz et al 1991) and this issue is addressed in the study described in Chapter 15. Nevertheless it is clear that the aetiology of symptoms in patients with diabetes mellitus is multifactorial and gastroparesis should be regarded as a marker of gastroduodenal motor abnormality rather than a direct cause of symptoms. Feedback from both mechano- and chemoreceptors in the stomach and small intestine may play a major role in mediating gastrointestinal symptoms (Mearin et al 1991). Perception of gastric distension has been demonstrated to be increased in patients with IDDM who had upper gastrointestinal symptoms, under euglycaemic conditions (Samsom et al 1995).

Studies measuring cortical evoked potentials after oesophageal balloon distension suggest that disordered perception in patients with diabetes mellitus, may potentially result from abnormal vagal conduction (Tougas et al 1992b). Like patients with functional dyspepsia (Hausken & Berstad 1992), in IDDM (Undeland et al 1996) both fasting and postprandial antral areas measured by ultrasound are greater than control subjects, suggesting that changes in antral tone may also be important in triggering symptoms.

5.5 THE EFFECT OF BLOOD GLUCOSE CONCENTRATION ON GASTRIC MOTOR AND SENSORY FUNCTION

Disordered gastric emptying and gastric motility in diabetes mellitus has traditionally been attributed to irreversible autonomic (vagal) neuropathy (Rundles 1945), but this assumption is clearly incorrect. There is currently no good method of assessing gastrointestinal autonomic nerve function, but studies using tests of cardiovascular autonomic nerve function as a surrogate marker have found that although there is a correlation between delay in gastric emptying and autonomic nerve dysfunction in patients with diabetes, it is rather weak (Wegener et al 1990, Horowitz et al 1991). This observation strongly suggests that factors unrelated to irreversible autonomic nerve dysfunction must contribute to the disordered gastric emptying observed in these patients. It is now well recognised that acute changes in the blood glucose concentration have a major, reversible, influence on gastric motor (Fraser et al 1990, Oster-Jorgensen et al 1990, Fraser et al 1991, Schvarcz et al 1993, Schvarcz et al 1995, Jebbink et al 1994, Hebbard et al 1996a, Hebbard et al 1996b, Hasler et al 1995) and sensory (Hebbard et al 1996a, Hebbard et al 1996b) function, as well as motility in other regions of the gastrointestinal tract (de Boer et al 1992a, de Boer et al 1992b, de Boer et al 1993, Chey et al 1995, Sims et al 1995, Russo et al 1996, Russo et al 1997).

5.5.1 *Gastric emptying*

A number of studies have shown that marked hyperglycaemia (blood glucose ≈15mmol/L) slows gastric emptying in both normal subjects and in patients with diabetes (MacGregor et al 1976, Horowitz et al 1989a, Fraser et al 1990, Oster-Jorgensen et al 1990). It has recently been demonstrated that changes in the blood glucose concentration within the normal postprandial range affect gastric emptying in both normal subjects and patients with IDDM, so that emptying of solid and nutrient-containing liquid meal components is slower at a blood glucose of 8mmol/L when compared to 4mmol/L (Schvarcz et al 1996). It has been suggested (Dao et al 1990), but not confirmed, that the threshold for slowing of gastric emptying by hyperglycaemia may be higher in patients with NIDDM. Insulin-induced hypoglycaemia increases the rate of gastric emptying of solids and liquids in both normal subjects (Schvarcz et al 1995) and in patients with IDDM (Schvarcz et al 1993). This acceleration of gastric emptying may be important in the counter-regulation of hypoglycaemia and it is not known whether the presence of gastroparesis, or autonomic neuropathy, is associated with an impaired gastric motor response to hypoglycaemia. It is also relevant to note that the effect of chronic, rather than acute, glycaemic control on gastric emptying in patients with diabetes has not been assessed adequately. Furthermore, it is also uncertain whether the gastric motor response to acute changes in the blood glucose concentration is influenced by previous blood glucose control.

5.5.2 *Gastroduodenal motility*

In normal subjects marked (acute) hyperglycaemia (≈15 mmol/L) reduces fundic tone (Hebbard et al 1996a, Hebbard et al 1996b), inhibits antral pressure waves (Barnett & Owyang 1988, Fraser et al 1991, Kawagishi et al 1994, Hasler et al 1995) and stimulates pressure waves which are localised to the pylorus (Fraser et

al 1991). This is a motor pattern which is known to be associated with retardation of gastric emptying, e.g. similar changes in motility occur when nutrients are infused into the small intestine (Heddle et al 1989). Fasting antral motility is suppressed at a blood glucose of 7.8 mmol/L (Barnett & Owyang 1988, Horowitz et al 1989a), whereas the threshold for suppression of postprandial antral motility may be higher at about 9.7 mmol/L (Horowitz et al 1989a, Hasler et al 1995). A recent study in patients with IDDM demonstrated that hyperglycaemia influences the organisation of antral pressure waves, so that at a blood glucose concentration of ≈16 mmol/L reduced the number of postprandial antral pressure waves which propagated over 4.5 cm, but not the total number of antral pressure waves which when compared to euglycaemia, was less (Samsom et al 1996). Hyperglycaemia (≈13-15 mmol/L) has also been shown to affect gastric pacemaker activity in both patients with IDDM (Jebbink et al 1994) and normal subjects (Hasler et al 1995, Hebbard et al 1997), with an increased prevalence of tachyarrhythmias that is likely to alter gastric motor function. It has not been established whether changes in the blood glucose concentration within the physiological range affect motility of the proximal stomach or pylorus, in either normal subjects or patients with diabetes mellitus. The effect of chronic, as opposed to acute, hyperglycaemia on gastric emptying and gastric motility, has also not been evaluated.

5.5.3 *Gastrointestinal symptoms*

In normal subjects, acute hyperglycaemia has been shown to influence perception of a number of sensations arising from the gastrointestinal tract including the stomach (Hebbard et al 1996a), the colon (Chey et al 1995), the oesophagus (Boexchstaens (in press)) and the small intestine (Lingenfelser et al 1996).

For example, sensations of nausea and fullness, induced by proximal stomach distension with a barostat (Hebbard et al 1996a) (Figure 5.3), and small intestinal nutrient infusion (Hebbard et al 1997) are more marked at a blood glucose concentration of ≈14 mmol/L when compared to euglycaemia (Hebbard et al 1997). It has not been established whether the blood glucose concentration influences perception of sensations arising from the gastrointestinal tract in patients with diabetes mellitus. This issue is discussed further in Chapters 14, 15 and 17.

5.5.4 *Mechanisms mediating the effects of the blood glucose concentration on motility and sensation*

There is little information about the mechanisms mediating the effects of the blood glucose concentration on gastric motor function and gastric emptying. In considering the effects of hyperglycaemia on motility, a central nervous system effect is supported by animal and human studies (de Boer et al 1992a, Sakaguchi et al 1994). A direct effect on smooth muscle seems unlikely as both smooth muscle stimulation (pylorus, small intestine) (Fraser et al 1991, Russo et al 1996) and inhibition (proximal stomach, antrum) (Barnett & Owyang 1988, Hasler et al 1995, Hebbard et al 1996a, Hebbard et al 1996b, Hebbard et al 1997) occur during hyperglycaemia. Indomethacin has been reported to block hyperglycaemia-induced tachyarrhythmias, in normal subjects suggesting that prostaglandin-dependent pathways may be important in this mechanism (Hasler et al 1995).

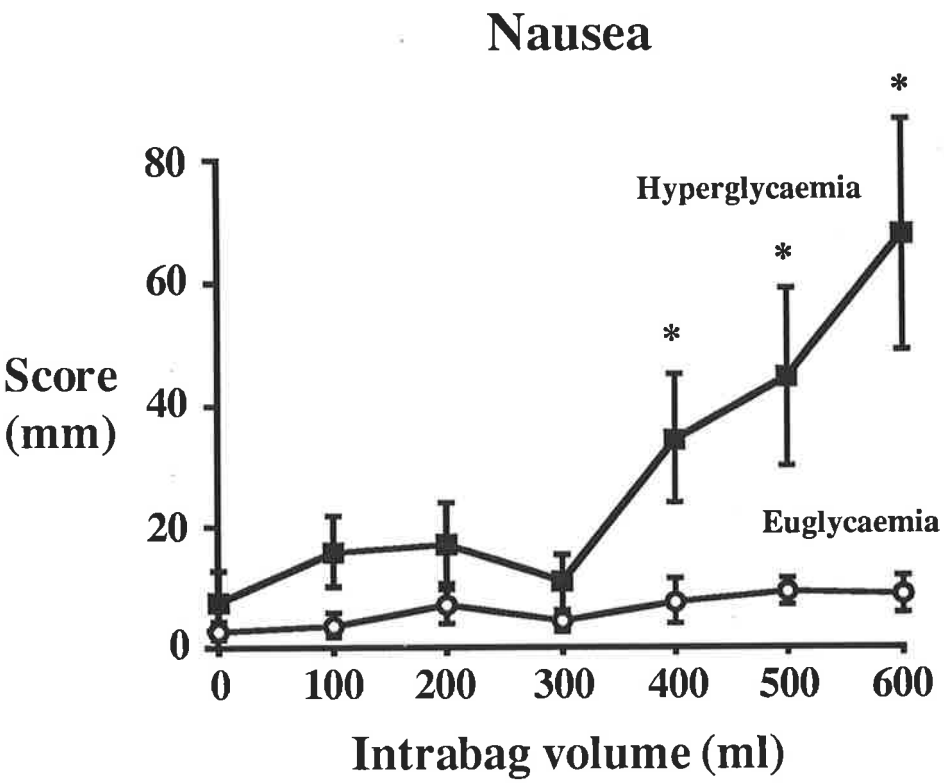

Fig 5.3: Score for nausea in normal subjects, after proximal stomach distension with a barostat during hyperglycaemia and euglycaemia. (Hebbard et al 1996).

It is uncertain whether insulin affects gastrointestinal motor function (Bjornsson et al 1995, Chey et al 1995, Eliasson et al 1995, Hasler et al 1995, Sims et al 1995). Although insulin may influence gastric motility (Bjornsson et al 1995, Eliasson et al 1995), this effect is unlikely to be major as hyperglycaemia slows gastric emptying in patients with IDDM who have no endogenous insulin secretion (Fraser et al 1990, Schvarcz et al 1996). Nevertheless, the effect of insulin on gastric motility requires clarification. The acceleration of gastric emptying induced by hypoglycaemia in normal subjects is dependent on vagal mechanisms (Schvarcz et al 1996).

5.6 CONCLUSIONS

While there has been a substantial increase in knowledge about gastric motor function in patients with diabetes mellitus, there are many unresolved issues, some of which have been addressed by the author. While there is unequivocal evidence that abnormal gastric emptying occurs frequently in longstanding diabetes mellitus and that this may be associated with abnormal meal distribution, the prevalence of abnormal intragastric meal distribution and whether measurement of intragastric distribution has diagnostic value, have not previously been assessed. The study reported in Chapter 13 deals with this issue.

Gastric emptying is frequently delayed in longstanding NIDDM, but the prevalence of abnormal gastric emptying in patients with recently diagnosed NIDDM is uncertain. In this group the relationship between postprandial blood glucose concentrations and gastric emptying has also not been evaluated. These issues form the focus of the study reported in Chapter 14.

While studies in normal subjects have demonstrated that acute changes in the blood glucose concentration may influence the perception of sensations arising from the gastrointestinal tract and there is a high prevalence of gastrointestinal symptoms in unselected patients with IDDM, the relationship between gastrointestinal symptoms and blood glucose control in patients with IDDM has not been evaluated. Although the correlation between gastrointestinal symptoms and gastric emptying in patients with diabetes is poor, symptoms have been assessed preprandially rather than after a meal. The relationship between pre and postprandial gastrointestinal symptoms and both gastric emptying and glycaemic control in IDDM have been evaluated in the study reported in Chapter 15.

CHAPTER 6

EVALUATION OF ANTRAL MOTILITY IN HUMANS USING MANOMETRY AND SCINTIGRAPHY

6.1 SUMMARY

Recent studies suggest that scintigraphy can be used to non-invasively evaluate antral motility in humans, although scintigraphic techniques have not yet been compared with more conventional measurements of intraluminal pressures by manometry. Simultaneous scintigraphic and manometric measurements of antral motility were performed in nine healthy volunteers. After intubation with a sleeve/sidehole catheter which incorporated five pressure sideholes located at 1.5 cm intervals spanning the antrum, each subject ingested 100 g minced beef labelled with 100 MBq ^{99m}Tc-chicken liver and 150 ml water. Between 40-43, 60-63, 80-83, and 100-103 minutes after meal ingestion, radioisotopic data were acquired in two second frames. Time-activity curves showing antral 'contractions' resulting from wall motion were derived by drawing small regions of interest over the antrum to coincide with the position of the antral manometric sideholes. Scintigraphic contraction rates approximated 3/minute, whereas antral pressure waves that occluded the lumen were less frequent ($p<0.01$ for all), particularly in the proximal antrum. The amplitude of wall motion, evaluated scintigraphically, and the amplitude of pressure waves were both inversely related to the distance from the pylorus ($r>-0.32$, $p<0.05$) and antral volume $r>-0.29$ ($p<0.05$). There were significant relationships between the amplitude of contractions assessed scintigraphically and the number of lumen-occlusive antral pressure waves in the distal antrum ($r-0.48$, $p<0.05$) but not in the more proximal antral regions.

It is concluded that scintigraphy can detect antral wall motion with greater sensitivity than manometry, particularly in the proximal antrum. As manometry gives information on the amplitude as well as the temporal and spatial organisation of those contractions which result in lumen occlusion, the combination of scintigraphic and manometric techniques in the evaluation of antral motility shows considerable promise.

6.2 INTRODUCTION

The mechanical factors responsible for normal and delayed gastric emptying are still poorly understood, largely because of the considerable technical challenges associated with the measurement of the several potentially relevant gastric and small intestinal mechanisms in humans (Horowitz & Dent 1991). Although it is clear that the motor functions of the proximal stomach, antrum, pylorus, and proximal small intestine are closely related (Heddle et al 1993), the emphasis of most studies has been to attempt definition of the role of individual motor components, particularly the contribution of antral contractions, to gastric emptying. Transpyloric flow of digesta is predominantly pulsatile, rather than continuous (Malbert & Ruckebusch 1991, Malbert et al 1992, Malbert & Mathis 1994). The characteristics of individual flow pulses, which vary considerably from one cycle to the next, may be more dependent on the temporal and spatial organisation of motor events in different regions of the stomach and proximal small intestine than their amplitude (Malbert et al 1992, Malbert & Mathis 1994). The impact of a contraction on luminal flow is influenced by patterns of lumen occlusion. When a contraction indents but does not occlude the lumen, flow can occur, but when the lumen is occluded antegrade and retrograde flow cannot occur (Horowitz & Dent 1991, Tougas et al 1992a). It follows that an optimum approach to the evaluation of normal and disordered gastric motor function would require concurrent

measurements of wall motion generated by muscular contractions, intraluminal pressures, and transpyloric flow on a second by second basis. Consequently, most information is obtained with the simultaneous use of a combination of techniques (Horowitz & Dent 1991).

Measurement of intraluminal antral, pyloric, and duodenal pressures is optimally performed by perfusion manometry using a closely spaced sidehole array and a pyloric sleeve sensor (Heddle et al 1988a, Fone et al 1990a, Edelbroek et al 1994, Sun et al 1997).

Manometry can readily evaluate the organisation, as well as the amplitude, of lumen-occlusive pressure waves (Heddle et al 1988a, Edelbroek et al 1994, Sun et al 1997). It is, however, a technically complex, invasive technique which is uncomfortable for the subject. Furthermore, it is an insensitive measure of contractions that do not occlude the lumen which occur frequently in the fundus and proximal antrum and may be important in determining both intragastric movement of digesta and transpyloric flow (Malbert et al 1992).

The use of radionuclide methods has contributed greatly to knowledge about normal and disordered gastric motor function (Akkermans et al 1980, Collins et al 1983, Camilleri et al 1985, Stacher et al 1987a, Collins et al 1988, Urbain et al 1990a, Urbain et al 1993). Our group was the first to describe a scintigraphic technique which can recognise intragastric movement of food that occurs as a result of gastric contractions. The frequency and amplitude of individual antral contractions are evaluated by measuring changes in radioactivity within small regions of interest drawn over the antrum (Akkermans et al 1980). Modifications of this technique have been used by others to evaluate normal (Urbain et al 1990a) and disordered (Stacher et al 1987a, Urbain et al 1993) gastric motility as well as

the effects of prokinetic drugs (Stacher et al 1987b). The non-invasive nature of scintigraphy and its apparent ability to recognise individual contractions represent potential advantages over manometry in the evaluation of antral motility.

The purpose of the present study was to compare scintigraphic and manometric measurements of postprandial antral motility in normal subjects.

6.3 MATERIALS AND METHODS

Studies were done in nine healthy volunteers (8 M, 1 F: age 23 (21-25) years, median weight, 67 kg (62-79); median BMI 22 kg/m^2 (19-25) who were all non-smokers, had no history of gastrointestinal disease or surgery, and were not taking any medication. The study protocol was approved by the Human Ethics committee of the Royal Adelaide Hospital and written informed consent was obtained from each subject.

6.3.1 *Experimental protocol*

Each of the subjects underwent simultaneous measurement of antral motility by intraluminal manometry and scintigraphy.

6.3.2 *Intraluminal Manometry*

The manometric technique used has been described in detail elsewhere (Heddle et al 1988, Edelbroek et al 1994). In brief, the manometric assembly, incorporating a pyloric sleeve sensor with a length of 4.5 cm, had a chain of 10 sideholes spaced at 1.5 cm intervals. Four of the sideholes were orad to the proximal sleeve end, four were parallel to the sleeve sensor, and two were aborad to the distal sleeve end.

The sideholes at each end of the sleeve sensor recorded both intraluminal pressure and antroduodenal transmucosal potential difference (TMPD) simultaneously (Heddle et al 1988, Edelbroek et al 1994). TMPD sideholes were perfused at 0.4ml.min^{-1} with degassed normal saline from separate, electrically isolated reservoirs; all other sideholes were perfused with degassed distilled water, also at 0.4ml.min^{-1}, from a third reservoir (Heddle et al 1988a, Fone et al 1990a, Edelbroek et al 1994, Sun et al 1997). After an overnight fast the manometric assembly was passed transnasally via an anaesthetised nostril and positioned across the pylorus with the correct position of the sleeve determined by measurements of the TMPD gradient at the gastroduodenal junction (Heddle et al 1988a, Edelbroek et al 1994). TMPD recordings were continued throughout each experiment in order to maintain the position of the sleeve sensor across the pylorus and five sideholes in the antrum. Antropyloroduodenal pressure waves and TMPD were recorded onto a 12 channel chart recorder (Grass polygraph model 7C, Grass Inc, Quincy, MA, USA), run at a paper speed of 100 mm.min^{-1}.

In three subjects, the position of the manometric catheter was further evaluated by incorporating markers, each containing 5 MBq ^{57}Co (Amersham Searles, USA), into the manometric assembly at the proximal and distal ends of the sleeve sensor and 4.5 cm orad and 4.5 cm aborad to the sleeve end. When the sleeve sensor was positioned correctly (according to TMPD criteria given below) each subject swallowed 150 ml of water, containing a very low dose (0.3 MBq) of ^{99m}Tc-sulphur colloid. In all three subjects the antral TMPD sidehole marker was shown to be three pixels (≈2 cm) orad to the pylorus and the sidehole 4.5 cm orad to the sleeve end was in the ninth pixel (≈6 cm).

6.3.3 *Radionuclide evaluation of gastric emptying and antral contractile activity*

Gastric emptying and antral contractile activity were evaluated for 150 minutes after ingestion of a meal of 100 g cooked minced beef containing 100 MBq of in vivo labelled ^{99m}Tc-sulphur colloid chicken liver (total caloric content 180 kcal; 18 g protein and 10 g fat) and 150 ml of unlabelled water (Collins et al 1983). The meal was eaten within five minutes. Throughout the recording period, the subject remained supine with the bed tilted 20^{o} to the horizontal to avoid possible overprojection of the intestine. An anteriorly positioned gammacamera (Nuclear Chicago, Pho-Gamma 111 HP, Digital Equipment Corporation) interfaced to a computer was used to collect data. Apart from periods of rapid acquisition used for evaluation of antral contraction, radionuclude data were acquired in three minute frames. For evaluation of antral contractions, data were acquired every two seconds for the three minute intervals between 40-43, 60-63, 80-83, and 100-103 minutes after meal completion. Corrections for subject movement, radionuclide decay, and tissue attenuation were done using previously described methods (Collins et al 1983).

A computer program was used to generate consecutive small regions of interest (ROI's) (two pixels width; 1.34 cm) across the antrum perpendicular to its long axis. The first region was three pixels orad to the pylorus, corresponding to the position of the antral TMPD sidehole, the more proximal regions (II through V) corresponding to the remaining antral sideholes. Time activity curves were generated for each ROI and displayed on a computer screen after a smoothing algorithm was applied (Figure 6.1).

Evaluation of total gastric emptying was based on time-activity curves generated from a ROI drawn around the stomach (Collins et al 1983, Collins et al 1988).

This analysis included counts from fast acquisition frames. The amount of isotope in the proximal and distal stomach was evaluated by drawing proximal and distal ROI's, in which the proximal region corresponds to the fundus and proximal corpus ad the distal region to the distal corpus and antrum (Collins et al 1988).

6.4 DATA ANALYSIS

Manometric and scintigraphic data from the remainder of the recording period obtained between 40-43, 60-63, 80-83, and 100-103 minutes after ingestion of the meal were evaluated separately.

6.4.1 *Manometry*

Pressure waves ere analysed only when the sleeve sensor was positioned correctly across the pylorus, according to previously defined TMPD criteria, and their amplitude was ≥ 10 mm Hg (Heddle et al 1988a, Edelbroek et al 1994). Using these criteria only 'lumen-occlusive' pressure waves were evaluated (Fone et al 1990a, Sun et al 1997). The TMPD criteria were that the duodenal TMPD should be equal to or more positive than -15 mV, the antral TMPD should be equal to or more negative than -20 mV, and the difference between the two readings should be at least 15 mV (Heddle et al 1988a, Edelbroek et al 1994).

The number and amplitude of phasic antral pressure waves in the proximal five antral sideholes (including the antral TMPD sidehole) were evaluated. Isolated pyloric pressure waves (IPPWs), classified as pressure waves ≥ 10 mm Hg recorded by the sleeve sensor in the absence of any discernible deflection in the antral or duodenal TMPD channels, provided that this pressure wave was recorded

by no more than one of the other two sideholes along the sleeve length (Heddle et al 1988a, Edelbroek et al 1994), were excluded from analysis.

6.4.2 *Scintigraphy*

The number of antral contractions (and antral contraction rate) were calculated in the five antral ROI's by a semiautomated program using the time interval between successive peaks and troughs. Peaks and troughs were both expressed as a percentage of counts/second/pixel in the total stomach. Based on the values for peak (P) and trough (T) counts the amplitude of antral wall movement was evaluated by deriving an 'occlusion percentage' as (1-T/P)x100. The number of contractions with an occlusion percentage ≥10% was counted. The amount of the solid meal (volume) in each antral ROI was calculated as $w\pi(d/2)$, in which 'd' represented the number of pixels across each region and 'w' the width of the region (1.34 cm).

Emptying curves (expressed as the percentage retention isotope *vs* time) were derived for total, proximal, and distal stomach ROI's. For the total stomach, the lag phase before any isotope emptied from the stomach; the amount of the solid meal remaining in the stomach at 40, 60, 80 and 100 minutes; and the 50% emptying time were calculated. The lag phase was determined visually by the frame preceding that in which activity appeared in the proximal small intestine (Horowitz & Dent 1991). The proximal stomach 50% emptying time and the maximum content of the distal stomach were calculated in addition to the retention of isotope in the proximal and distal stomach at 40, 60, 80 and 100 minutes (Collins et al 1983, Collins et al 1988).

6.4.3 *Statistical analysis*

Manometric and scintigraphic data (expressed as median values and interquartile range) were evaluated independently for the effect of postprandial time, position relative to the pylorus, and antral volume by analysis of covariance. The relationship between pressure waves and wall movements in each ROI were evaluated by ANOVA and Fisher's PLSD test. A p value <0.05 was considered significant in all analyses.

6.5 RESULTS

All subjects tolerated the study well and there were no adverse effects. The sleeve sensor was correctly positioned across the pylorus throughout all three minute, fast frame acquisitions

6.5.1 *Scintigraphy*

The overall emptying pattern of the minced beef approximated a linear function after an initial lag phase. The mean ± SEM lag phase was 21.9 ± 3.4 minutes, the total stomach 50% emptying time was 122 ± 9.8 minutes, the proximal stomach 50% emptying time 98 ± 8.2 minutes, and the maximum content of the distal stomach 23.8 ± 4.3 % (Figure 6.2).

When the content of the antrum was maximum, the count rate was 25.2 ± 3.6 counts/s/pixel in each antral ROI (Figure 6.2).

Contraction rate

Figure 6.1 shows time-activity curves in the five antral regions (two pixel width), from the distal (region I) to the proximal antrum (region V) in one subject at 60-63

minutes after ingestion of the meal. There are about nine cycles of varying amplitude in the three minute frame. Peaks are presumed to relate to the onset of a contraction and troughs to maximum contraction. There was no change in contraction rate over time. There were fewer contractions in the more proximal region(s) (IV, V) compared with more distal regions (I, II, III) ($p<0.05$) (Table 6.1).

Occlusion

The amplitude of antral wall movement assessed scintigraphically was inversely related to the postprandial time ($p<0.001$). The occlusion percentage also decreased ($p<0.001$) with increasing distance from the pylorus. Moving from the most distal antral region (I) to the most proximal region (V), the percentages of wall movements with ≥10% occlusion were 94.9%, 87.7%, 82.8%, 75.7% and 69.6% respectively (Table 6.1). There were significant inverse relationships between occlusion percentages and both orad distance from the pylorus ($r=-0.47$, $p<0.001$) and regional volume ($r=0.29$, $p<0.005$).

6.5.2 *Manometry*

Frequency of pressure waves

There was no change in the frequency of pressure waves over time (Table 6.2). There were fewer antral waves ($p<0.01$), and pressure waves were virtually absent in the more proximal region(s) (III, IV, V). There was an inverse relationship ($r=-0.51$, $p<0.001$) between the number of antral waves and the orad distance from the pylorus.

Amplitude

The amplitude of pressure waves did not change with time. The amplitude of pressure waves decreased from the distal to the proximal antrum ($p<0.01$). Moving from the most distal region (I) to the most proximal region (V), the percentages of pressure waves ≥10 mm Hg were 76%, 61%, 44%, 35% and 41% respectively (Table 6.2). There was an inverse relationship between the amplitude and both orad distance from the pylorus ($r=-0.32$, $p<0.05$) and regional volume ($r=-0.49$, $p<0.0001$).

6.5.3 *Relationship between scintigraphic and manometric measurements*

The frequency of lumen-occlusive antral pressure waves was less than the number of scintigraphic contractions in all regions ($p<0.01$) (Figure 6.3). There were significant relationships between the extent of antral wall motion evaluated scintigraphically (occlusion %) and the number of antral pressure waves in region I ($r=0.48$, $p<0.05$), but not in more distal regions (Figure 6.4). There was no significant relationship between the occlusion percentage and the median amplitude of pressure waves. There were also no significant relationships between either scintigraphic or manometric measurements of antral motility and overall rates of gastric emptying.

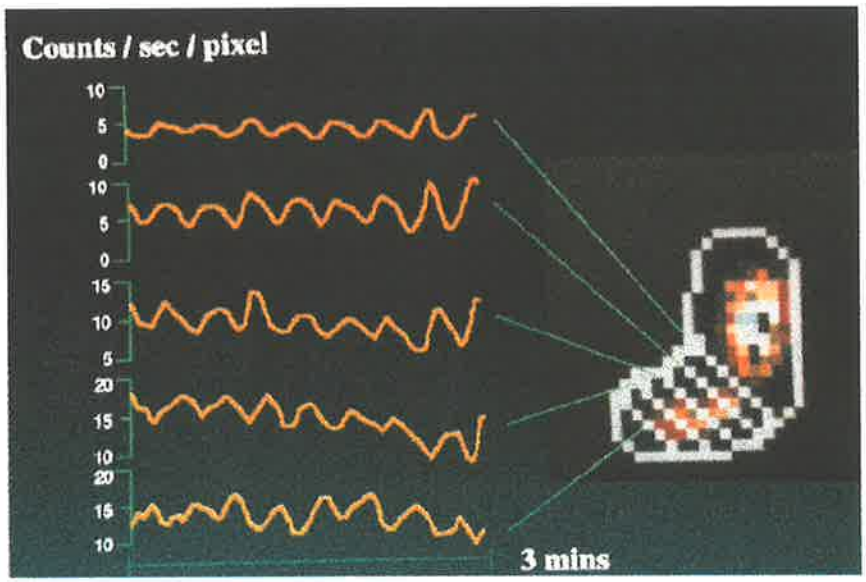

Figure 6.1: Diagram showing location of antral regions of interest used for the gensration of scintigraphic measurements. Time activity curves, representing antral contractile events, are shown in five antral adjacent regions in one subject 60-63 minutes after ingestion of the meal. All adjacent regions of interest were drawn perpendicular to the long axis of the antrum with a width of two pixels but are shown in the figure with a width of one pixel for clarity. Antral curves show periodic rhythmic contractions occurring at a frequency of 3 cycles per minute.

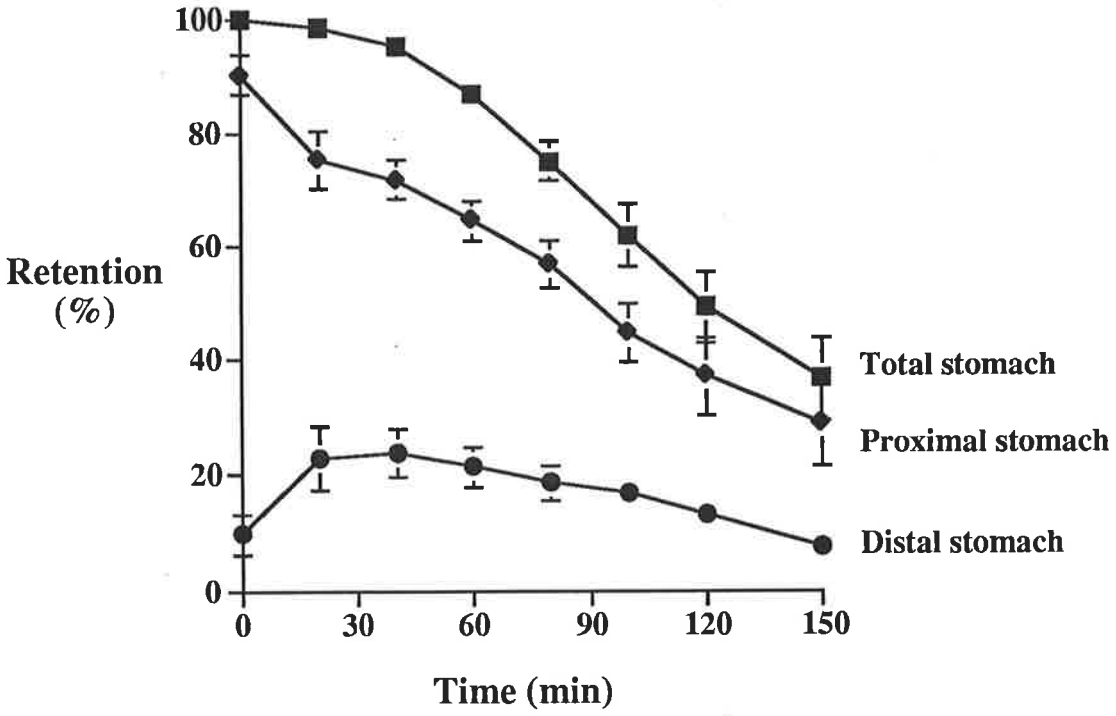

Figure 6.2: Gastric emptying curves for the solid (minced beef) meal for the total, proximal and distal stomach. Data are mean values ± SEM.

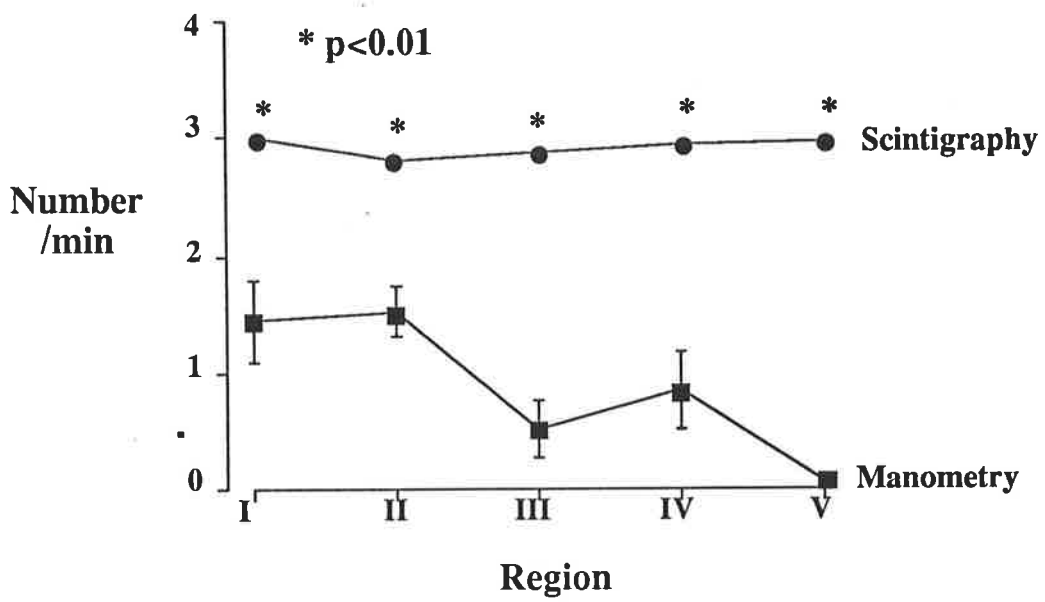

Figure 6.3: Frequency of scintigraphic and manometric events at five antral sites at 60 minutes postprandially. There are more scintigraphic than manometric events at all antral sites (p<0.01). Data are mean values ± SEM.

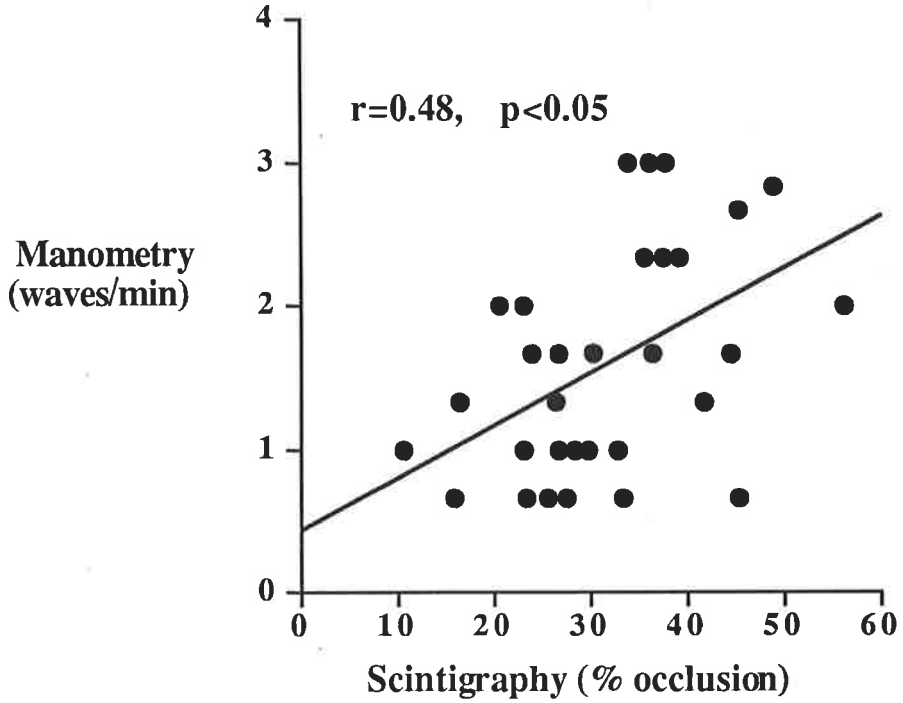

Figure 6.4: Relationship between the extent of wall motion (scintigraphy) and pressure waves (manometry) in the distal antrum (4-5.5 cm aborad to the pylorus). The number of lumen-occlusive pressure waves is significantly related to the amplitude of wall motion in this region (r=0.48;p<0.05).

Table 6.1: Frequency of antral contractions assessed scintigraphically (no/min) in the five regions of interest (ROI), from distal to proximal antrum, between 40-43, 60-63, 80-83 and 100-103 minutes after meal ingestion. The total number of contractions and the number with an occlusion percentage ≥ 10% are shown. Values are median, interquartile range.

		Contractions per minute			
ROI	***Threshold***	***40-43 minutes***	***60-63 minutes***	***80-83 minutes***	***100-103 minutes***
I	none	2.83(2.71-3.00)	3.00(2.96-3.00)	2.83(2.83-3.00)	3.00(2.67-3.00)
	≥10% occlusion	2.75(2.67-2.92)	2.67(2.58-3.08)	2.67(2.58-2.71)	2.83(2.67-3.00)
II	none	2.83(2.83-3.00)	2.83(2.67-2.88)	2.83(2.67-2.88)	2.83(2.71-2.96)
	≥10% occlusion	2.50(2.33-2.67)*†	2.67(2.50-2.67)*	2.33(2.00-2.67)*†	2.33(2.00-2.67)*†
III	none	2.67(2.67-2.96)	2.83(2.79-3.00)	2.67(2.67-3.00)	2.83(2.54-2.96)
	≥10% occlusion	2.67(2.00-2.67)*†	2.67(2.25-2.67)*†	2.33(1.58-2.42)*†	2.00(2.00-2.67)*†
IV	none	2.83(2.77-3.12)	3.00(2.79-3.00)	2.83(2.67-3.00)	2.67(2.67-3.00)
	≥10% occlusion	2.17(1.50-2.67)*†	2.67(1.33-2.75*	2.67(2.33-2.67)*	2.17(1.67-2.67)*†
V	none	2.83(2.83-3.00)	3.00(3.00-3.00)	3.00(2.79-3.00)	3.00(2.75-3.00)
	≥10% occlusion	1.67(0.83-2.00)*†	1.67(0.67-2.42)*†	2.33(1.92-2.38)*†	2.67(2.67-2.67)*

*p<0.05 contractions ≥ 10% occlusion versus all contractions. †p<0.05 proximal regions versus most distal region (I).

Table 6.2: Frequency of antral motor events (no/min) assessed scintigraphically (contractions) and manometrically (lumen-occlusive pressure waves) for the five regions of interest (ROI), from distal to proximal antrum, between 40-43, 60-63, 80-83 and 100-103 minutes after meal ingestion. The total number of pressure waves with a pressure ≥10 mm Hg and contractions with an occlusion percentage ≥ 10% are shown. Values are median, interquartile range.

		No. of pressure waves and contractions			
ROI	***Threshold***	***40 -43 minutes***	***60-63 minutes***	***80-83 minutes***	***100-103 minutes***
I	≥10% occlusion	2.75(2.67-2.92)	2.67(2.58-3.08)	2.67(2.58-2.71)	2.83(2.67-3.00)
	≥10 mm Hg	1.67(1.33-1.83)	1.67(0.67-2.08)	0.67(0.33-1.42)†	0.50(0.00-1.00)†
II	≥10% occlusion	2.50(2.33-2.67)*	2.67(2.50-2.67)	2.33(2.00-2.67)*	2.33(2.00-2.67)*
	≥10 mm Hg	1.33(0.50-1.50)*	0.67(0.58-1.17)*	0.33(0.25-1.33)*†	0.17(0.00-0.67)*†
III	≥10% occlusion	2.67(2.00-2.67)*	2.67(2.25-2.67)*	2.33(1.58-2.42)*	2.00(2.00-2.67)*
	≥10 mm Hg	0.00(0.00-0.67)*	0.00(0.00-0.42)*	0.00(0.00-1.00)*	0.17(0.00-0.67)*
IV	≥10% occlusion	2.17(1.50-2.67)*	2.67(1.33-2.75)	2.67(2.33-2.67)*	2.17(1.67-2.67)*
	≥10 mm Hg	0.00(0.00-0.00)*	0.00(0.00-0.33)*	0.00(0.00-0.17)*	0.00(0.00-0.33)*
V	≥10% occlusion	1.67(0.83-2.00)*	1.67(0.67-2.42)*	2.33(1.92-2.38)*	2.67(2.67-2.67)*
	≥10 mm Hg	0.00(0.00-0.00)*	0.00(0.00-0.00)*	0.00(0.00-0.00)*	0.00(0.00-0.00)*

*p<0.05 proximal regions versus most distal region (I). †p<0.05 earlier postprandial time periods versus 40-43minutes.

6.6 DISCUSSION

This is the first study which has evaluated the precision of intraluminal perfusion manometry and scintigraphy in the evaluation of antral motility in humans. Our results confirm the previous suggestion (Akkermans et al 1980, Stacher et al 1987a, Stacher et al 1987b, Urbain et al 1990a, Urbain et al 1993) that scintigraphy can provide a sensitive measure of movement of intragastric content resulting from antral contractions in both the distal and the proximal antrum. In contrast, the frequency of lumen-occlusive antral pressure waves decreased considerably with increasing distance from the pylorus, and these were virtually absent in the proximal antrum. Only in the distal antrum was there a relatively close correlation between motor events evaluated by scintigraphy and manometry.

It is now recognised that disordered gastric motility, particularly that which results in delayed emptying, occurs frequently and may contribute to upper gastrointestinal symptoms, impaired oral drug absorption, and, in patients with diabetes mellitus, poor blood glucose control (Horowitz & Dent 1991). Although the results of animal studies indicate that no single motor region should be considered to exert the dominant control over gastric emptying (Malbert et al 1992, Heddle et al 1993, Malbert & Mathis 1994, Horowitz & Dent 1994) and that the rate of emptying is dependent on the relationship between motor events in the proximal stomach, antrum, pylorus, and proximal small intestine (Heddle et al 1993, Horowitz & Dent 1994), many studies have attempted to ascribe delay in gastric emptying to dysfunction of one region of the stomach, usually the antrum. While the antrum is involved in the grinding of solid food into small particles (Meyer et al 1979) and both fasting and postprandial antral hypomotility have been shown in patients with gastroparesis (Camilleri & Malagelada 1984, Kerlin 1989, Bortolotti et al 1991, Horowitz & Dent 1991), the role of the antrum in the control of the transpyloric flow of digesta remains uncertain (Malbert & Mathis 1994). Furthermore, antral

motility has characteristically been evaluated as an 'index' (Camilleri & Malagelada 1984) which takes into account both the frequency and amplitude of pressure waves or contractions, but provides no information about the organisation of these motor events. The latter is likely to be an important determinant of their mechanical consequences (Malbert et al 1992, Malbert & Mathis 1994). Recent studies, including ours, indicate that the motor dysfunctions in gastroparesis are heterogenous and that abnormal organisation of postprandial gastropyloroduodenal motility is an important factor (Fraser et al 1993c, Heddle et al 1993). In contrast to the relatively stereotyped gastric pacemaker discharge, which determines the frequency of antral contractions, patterns of lumen occlusion generated by antral contractions are exremely complex, variable, and rarely conform to peristaltic pattern (Sun et al 1997). It is therefore not surprising that whether a contraction resutls in occlusion of the lumen or not is critically important in determining its impact on luminal flow. For example, localised pyloric contractions probably play a major role in the regulation of gastric emtpying by acting as a brake (Tougas et al 1992a). Patterns of transpyloric flow (pulse volume and frequency) also vary widely from one contraction cycle to the next depending on intragastric volume and feedback from small intestinal luminal receptors (Malbert et al 1991, Edelbroek et al 1994, Horowitz & Dent 1994, Malbert & Mathis 1994).

Our observations confirm that intraluminal manometry is an insensitive technique for the evaluation of contractile activity in the proximal antrum (Valori et al 1986, Fone et al 1990a). In contrast, scinitgraphy was able to detect regular contractions at the pacemaker frequency throughout the distal stomach after a solid meal, but could not identify those contractions which resulted in lumen occlusion. Scintigraphy is therefore probably the most sensitive non-invasive technique for measurement of antral contractions. With the previously established roles of scintigraphy in measuring both total stomach emptying (Horowitz & Dent 1991)

and the intragastric distribution of digesta (Collins et al 1988), this finding strengthens its use as both a clinical and research technique. Real time ultrasound techniques can also be used to measure both wall motion and gastric emptying (Hausken et al 1992). However, while ultrasound and scintigraphic measurements of wall motion have not been compared formally, the utility of scintigraphy is likely to be much greater. Our observations therefore indicate that the combination of scintigraphic evaluation of antral contractile activity with manometric measurements of gastroploroduodenal pressures will provide complimentary information about both normal and disordered gastric motility.

CHAPTER 7

SCINTIGRAPHIC MEASUREMENT OF GASTRIC EMPTYING AND ULTRASONOGRAPHIC ASSESSMENT OF ANTRAL AREA - RELATIONSHIP TO APPETITE

7.1 SUMMARY

Ultrasound measurement of gastric emptying has potential advantages over scintigraphy, however, there is little information about its accuracy. The relationship between ultrasonographic measurements of antral area and (i) scintigraphic measurements of gastric emptying and intragastric distribution of liquids and (ii) postprandial satiation were evaluated. Seven normal volunteers were studied. Each subject drank 75g dextrose dissolved in 350 ml of water (300 kcal) or beef soup (20 kcal), both labelled with ^{99m}Tc-sulphur colloid on separate days and had measurement of gastric emptying by scintigraphy and ultrasound. Scintigraphic and ultrasound 50% emptying times (T50's) were comparable and longer ($p<0.001$) for dextrose than soup (dextrose 107 ± 16 min vs 108 ± 18 min, soup 24 ± 4 min vs 23 ± 5 min). There were close correlations between scintigraphic and ultrasound T50's (dextrose $r=0.94$, $p<0.005$, soup $r=0.97$, $p<0.001$) and between the time at which the distal stomach content decreased from its maximum value by 50% (measured scintigraphically) and the ultrasound T50 (dextrose $r=0.95$, $p<0.005$, soup $r=0.99$, $p<0.0001$). In contrast, there was no significant relationship between the distal stomach content when expressed as a percentage of the maximum content in the total stomach and the ultrasound T50. After dextrose, fullness was related ($r=0.92$, $p<0.01$) to the postprandial increase in antral area measured by ultrasound. Ultrasound measurements of gastric emptying are: (i) of comparable sensitivity to scintigraphy in quantifying emptying of both

low and high nutrient liquids (ii) correlate with postprandial satiation, suggesting that the latter may be mediated by antral distension.

7.2 INTRODUCTION

Although a number of methods have been used to assess gastric emptying in humans (Meeroff et al 1973, Collins et al 1983, Scarpignato 1990, Horowitz & Dent 1991, Schwizer et al 1992, Maes et al 1994a), many of these have technical limitations or are complex to perform. Scintigraphy is at present the "gold standard" for clinical measurement of gastric emptying (Collins et al 1983, Scarpignato 1990, Collins et al 1991, Malbert & Mathis 1994). Scintigraphy, however, requires expensive equipment that is often not readily available and is associated with a radiation burden. Real-time ultrasound can be used to assess gastric emptying (Holt et al 1980a, Bateman & Wittingham 1982, Bolondi et al 1985, Bolondi et al 1986, Holt et al 1986, Marzio et al 1989) and has major advantages over other techniques in that it is non-invasive, does not involve radiation and is widely available. Doppler ultrasound techniques allow evaluation of antral wall motion and transpyloric flow (King et al 1984, Hausken et al 1992). Because there have been few comparisons between ultrasound and scintigraphic techniques, the precision and clinical utility of ultrasonographic measurement of gastric emptying remain uncertain (Scarpignato 1990, Vantrappen 1994).

Using ultrasound, gastric emptying has characteristically been assessed by measurement of changes in antral cross-sectional area (Hausken & Berstad 1992, Hausken et al 1993) or diameter (Bolondi et al 1985, Bergmann et al 1992). The rate at which antral diameter decreases from the maximum achieved soon after a drink correlates with gastric emptying measured scintigraphically (Bolondi et al 1986, Holt et al 1986, Marzio et al 1989). It is, however, uncertain why gastric

emptying of liquids should be related to changes in antral area. In particular, emptying of liquids is dependent on the relationship between motor events in the proximal stomach, antrum, pylorus and small intestine, rather than the motor function of the proximal stomach alone (Collins et al 1991, Horowitz & Dent 1991). Antral width reflects the interplay of passive and active forces favouring distension (including intragastric volume, gravity and fundic tone) and resistance to distension occurring as a result of muscular contractions. It is therefore potentially both a determinant of, and determined by, the content of the distal stomach. The factors which regulate emptying differ fundamentally between nutrient and non-nutrient liquids (Horowitz & Dent 1991) - feedback from small intestinal luminal receptors predominates in the control of nutrient-containing liquids (Hunt et al 1985, Horowitz et al 1993), whereas gravity and intragastric volume are important determinants of emptying of isotonic liquids, which empty faster from the stomach than nutrient-containing liquids (Horowitz & Dent 1991). While the observed relationship between ultrasound measurements of antral area and gastric emptying (Bolondi et al 1986, Holt et al 1986, Marzio et al 1989) suggests that the distal stomach, and in particular antral "tone", has a role in regulating gastric emptying of liquids, gastric emptying of liquids is known to correlate with the content of the proximal stomach and not that of the distal stomach measured scintigraphically ie. the proximal stomach usually "empties" in parallel with the total stomach, whereas the distal stomach content initially increases and subsequently decreases (Collins et al 1991). However, the possibility that there is a relationship between emptying from the total stomach and the rate at which the antral content decreases, ie. antral content expressed as a percentage of its maximum, rather than the maximum content of the total stomach, has not been evaluated. We have therefore examined the relationship between scintigraphic measurements of the content of the distal stomach, with ultrasound measurements of antral area after ingestion of low and high nutrient liquids.

The factors which regulate appetite in humans are complex, but it is clear that signals from the gastrointestinal tract are important (Sepple & Read 1989, Gregory et al 1989, Greenberg et al 1990). The relationship between gastric emptying and postprandial hunger is, however relatively weak (Sepple & Read 1989). It is possible that antral distension may itself contribute to satiation and this concept has been strengthened by recent observations in patients with non-ulcer dyspepsia that both fasting and postprandial antral area are often increased (Hausken & Berstad 1992, Hausken et al 1993, Hausken & Berstad 1994) and intragastric meal distribution is abnormal (Troncon et al 1994). We have examined the relationship between postprandial hunger and fullness and postprandial antral area in normal subjects.

7.3 MATERIALS AND METHODS

Seven healthy volunteers (3F, 4M) with a median age of 23 yr (range 20-27) and body mass index of 22 kg/m^2(range 16.5-24.7 kg/m^2) were studied. None was taking medication, had gastrointestinal symptoms, or had any history of gastrointestinal disease. Smoking was prohibited on the morning of and during gastric emptying measurements.

7.3.1 *Experimental protocol*

Simultaneous measurements of gastric emptying by scintigraphy and ultrasound were performed in each subject after ingestion of either a low or high nutrient drink on two separate days. After an overnight fast (14 hours for solids and a 12 hours for liquids) subjects ingested 350 ml of low nutrient beef soup (20 kcal) or dextrose (75 g dissolved in 350 ml water, 300 kcal). The drinks were consumed at either 10.00 a.m. or 2.00 p.m., but at the same time of day for each individual. The time

period separating the two test days was 3-7 days. Gastric emptying was quantified scintigraphically (Collins et al 1983, Collins et al 1991) and antral area by ultrasound (Bolondi et al 1985, Bolondi et al 1986, Holt et al 1986). Feelings of hunger and fullness were assessed via a visual analogue scale administered immediately before ingestion of the drink and at regular intervals thereafter (Sepple & Read 1989). Written informed consent was obtained from all subjects and the protocol was approved by the Ethics Committee of the Royal Adelaide Hospital.

7.3.2 *Scintigraphic measurement of gastric emptying*

Details of this single isotope test which measures total, proximal and distal stomach emptying have been reported (Collins et al 1988). Both the beef soup and the dextrose contained 20 MBq of ^{99m}Tc-sulphur colloid and were heated to 37^{o}C immediately prior to ingestion. Subjects consumed the test drinks over 1 min, and time zero was defined as the time of completion. Each study was performed with the subject seated with their back against the gamma camera (Siemens Basicam 300). Radionuclide data were acquired at a rate of one frame every 30 seconds for the first 30 min and thereafter in 3 min frames until at least 90% of the drink had emptied, or for a maximum period of 180 min. Data were corrected for subject movement and radionuclide decay using previously described methods (Collins et al 1983, Collins et al 1991). Correction for gamma ray attenuation was performed using factors derived from a lateral image of the stomach (Collins et al 1983, Collins et al 1991). A region-of-interest (ROI) was drawn around the total stomach, which was subsequently divided into proximal and distal regions - the proximal region corresponding to the fundus and proximal corpus and the distal region representing the distal corpus and antrum. Gastric emptying curves for total, proximal and distal stomach (representing % retention over time) were derived. Several parameters were obtained from the curves for subsequent statistical

analysis. For the total, proximal and distal stomach the retention of isotope every 5 min until 60 min (expressed as the % of maximum counts in the total stomach) were derived. For the dextrose drink, which emptied more slowly than the soup, the amount remaining in each of these regions was also calculated every 10 min between 60 - 180 min. The content of the distal stomach was also expressed as a percentage of its maximum. For the total stomach the lag phase before any liquid had left the stomach, and the 50% emptying time (T50) were also calculated. The lag phase was determined visually by the frame preceding that in which activity was first seen in the proximal small intestine (Collins et al 1983).

7.3.3 *Ultrasound measurement of antral area*

Measurements of antral area were performed using a Diasonic DRF 400 Ultrasound Machine with a 5 MHz sector transducer and real-time images were stored on a video recorder. While the subject was seated with his or her back against the gamma camera, the ultrasound transducer was positioned in the region of the umbilicus. For evaluation of antral area, the transducer was positioned vertically to visualise the antrum in cross section with the superior mesenteric vein and the abdominal aorta in a longitudinal section (Bolondi et al 1985, Hausken & Berstad 1992). Antral area was measured using a built-in calliper and calculation programme (Hausken & Berstad 1992). The first measurement was performed within 1 min after meal ingestion and was followed by images at 5 min intervals for the first hour and 10 min intervals thereafter, until 90 % had left the stomach for a maximum of 180 min. Ultrasound T50 was defined as the time when antral area decreased to half its maximum (Hausken & Berstad 1992).

7.3.4 *Assessment of appetite*

Subjective ratings of a variety of symptoms including hunger and fullness were assessed by marking line analogues 100 mm long, whereby a score of 0 is equal to no symptom and 100 is the maximum score for the symptom. Complete details of this questionnaire have been given previously (Sepple & Read 1989). Subjects completed the questionnaire immediately before ingestion of the drinks and then at 15, 30, 45 and 60 min (soup and dextrose) and also at 90 and 120 min for dextrose.

7.3.5 *Statistical analysis*

Data are presented as mean values ± SEM and were evaluated using repeated measures analysis of variance (ANOVA). Non-parametric comparisons between groups (T50, lag-phase) were performed by the Wilcoxon rank sum test. Relationships were assessed by linear regression analysis. The difference between scintigraphic and ultrasound T50s was plotted against the mean of the two methods (difference plot) (Bland & Altman 1986, Pollock et al 1992) and limits of agreement were defined as the mean difference (%) ± 2SD (Bland & Altman 1986). A p value of < 0.05 was considered significant in all analyses.

7.4 RESULTS

All subjects tolerated the study well. The resolution of ultrasound images was satisfactory in all cases.

7.4.1 *Scintigraphic measurements of gastric emptying and intragastric distribution*

Gastric emptying of the soup was much faster than the dextrose (T50 = 22.9 ± 4.6 min vs 108.1 ± 17.5 min, $p<0.001$) (Figure 7.1). After an initial lag phase (0.9 ± 0.2 min for soup, 4.3 ± 2.2 min for dextrose, $p<0.05$), emptying of soup approximated a mono-exponential function with a slope that decreased with time. In contrast, the emptying pattern of dextrose was linear. For both soup and dextrose the retention in the proximal stomach closely paralleled that for the total stomach, whilst the distal stomach content did not. The slower emptying of dextrose compared to soup from the total stomach was associated with increased retention in both the proximal stomach at 15 min ($p<0.05$), 30 min ($p<0.005$), 45 min ($p<0.001$) and 60 min ($p<0.001$) and the distal stomach at 30 min ($p<0.005$), 45 min ($p<0.001$) and 60 min ($p<0.005$). For both drinks, the content of the proximal stomach was initially greater than that of the distal stomach, and subsequently more isotope was retained in the distal stomach. The content of the distal stomach was greatest soon after completion of each drink.

7.4.2 *Relationship and limits of agreement between scintigraphic and ultrasound measurements*

Scintigraphic and ultrasound T50s were not significantly different (22.9 ± 4.6 min and 24.0 ± 3.8 min for soup and 108.1 ± 17.5 min and 107.3 ± 15.6 min for dextrose) (Figure 7.2) and the overall scintigraphic and ultrasound curves for total stomach emptying were comparable. As assessed by ultrasound, emptying of dextrose was faster ($p<0.05$) at 15 min (Figure 7.2). There was a close correlation between the scintigraphic total stomach T50 and ultrasound T50 for both dextrose ($r=0.94$, $p<0.005$) and soup ($r=0.97$, $p<0.001$) (Figure 7.3). For the T50 the limits of agreement were +5.7 min (24%) and -7.9 min (-41%) for the soup (mean

difference -1.1 min) and +32.5 min (30%) and -30.7 min (-31%) for dextrose (mean difference 0.9 min). Limits of agreement were less than ± 15% for 10 of the 14 tests.

There was a poor relationship between ultrasound measurements of antral area and scintigraphic measurements of the content of the distal stomach when the latter was expressed as a percentage of the maximum total stomach content (Figure 7.4). However, when the scintigraphic content of the distal stomach was expressed as a percentage of the maximum content of the distal stomach, rather than the total stomach, there was a much closer concordance (Figure 7.4), so that the time for the distal stomach content, measured scintigraphically to decrease to 50% of maximum correlated closely with the ultrasound T50 for both dextrose ($r=0.95$, $p<0.005$) and soup ($r=0.99$, $p<0.0001$) (Figure 7.5).

7.4.3 *Hunger and fullness*

At 15 min hunger had decreased ($p<0.05$) and fullness increased ($p<0.05$) after ingestion of both dextrose and soup (Figure 7.6). Hunger tended to be less and fullness greater after dextrose than soup, but these differences were not significant. There were significant inverse relationships between scores for hunger and fullness at 15 min ($r = -0.75$, $p<0.05$), 30 min ($r = -0.77$, $p<0.05$) and 45 min ($r = -0.75$, $p<0.05$) for soup, but not dextrose.

7.4.4 *Relationships between hunger, fullness and gastric emptying*

There was no significant relationship between postprandial hunger and scintigraphic or ultrasound measurements of gastric emptying for either soup or dextrose. In

contrast, for dextrose but not soup, the score for fullness at 15 min was closely related to the magnitude of the postprandial increase in antral area measured by ultrasound ($r = 0.92$, $p<0.01$) (Figure 7.7). At 60 min fullness was related to the content of the distal stomach measured scintigraphically ($r = 0.75$, $p<0.05$) but not to total stomach emptying.

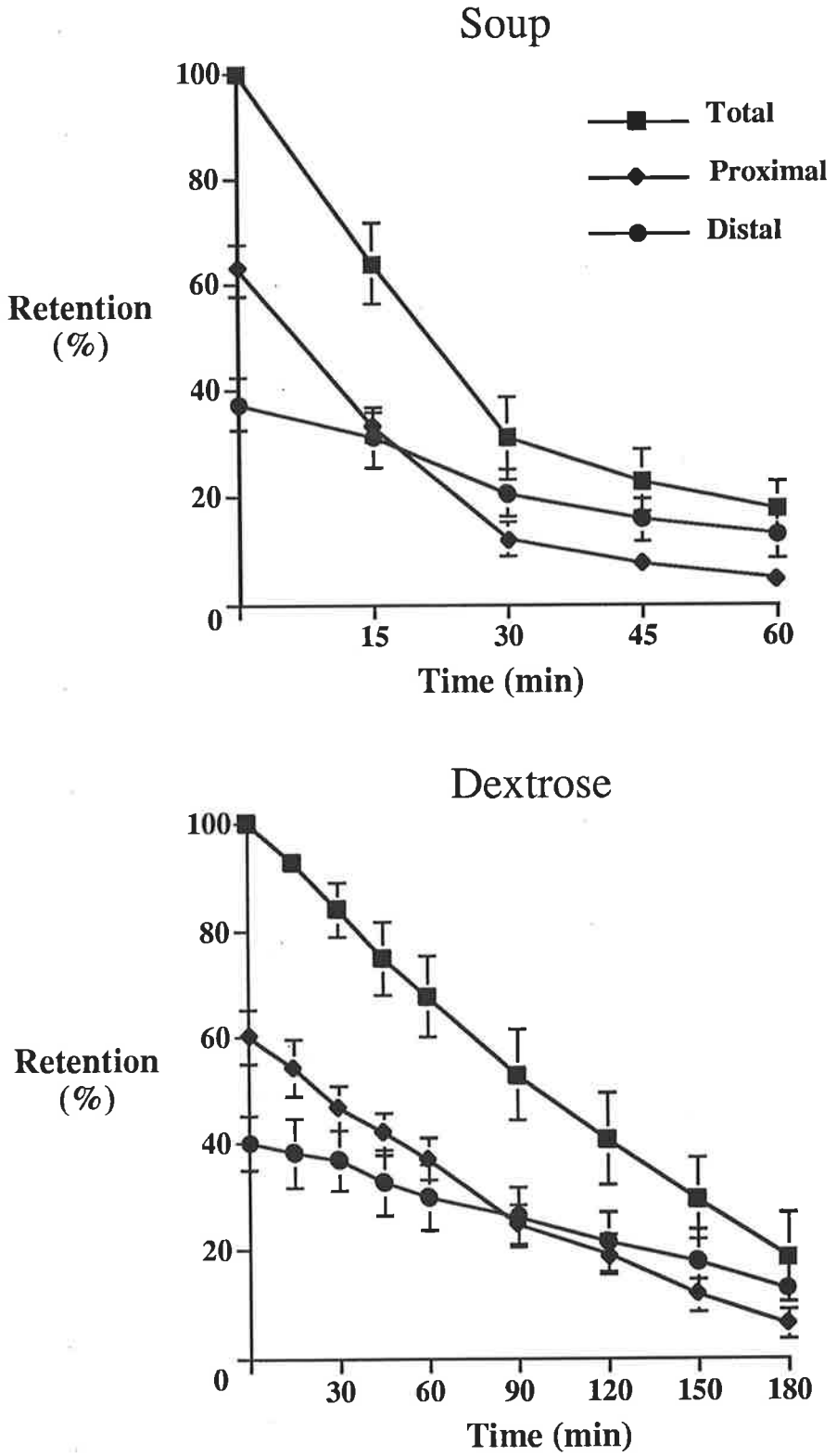

Figure 7.1: Retention of soup and dextrose in total, proximal and distal stomach regions-of-interest. Data are mean values ± SEM.

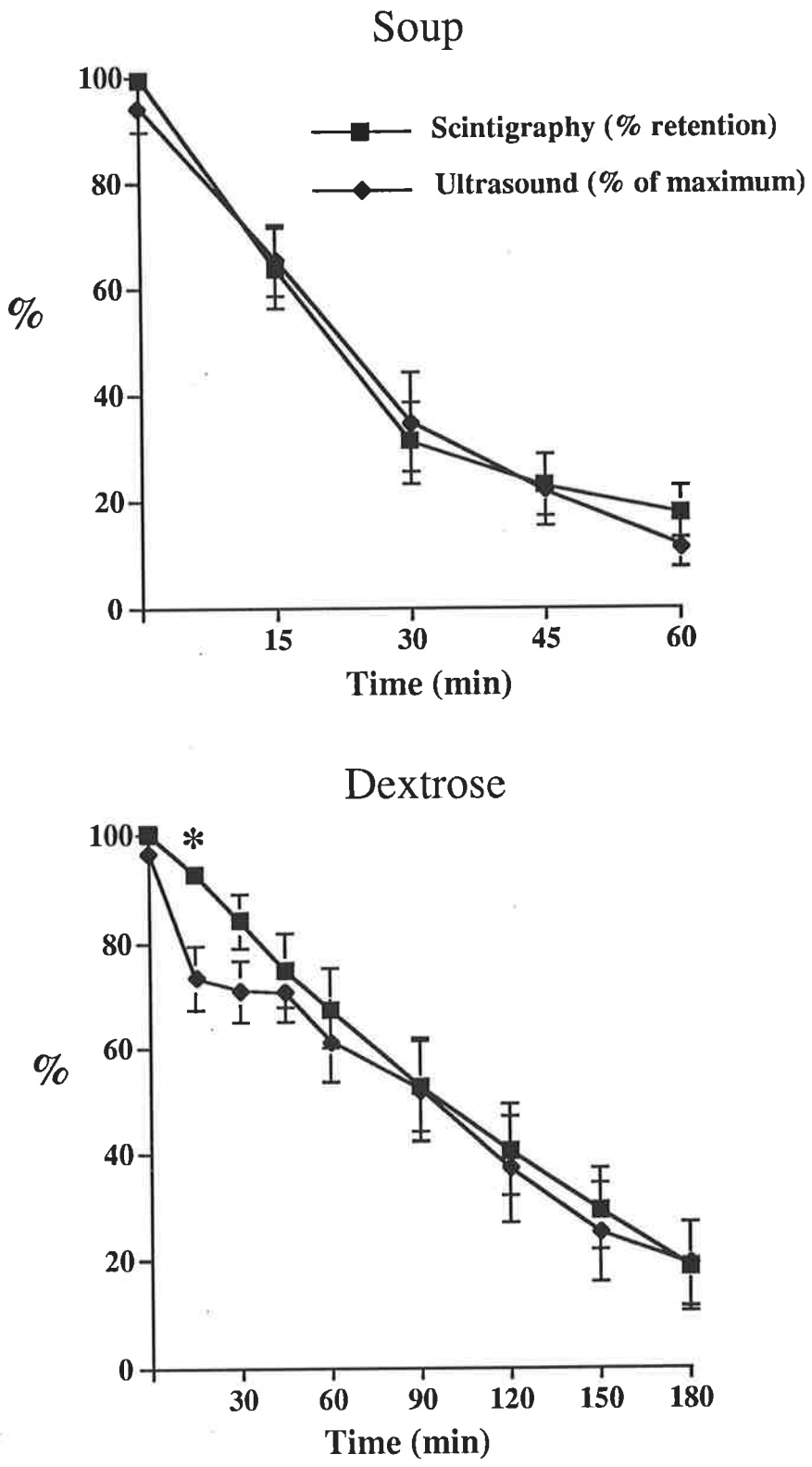

Figure 7.2: Gastric emptying of soup and dextrose measured scintigraphically (intragastric retention of isotope) and by ultrasound (changes in antral area). Data are mean values ± SEM.

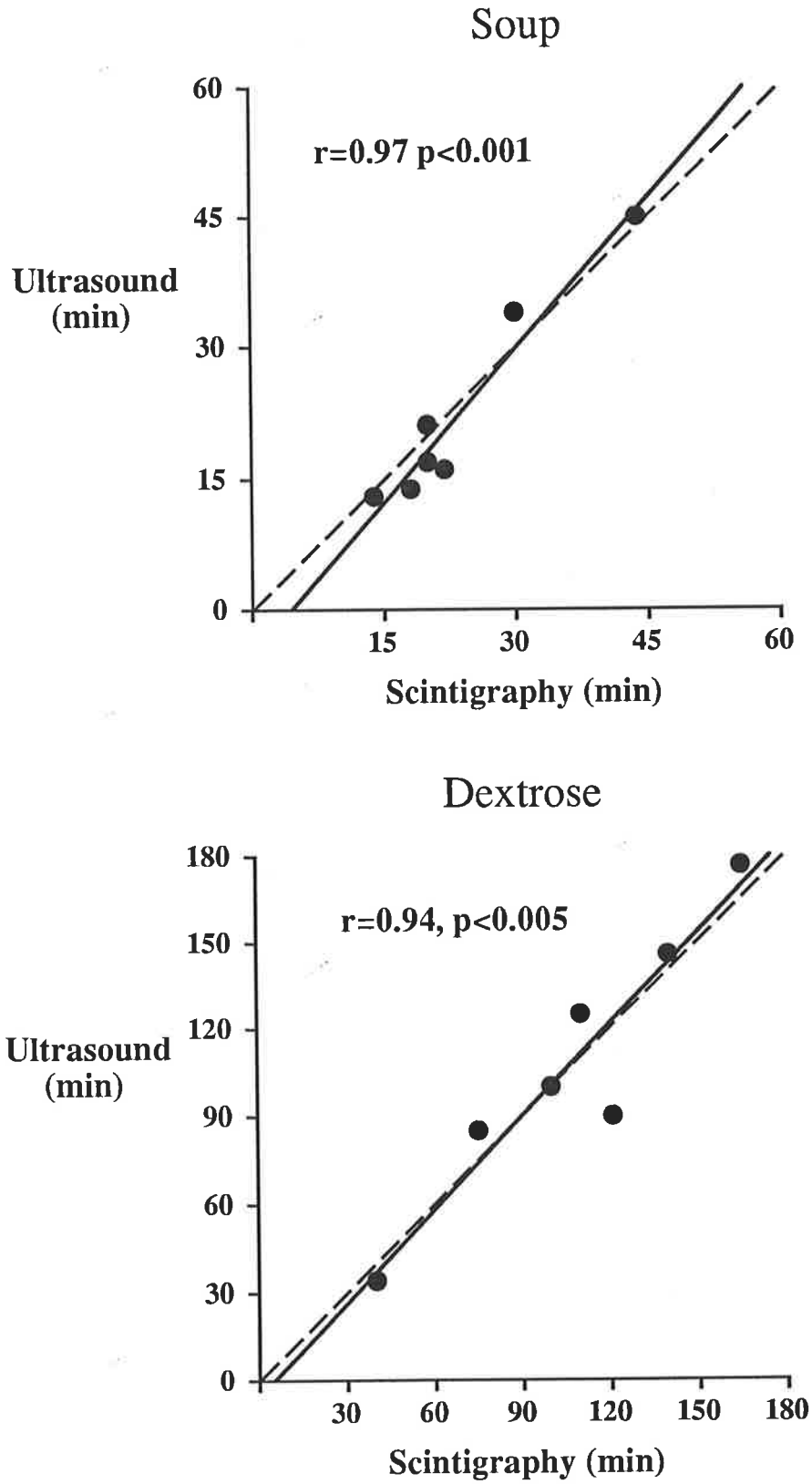

Figure 7.3: Relationship between ultrasound and scintigraphic 50% emptying times (T50) for soup and dextrose.

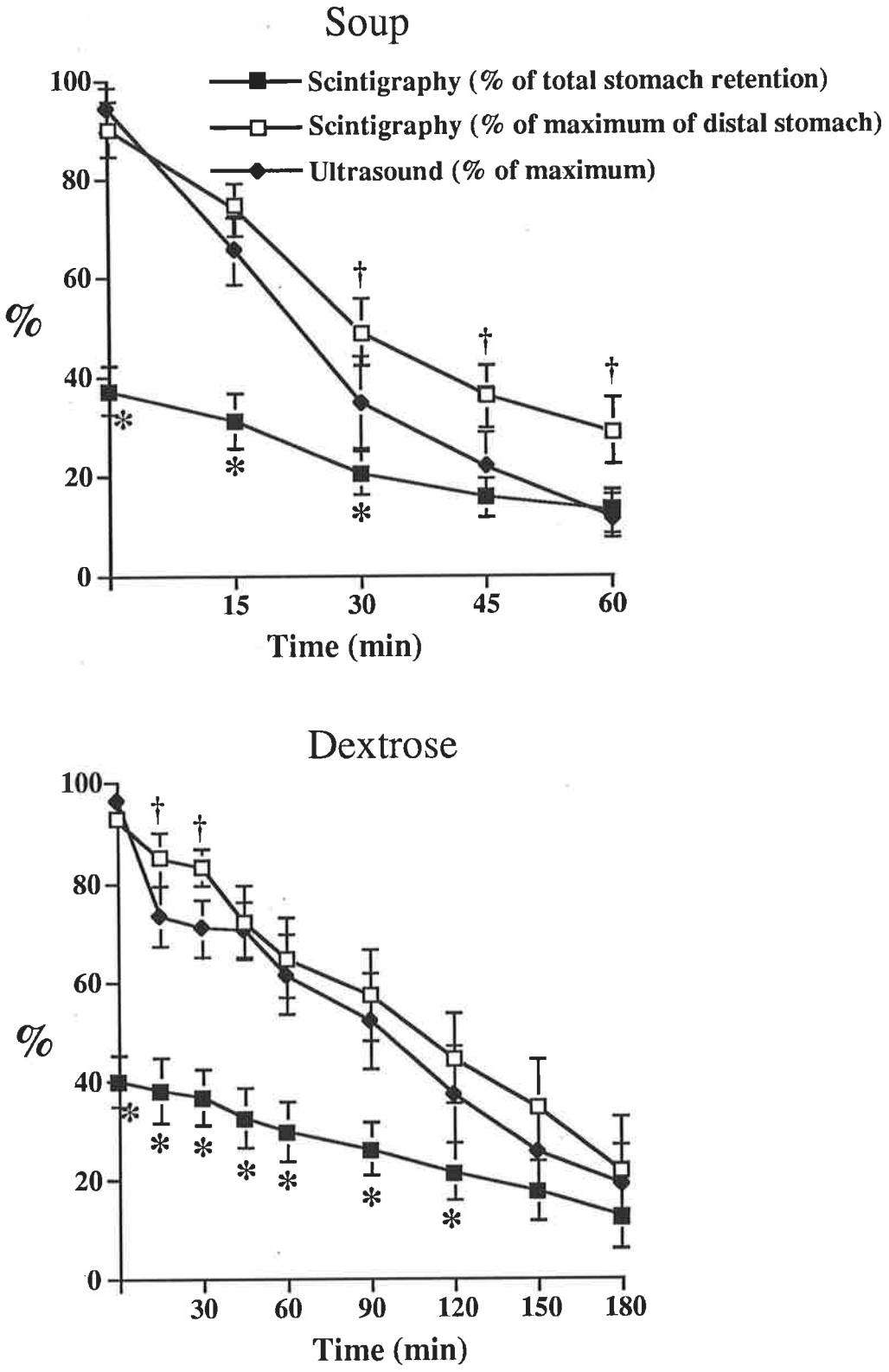

*Figure 7.4: Retention in the distal stomach measured scintigraphically (expressed as the % of the total stomach counts and % of the maximum content of the distal stomach) and ultrasound measurements of changes in antral area, for soup and dextrose. Data are mean values ± SEM. *p<0.05 scintigraphy vs ultrasound.*

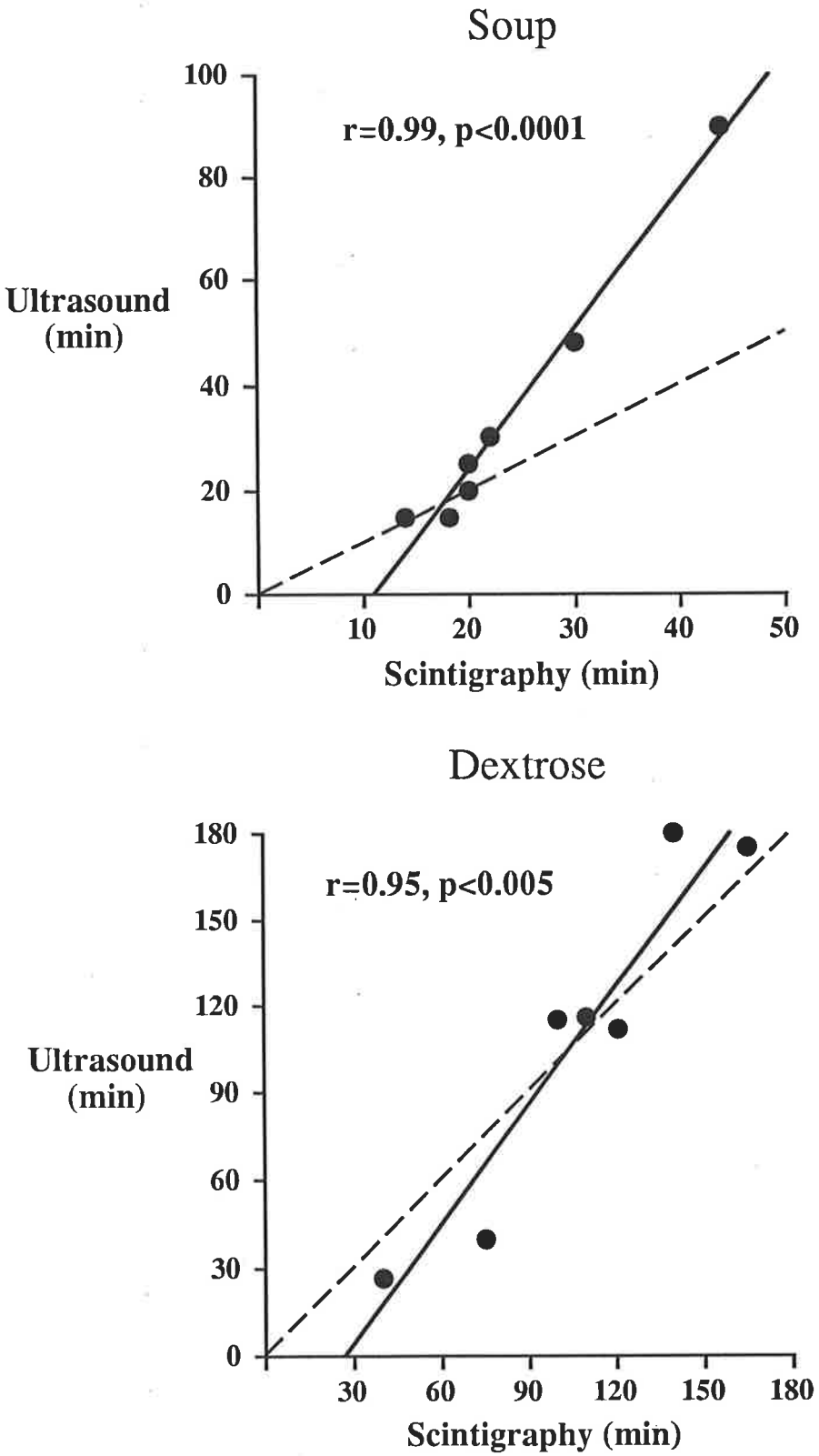

Figure 7.5: Relationships between ultrasound T50 and the T50 for the distal stomach measured scintigraphically (expressed as the % of the maximum content of the distal stomach) for soup and dextrose.

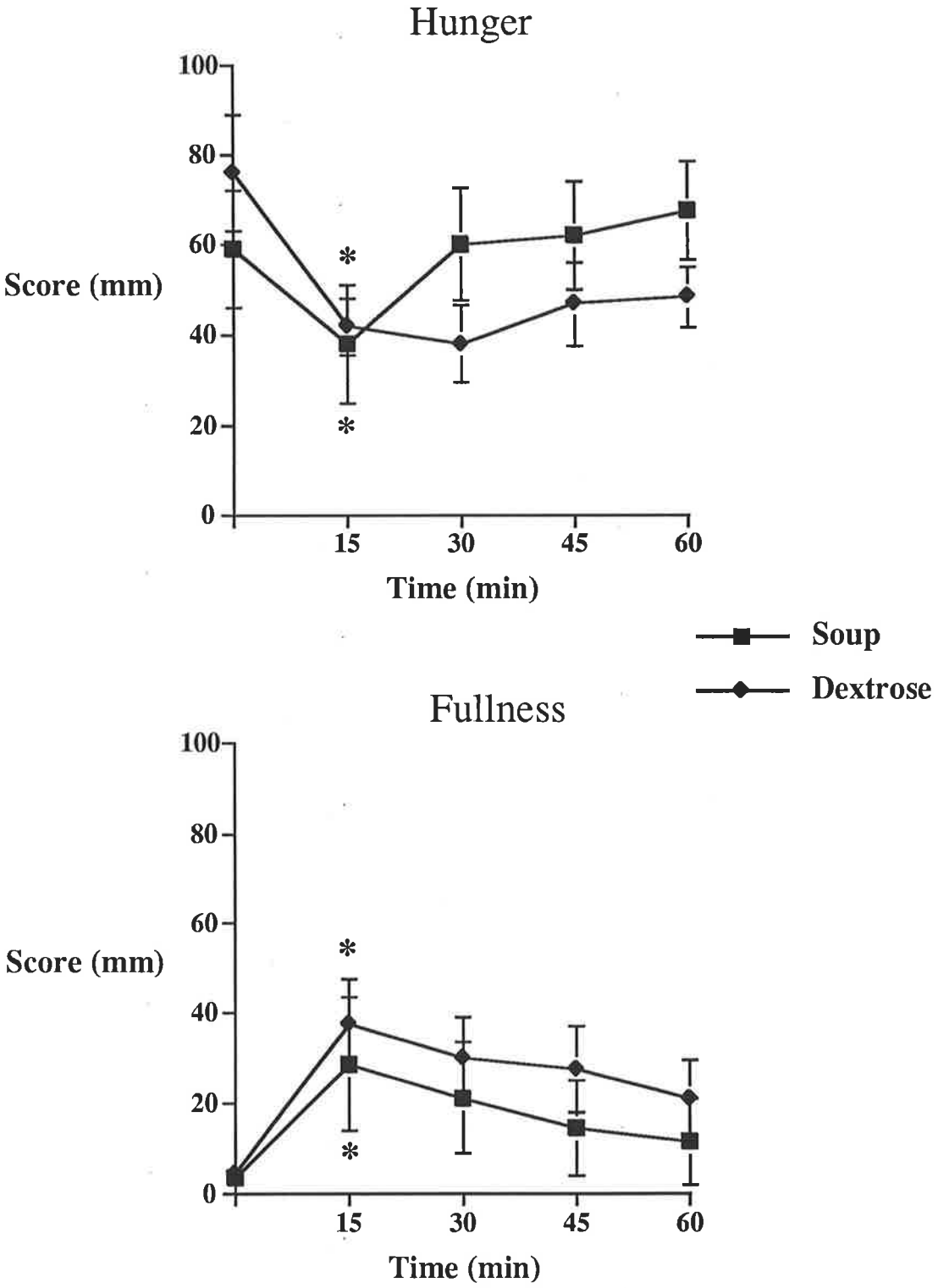

*Figure 7.6: Scores for hunger and fullness before and after ingestion of soup and dextrose. Data are mean values ± SEM. *p<0.05 change from baseline.*

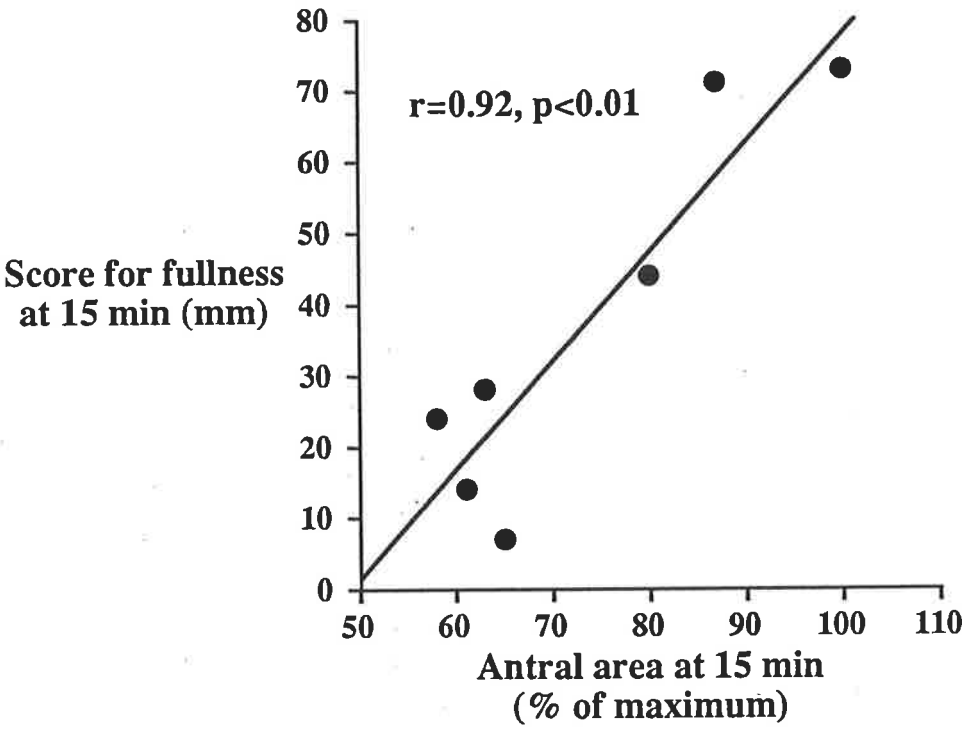

Figure 7.7: Relationship between the score for fullness and the change in antral area measured by ultrasound 15 min after ingestion of dextrose.

7.5 DISCUSSION

We have shown in normal, healthy subjects that (i) there is a close correlation between scintigraphic measurements of total stomach emptying of liquids and changes in antral area and (ii) postprandial fullness is related to the retention of dextrose in the distal stomach when measured by either scintigraphy or ultrasound.

In considering the potential use of ultrasound as opposed to scintigraphy, for measurement of gastric emptying for clinical and research purposes, it is essential that the limits of agreement between the two techniques are acceptable. A number of different methods to measure the size of the antrum by ultrasound have been used to calculate the rate of gastric emptying, including the volume (Bateman & Wittingham 1982), cross-sectional diameter, product of two diameters (Bolondi et al 1985), and para-sagittal or longitudinal area (Hausken et al 1993). The previous demonstration of a close relationship between rates of gastric emptying of liquids measured by scintigraphy and many of these measures (Bolondi et al 1986, Holt et al 1986, Marzio et al 1989) has formed the basis of the assertion that ultrasound has the capacity to measure gastric emptying precisely. The use of regression analysis and correlation coefficients, however, may not provide accurate information about the concordance between two methods because r measures the strength of the association, not the agreement (Bland & Altman et al 1986). In particular, it would be surprising if methods designed to measure the same quantity were not related. Furthermore, the range of values evaluated influences the correlation but not the agreement. In our study, limits of agreement were approximately ± 30% for the overall group, but less than ± 15% in 10 of the 14 tests. The correlation between ultrasound and scintigraphic measurements of gastric emptying was very close with r values of 0.95 and 0.99 for the two drinks. Holt et al (1986), Marzio et al (1989) and Bolondi et al (1986), have reported similar correlations, but estimations of limits of agreement were not performed. Based on our calculations, in the study by

Holt et al, the limits of agreement were approximately ± 41% (Holt et al 1986). In the study of Marzio et al, ultrasonographic gastric emptying was substantially faster (23% for a milk drink) than scintigraphic measurements (Marzio et al 1989). In contrast, in the study by Bolondi et al, the ultrasound measurement of gastric emptying (T50) was more than 50% slower than that measured by scintigraphy (Bolondi et al 1986). These discrepancies are likely to be attributable to differences in the techniques used to measure gastric emptying ultrasonographically, as the scintigraphic techniques were similar in each study. There was no such discrepancy in our study and the ultrasonographic method used has been shown to have low inter observer variability (Irvine et al 1993, Hveem et al 1994). Previous studies have demonstrated that the intra individual variation in gastric emptying of liquids in normal subjects is relatively large. This was confirmed in our study in that the ranges for gastric emptying (50% emptying time) were 13-44 min for soup and 37-177 min for dextrose. As the limits of agreement for dextrose were about four times greater, the precision of measurement of emptying of low and high nutrient liquids was similar. This indicates that our ultrasonographic method has the capacity, at least in normal subjects, to discriminate between fast and slow emptying of both low and high nutrient liquids.

Our observations therefore confirm the validity of using changes in antral "size" as a measure of gastric emptying of liquids in normal subjects and demonstrate for the first time that this is accounted for by the close correlations between: (i) total stomach emptying and the content of the distal stomach when the latter is expressed as a percentage of its maximum and (ii) the changes in antral area measured ultrasonographically and the content of distal stomach measured scintigraphically. The validity of using measurement of antral diameter to evaluate gastric emptying is consistent with the concept that antral tone plays a major role in regulating gastric emptying of liquids (Collins et al 1983, Collins et al 1991) in concert with other

factors including the tone of the proximal stomach, antral phasic contractions, pyloric resistance and proximal small intestinal motility (Horowitz & Dent 1991). However, it should be recognised that a relationship between the diameter of the antrum and antral tone has not yet been established. There was a significant, albeit small, discrepancy between ultrasound and scintigraphic measurements of gastric emptying of dextrose, the former being faster at 15 min. This may reflect retrograde shift of intragastric content from the distal into the proximal stomach as a result of the stimulation of small intestinal nutrient receptors (Edelbroek et al 1992b), particularly as there was a close concordance between measurements at all time intervals for the low nutrient drink.

In considering the potential clinical utility of ultrasound it should be recognised that ultrasonographic measurement of gastric emptying of solids is technically more complicated and has substantial limitations (Ricci et al 1993). Ultrasound also cannot discriminate between solid and liquid components of the meal. The close concordance between the two methods demonstrated in normal subjects, has to be confirmed in patients with disordered gastric emptying and obviously, ultrasound of the antral region cannot be used after antral resection and also probably other gastric surgery. Ultrasound techniques do, however, have the capacity to measure contractile activity in the distal stomach (Hausken et al 1993) and transpyloric flow (Hausken et al 1992).

In normal subjects, perception of gastric distension is influenced by gastric tone (Feinle et al 1995), and postprandial sensations of hunger and fullness are likely to be related to intragastric volume, gastric muscle tension and feedback from small intestinal nutrient receptors (Bergmann et al 1992, Feinle et al 1995). Ingestion of both the low and high nutrient drinks resulted in a decrease in hunger and increase in fullness. The observation of a direct relationship between fullness and the

retention of the drink in the antrum is consistent with the concept that fullness is related to antral distension (Bergmann et al 1992). In previous studies in which an identical meat soup drink was given to patients with functional dyspepsia, postprandial symptoms and antral area were greater in the patients when compared to healthy controls (Hausken et 1993, Hausken & Berstad 1994). It has also been demonstrated that intragastric meal distribution is frequently abnormal in patients with non-ulcer dyspepsia (Mangnall et al 1994, Troncon et al 1994). In normal subjects gastric distension and small intestinal nutrient stimulation have additive effects to induce nausea (Feinle et al 1995) and it is likely that both of these mechanisms are important in the aetiology of postprandial symptoms in normal subjects.

CHAPTER 8

RELATIONSHIP BETWEEN POSTPRANDIAL SATIATION AND ANTRAL AREA IN NORMAL SUBJECTS

8.1 SUMMARY

The factors influencing appetite in humans are poorly understood. There is a weak relationship between appetite and the rate of gastric emptying in normal subjects. Similarly, in patients with gastroparesis, gastrointestinal symptoms correlate poorly with gastric emptying. Recent studies have demonstrated that both fasting and postprandial antral area is increased in patients with functional dyspepsia when compared to normal subjects. We have evaluated the hypothesis that antral area, and hence antral distension, is a significant determinant of postprandial fullness.

Fourteen normal subjects had simultaneous measurements of gastric emptying by scintigraphy and antral area by ultrasound after ingestion of 350 ml of 20% glucose. Fullness and hunger were assessed by visual analogue scales.

Measurements of the 50% gastric emptying time (T50) by scintigraphy and ultrasound were not significantly different (129.6 ± 11.8 min vs 115.6 ± 11.4 min). Fullness increased ($p<0.001$) and hunger decreased ($p<0.001$) after the drink and there was an inverse relationship between them ($r= -0.56$ $p<0.05$). Both fullness and the magnitude of the increase in fullness after the drink were related to postprandial antral area ($r>0.68$ $p<0.01$), the increase in antral area ($r>0.79$, $p<0.005$) and the scintigraphic content of the distal stomach ($r>0.60$, $p<0.05$) but not to the ultrasound or scintigraphic T50's. In contrast, hunger and the magnitude

of the decrease in hunger after the drink were not related to either antral area, the increase in antral area or the rate of gastric emptying.

We conclude that postprandial fullness, but not hunger, is closely related to antral distension in normal subjects.

8.2 INTRODUCTION

Although the factors which regulate appetite in humans are complex and poorly understood (Gregory et al 1989, Sepple & Read 1989, Greenberg et al 1990), it is recognised that signals arising from the stomach and small intestine play an important part in the genesis of these feelings. Both gastric distension (Bergmann et al 1992) and nutrients in the small intestine (Lavin et al 1996) have been demonstrated to produce satiation in humans. Food substances, such as xylitol, that delay gastric emptying also decrease food intake (Shafer et al 1987). There is evidence that sensations of hunger and fullness are mediated by different gastrointestinal mechanisms. For example, in a recent study by Benini et al., in which hunger and fullness were assessed after ingestion of a fatty meal, postprandial fullness but not hunger, was directly related to the intragastric content measured by ultrasound (Benini et al 1994). After ingestion of a meal containing 60ml olive oil and 290ml low nutrient beef soup in normal subjects postprandial fullness is inversely related to gastric emptying of soup, whereas hunger is inversely related to gastric emptying of oil (Chapter 10, Chapter 11). These observations suggest that gastric distension occurring as a result of an increase in intragastric volume, may play a major role in triggering satiation, whereas the decrease in hunger after a meal, mainly results from the interaction of nutrients with receptors in the small intestinal lumen. Although other studies, using ultrasound and scintigraphic techniques to quantify gastric emptying, have confirmed that

fullness is inversely related to gastric emptying (Bergmann et al 1992, Chapter 7) the reported correlations are relatively weak, indicating that there is not a close relationship between gastric distension and intragastric volume with normal meal volumes.

Animal studies also support the concept that the stomach plays an important role in the termination of a meal. When food is restricted to the stomach by occlusion of the pylorus in rats, meal size decreases (Rauhofer et al 1993). Infusion of a liquid diet into an extra stomach implanted in rats, while the pylorus is clamped, also reduced food intake (Koopmans 1983). These studies demonstrating that signals from a totally denervated stomach affect appetite suggest that the stomach may produce humoral factors that reduce food intake. In rats, stomach distension decreases vagal firing rate and vagotomy blocks the satiating effect of stomach distension (Paintal 1954, Powley 1977). There is evidence both in monkeys (McHugh et al 1975) and humans (Shafer et al 1985) that the stomach can sense both nutrient quality and quantity and utilise this information to alter rate of gastric emptying and amount of food ingested.

The site of gastric distension (proximal stomach or antrum) may also be important in triggering satiation (Dozois et al 1971, Houghton et al 1992). In patients with non-ulcer dyspepsia postprandial antral area is, as a group, increased (Hausken & Berstad 1992), suggesting that an increase in antral width, secondary to antral distension may be associated with satiation. In a recent study by Undeland antral area was also found to be increased in both patients with insulin dependent diabetes mellitus (IDDM) when compared to normal subjects (Undeland et al 1996). Measurement of antral area can be performed readily by ultrasound (Holt et al 1980a, Bolondi et al 1985, Bolondi et al 1986, Holt et al 1986, Marzio et al 1989). However, in previous studies which have evaluated the relationship between

appetite and gastric emptying using ultrasound, absolute antral area was not reported. Scintigraphic techniques allow the intragastric distribution of ingested food to be evaluated (Chapter 10, Chapter 11). Antral area is likely to be related to the content of the distal stomach which can be quantified scintigraphically (Chapter 7).

The aims of this study were to examine in normal subjects, the relationships between both gastric emptying and intragastric distribution measured scintigraphically and antral area measured by ultrasound, with sensations of hunger and fullness. The broad hypothesis was that postprandial satiation would be more closely related to both antral area and the content of the distal stomach (as indirect measures of antral distension) than scintigraphic or ultrasound measures of the rate of gastric emptying.

8.3 MATERIALS AND METHODS

Fourteen healthy volunteers (10F, 4M) with a median age of 21.5 yr (range 19-43) and body mass index of 22.4 kg/m^2(range 16.5 - 24.7 kg/m^2) were studied. None was taking medication, had gastrointestinal symptoms, or a history of gastrointestinal disease. Smoking was prohibited on the morning of and during gastric emptying measurements.

8.3.1 *Experimental protocol*

Simultaneous measurements of gastric emptying, antral area and appetite (hunger and fullness) were performed in each subject immediately before and after ingestion of a 75 g of dextrose dissolved in 350 ml water (300 kcal). Subjects consumed the drink at either 10.00 a.m. or about 2.00 p.m. after a fast of at least 7 hours.

Gastric emptying and intragastric meal distribution were quantified scintigraphically (Collins et al 1988) while measurements of antral area were made by ultrasound (Bergmann et al 1992, Hausken & Berstad 1992, Benini et al 1994, Chapter 7). Feelings of hunger and fullness were assessed via a visual analogue scale (Sepple et al 1989, Chapter 7). In females, all studies were performed in the follicular phase of the menstrual cycle. Written informed consent was obtained from all subjects and the protocol was approved by the Ethics Committee of the Royal Adelaide Hospital.

8.3.2 *Assessment of appetite*

Subjective ratings of a variety of symptoms including hunger and fullness were assessed by marking line analogues 100 mm long, whereby a score of 0 is the minimum and 100 the maximum for the symptom. Complete details of this validated questionnaire have been reported (Sepple et al 1989). Subjects completed the questionnaire immediately before ingestion of the drink and then at 15, 30, 45, 60, 90, 120, 150 and 180 min.

8.3.3 *Scintigraphic measurement of gastric emptying*

Details of this technique which measures total, proximal and distal stomach emptying have been reported (Collins et al 1988). The dextrose drink was labelled with 20 MBq of ^{99m}Tc - sulphur colloid and heated to 37°C. Subjects consumed the drink over 1 min, and time zero was defined as the time of completion. Studies were performed in the sitting position with the subject resting their back against the gamma camera (Siemens Basicam 300). Radionuclide data were acquired at a rate of one frame every 30 seconds for the first 30 min and subsequently in 3 min frames until at least 90% of the drink had emptied, or for a maximum period of 180

min. Data were corrected for subject movement and radionuclide decay using previously described methods (Collins et al 1983, Collins et al 1991). Correction for gamma ray attenuation was performed using factors derived from a lateral image of the stomach (Collins et al 1983, Collins et al 1991). A region-of-interest (ROI) was drawn around the total stomach, which was also divided into proximal and distal regions - the proximal region corresponding to the fundus and proximal corpus and the distal region representing the distal corpus and antrum (Collins et al 1988). Gastric emptying curves for total, proximal and distal stomach (representing % retention over time) were derived. Several parameters were obtained from the curves for subsequent statistical analysis. For the total, proximal and distal stomach the retention of isotope (expressed as the % of maximum counts in the total stomach) were derived every 15 min for the first 60 min and thereafter every 30 min. For the total stomach the lag phase before any of the drink had left the stomach, and the 50% emptying time (T50) were also calculated. The lag phase was determined visually by the frame preceding that in which activity was first seen in the proximal small intestine (Collins et al 1988). The content of the distal stomach was also expressed as a percentage of its maximum (Chapter 7).

8.3.4 *Ultrasound measurement of antral area*

Measurements of antral area were performed using a Diasonic DRF 400 Ultrasound Machine with either a 3.5 MHz or 5 MHz sector transducer (Chapter 7). Real-time images were stored on a video recorder. The ultrasound transducer was placed on the abdomen while the subject was seated with his or her back against the gamma camera. Measurements of antral area were made immediately before the drink (fasting area), within 1 min after ingestion of the drink (time zero), every 5 min for the first 60 min and subsequently at 15 min intervals for a maximum of 180 min (Chapter 7). To optimise the precision of measurements of antral area, the

transducer was positioned vertically to obtain a parasagittal image of the antrum with the superior mesenteric vein and the abdominal aorta in a longitudinal section (Hausken & Berstad 1992) and images were always obtained at end of inspiration. Antral area (cm^2) was measured using a calliper and calculation programme (Chapter 7). As well as absolute antral area, the change in absolute antral area from the area measured immediately before consumption of the drink and the time when antral area decreased to half of its maximum (ultrasound T50) were calculated.

8.3.5 *Statistical analysis*

Data were distributed normally and evaluated using repeated measures analysis of variance (ANOVA) and Student's paired t-test. Relationships between variables were assessed by linear regression analysis. Data are shown as mean ± SEM. A p value of < 0.05 was considered significant in all analyses.

8.4 RESULTS

All subjects tolerated the study well and satisfactory resolution of ultrasound images was achieved in all cases.

8.4.1 *Appetite*

Hunger decreased ($p<0.05$) and fullness increased ($p<0.05$) after the drink (with the largest change from baseline being established by 30 minutes between (0 - 30 min) (Figure 8.1). Scores for both hunger and fullness had returned to baseline by 180 min. Hunger and fullness were inversely related at 15 min ($r=-0.53$, $p<0.05$) and 30 min ($r=-0.54$, $p<0.05$) but not at other times.

8.4.2 *Gastric emptying*

The overall emptying pattern of the dextrose drink measured scintigraphically was linear after a short lag phase (4.1 ± 1.6 min). The content of the proximal stomach closely paralleled that of the total stomach (Figure 8.2). The maximum content of the distal stomach occurred soon after ingestion of the drink (12.6 ± 2.6 min). The content of the proximal and distal stomach were inversely related ($r=-0.96$, $p<0.0001$) at 15 min, ($r=-0.77$, $p<0.005$) at 30 min and ($r=-0.55$, $p<0.05$) at 45 min.

Scintigraphic and ultrasound T50's were not significantly different (129.6 ± 11.8 min vs 115.6 ± 11.4 min) and were highly correlated with one another ($r=0.71$, $p<0.005$) (Figure 8.3). The absolute antral area was not significantly related to measurement of total stomach emptying by scintigraphy at any time but was directly related to the retention of the drink in the distal stomach immediately after meal ingestion ($r=0.65$, $p<0.05$), 15 min ($r=0.75$, $p<0.005$), 30 min ($r=0.53$, $p<0.05$) and at 45 min ($r=0.70$, $p<0.01$). There were also significant relationships between the change in antral area from baseline and retention in the distal stomach immediately after the drink ($r=0.72$, $p<0.005$), at 15 min ($r=0.69$, $p<0.01$), at 45 min ($r=0.61$, $p<0.05$) and at 120 min ($r=0.56$, $p<0.05$).

8.4.3 *Relationships of appetite to antral area and gastric emptying*

There were no significant relationships between hunger or the magnitude of the decrease in hunger after the drink with either the rate of gastric emptying measured scintigraphically or the content of the proximal or the distal stomach. There were also no significant relationships between hunger or the change in hunger from

baseline, and ultrasound measurements of antral area, the change in antral area from baseline or gastric emptying.

Fullness was not related to total stomach emptying measured scintigraphically, but there was a significant relationship between fullness and the retention of the drink in the distal stomach at 45, 60 and 90 min ($r \geq 0.60$, $p < 0.05$) (Figure 8.4a) but not the proximal stomach. The magnitude of the increase in fullness from baseline was also related to the retention of the drink in the distal stomach at 45, 60, 90 and 150 min ($r \geq 0.67$, $p < 0.05$) (Figure 8.4b). Neither fullness, nor the increase in fullness from baseline correlated significantly with the ultrasound T50. Fullness was related to the absolute antral area at 30 and 45 min ($r \geq 0.68$, $p < 0.01$) (Figure 8.5a) and also to the magnitude of the increase in antral area at 30, 45 and 60 min ($r \geq 0.57$, $p < 0.05$) (Figure 8.5b). The magnitude of the increase in fullness after the drink was also related to the absolute antral area at 30, 45 and 60 min ($r \geq 0.73$, $p < 0.005$) (Figure 8.6a) and the increase in antral area at 30, 45 and 60 min ($r \geq 0.61$, $p < 0.05$) (Figure 8.6b).

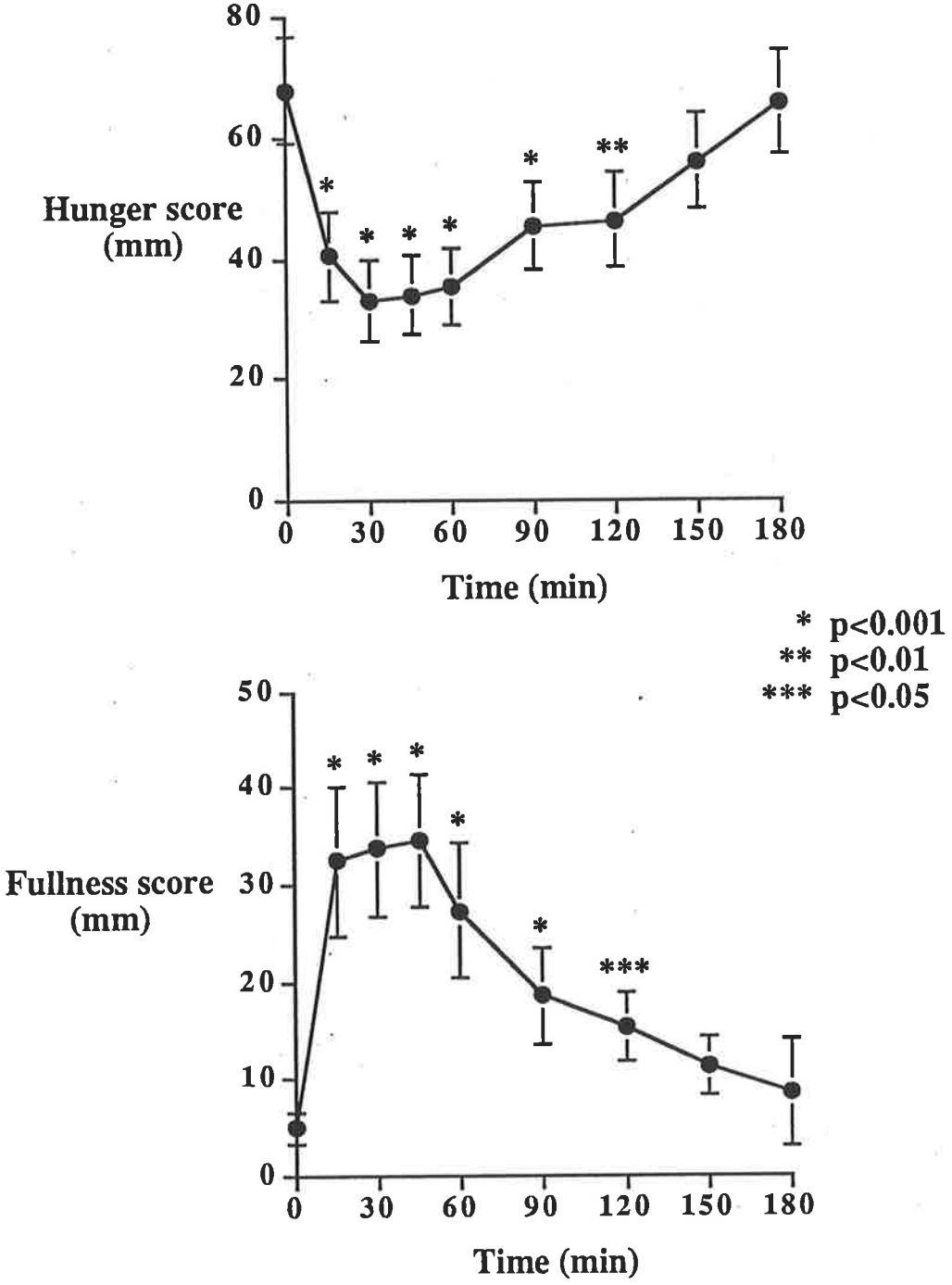

*Figure 8.1: Scores for hunger and fullness before and after ingestion of dextrose. Data are mean values ± SEM. *p<0.001, **p<0.01, ***p<0.05 change from baseline.*

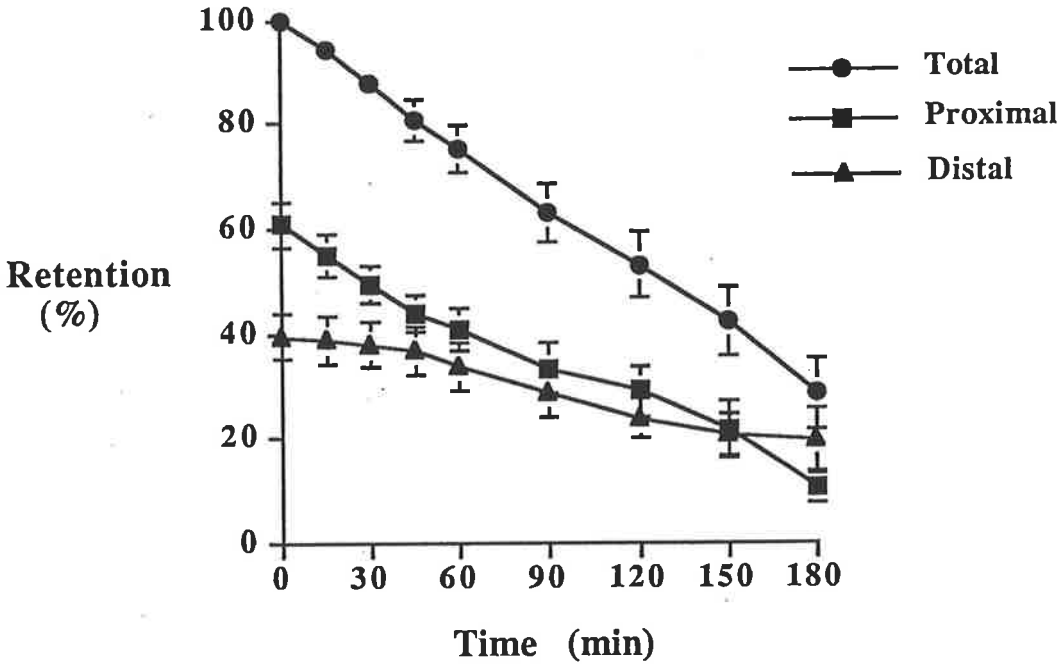

Figure 8.2: Gastric emptying of dextrose measured scintigraphically showing total, proximal and distal stomach retention. Data are mean values ± SEM.

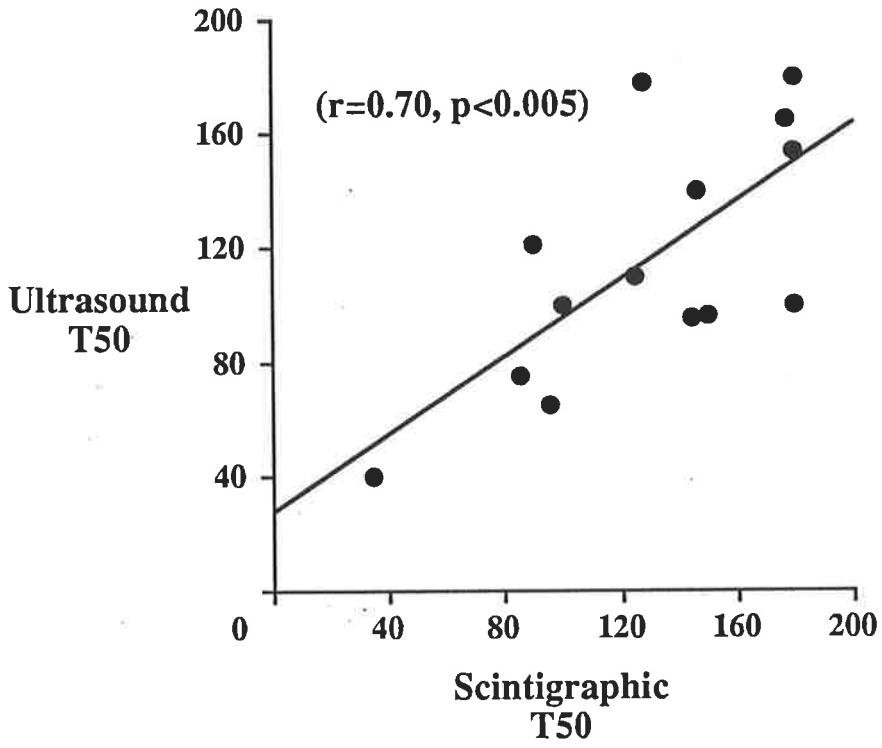

Figure 8.3: Relationship between ultrasound and scintigraphic 50% emptying times (T50) for dextrose (r=0.70,p<0.005).

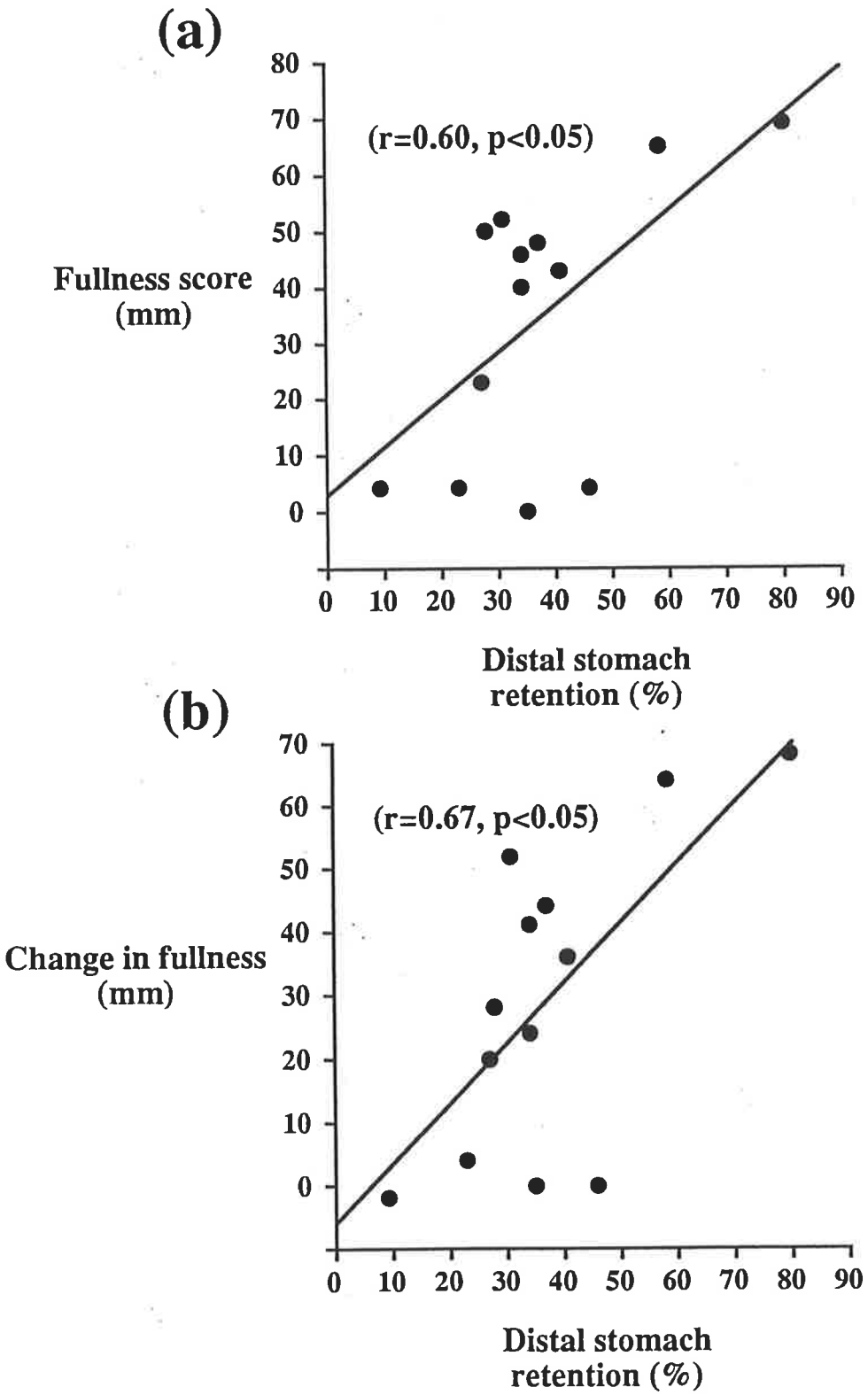

Figure 8.4: Relationships between (a) score for fullness and (b) change in fullness from baseline with % retention in the distal stomach.

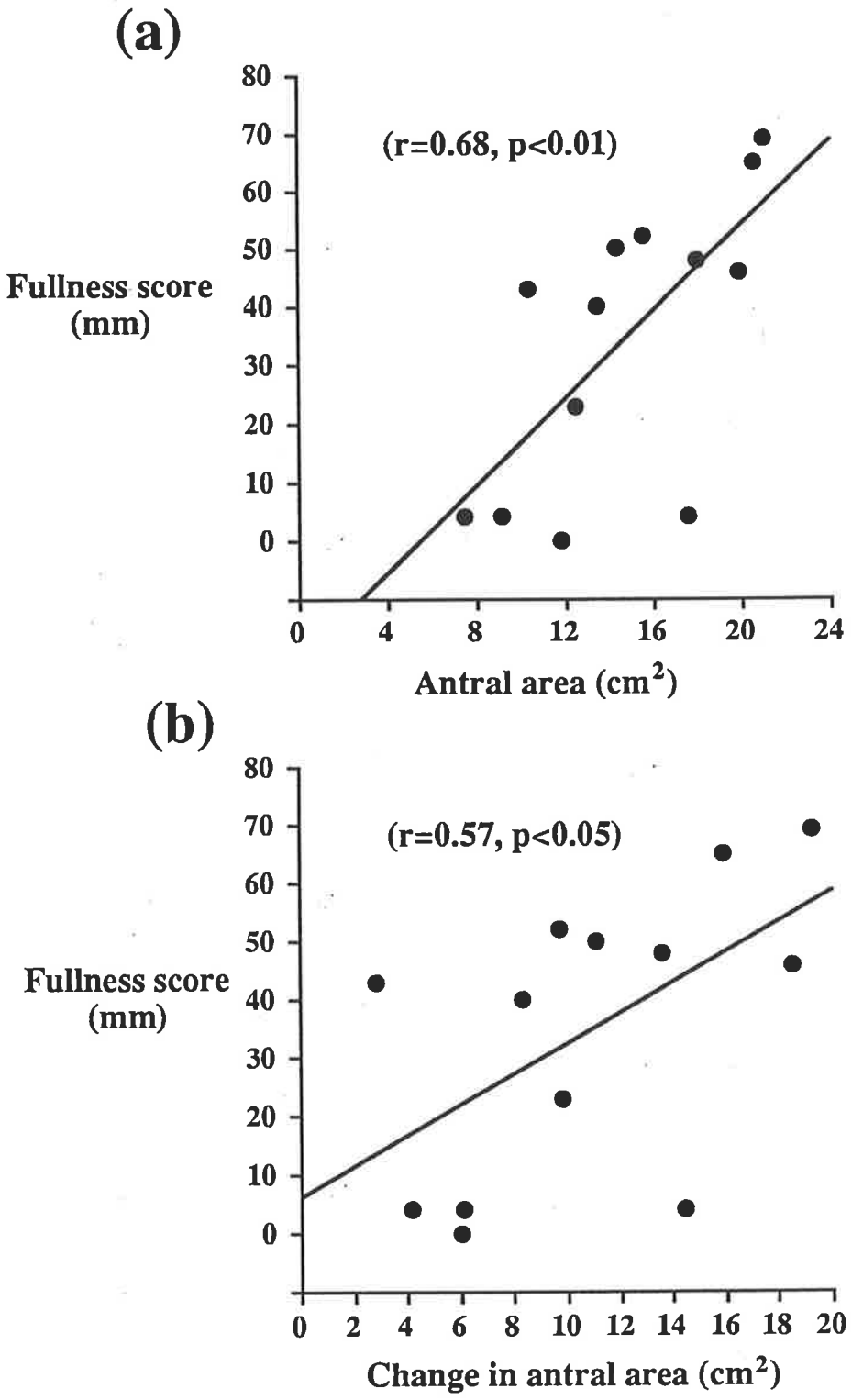

Figure 8.5: Relationships between score for fullness with (a) antral area and (b) change in antral area from fasting.

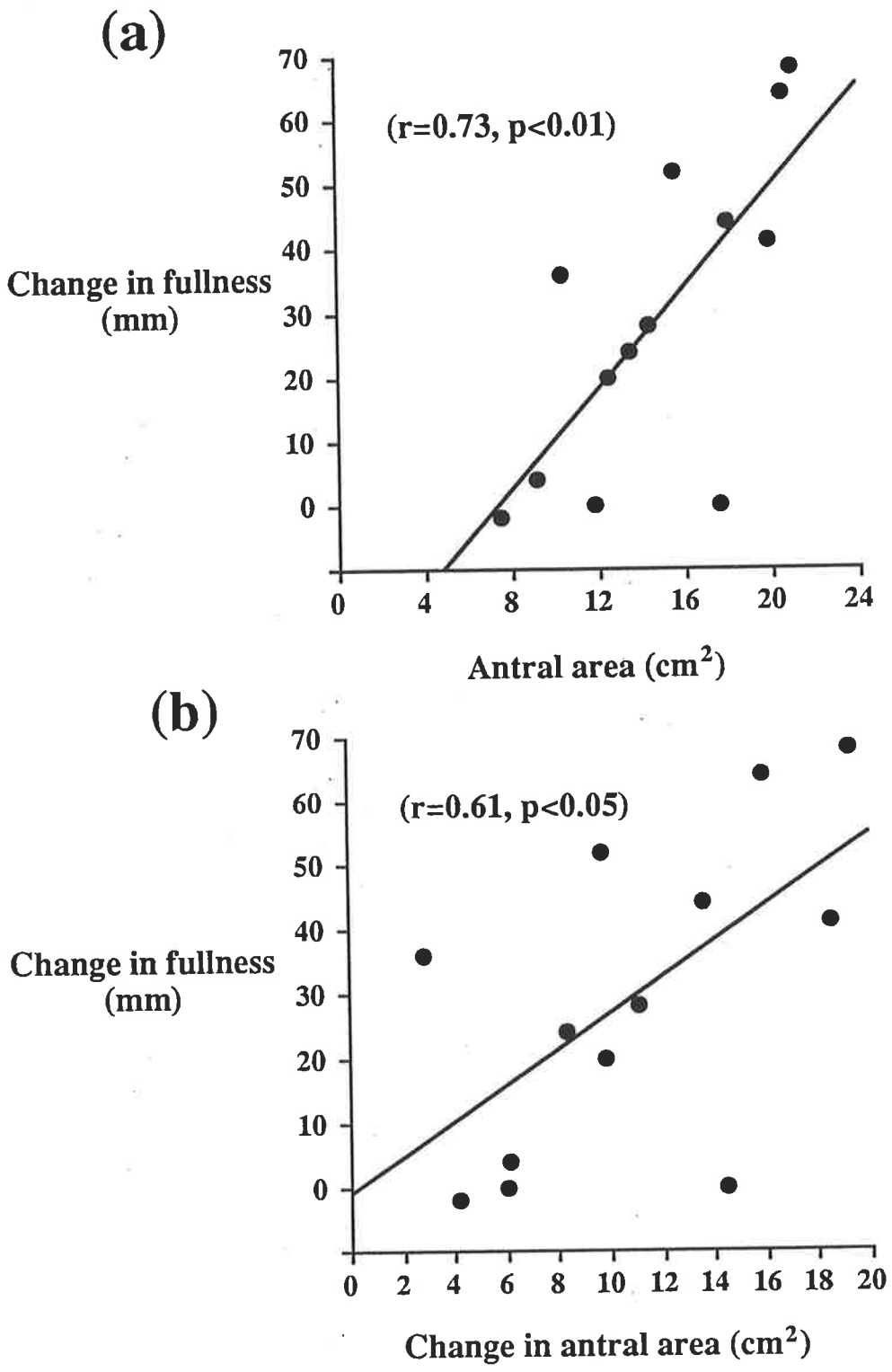

Figure 8.6: Relationships between the change in fullness from baseline with (a) antral area and (b) change in antral area from fasting.

8.5 DISCUSSION

In the present study, we have shown in normal subjects, after ingestion of a nutrient liquid that (i) postprandial fullness, but not hunger, is closely related to both antral area and the content of the distal stomach and (ii) postprandial antral area is related to the content of the distal stomach, but not gastric emptying. The close concordance between scintigraphic and ultrasound measurements of gastric emptying has been reported previuosly (Chapter 7) and by others (Bolondi et al 1986, Holt et al 1986, Marzio et al 1989).

Studies in both animals and humans indicate that postprandial satiation is influenced by a number of factors including gastric tone (Feinle et al 1995), intragastric content (Bergmann et al 1992) and feedback from small intestinal receptors (Chapter 10, Chapter 11). In animlas, gastric distension is well recognised as a signal for satiation (Morley 1987). Our observations suggest that antral, as opposed to proximal gastric distension, plays a major role in triggering satiation. In particular, it seems reasonable to assume that antral distension will be related to both postprandial antral area and the content of the distal stomach. There were close relationships between postprandial fullness and both of these parameters, but not between satiation and either the rate of gastric emptying (measured by scintigraphy or ultrasound) or the content of the distal stomach quantified scintigraphically. There was no significant relationship between postprandial hunger and either antral area or the content of the distal stomach, suggesting that hunger and fullness are regulated by different mechanisms. This concept is consistent with a recent study by Benini et al who compared, using ultrasound, emptying of two meals which were identical in energy content and composition, but differed in the way in which they were cooked (fried or non-fried) (Benini et al 1994). Fullness increased after both meals, but was greater after ingestion of the fried meal. Although it was noted that antral area was also greater, after the fried

meal, a formal correlation was not performed. Whereas hunger decreased after ingestion of both meals, there were no differences between the fried and non-fried meal.

Studies of the relationship between gastrointestinal sensations (including appetite) and gastric distension have mainly assessed the effects of proximal gastric tone, often using a barostat technique (Samsom et al 1995, Hebbard et al 1996b) and there is little information about the role of antral tone or distension. It is clear that the perception of gastric distension is modified by a number of factors including the presence of nutrients in the small intestine (Hebbard et al 1996b) and sympathetic nerve activity (Iovino et al 1995). Animal studies have suggested the role of a humoral factor released from the stomach in producing satiation in response to food in the stomach (Koopmans 1983) A number of gastrointestinal hormones have been demonstrated to have a satiating effect both in animals and humans (Morley 1987). Both gastrin releasing peptide and somatostatin are released from the antrum (Wittert et al 1997) and have been demonstrated to have a satiating effect on food intake in both animals and humans (Morley 1990, Gutzwiller et al 1994, Liverse et al 1995) making these potential candiates for mediating the postprandial satiation associated with antral distension. Bloating, or sensations of fullness, are the result of stimulation of visceral mechanoreceptors (Blackshaw & Grundy 1993) and subjective sensations of discomfort are thought to be mediated via vagal pathways. Mechanoreceptors in different regions of the stomach demonstrate different patterns of activity (Andrews et al 1980). The fundus and corpus show tonic motor activity while the antrum demonstrates a pattern of phasic contractile activity (Andrews et al 1980). During antral distension, rythmic activity becomes more prominent and is sometimes associated with increased background tonic activity in this region. It has been suggested that it is this tonic discharge which gives rise to sensations of discomfort (Grundy et al 1991).

Although our observations require confirmation with test meals of different composition and volume, they are likely to be clinically relevant. In particular, it is now well documented that in patients with non-ulcer dyspepsia (Hausken & Berstad 1992) both fasting and postprandial antral area are increased, when compared to normal subjects and this is associated with abnormal intragastric meal distribution (Troncon et al 1994). In the study by Hausken and Berstad postprandial gastrointestinal symptoms in patients with non-ulcer dyspepsia, particularly bloating, were related to antral area (Hausken & Berstad 1992). Undeland recently reported that patients with insulin dependent diabetes mellitus (IDDM) also have a greater antral area than normal (Undeland et al 1996). The fasting width of the antrum and the score for bloating are postively correlated in both the patients with dyspepsia and IDDM (Undeland et al 1996). These studies, therefore strongly support the concept that antral tone plays a major role in the aetiology of upper gastrointestinal symptoms in both health and disease.

CHAPTER 9

EFFECTS OF MEAL VOLUME AND POSTURE ON GASTRIC EMPTYING OF SOLIDS AND APPETITE

9.1 SUMMARY

The effects of volume and posture on gastric emptying and intragastric distribution of a solid meal and appetite were evaluated. Eight normal volunteers were studied on four occasions, each after ingesting a meal comprising ground beef mixed with tomato sauce of either 650 g ("large") or 217 g ("small"). Two studies were performed while the subject was lying in the left lateral decubitus position, and two while the subject was sitting, so that data was available from each subject for both meals, in both postures. Hunger and fullness were evaluated using a visual analogue questionnaire. In both postures and after both meals, gastric emptying approximated a linear pattern after an initial lag phase. The lag phase was shorter for the "large" meal when compared to the "small" meal (sitting: "large" 13 ± 5 min vs "small" 29 ± 7 min, $p<0.02$; left lateral: "large" 16 ± 3 min vs "small" 24 ± 3 min, $p<0.05$). In both postures the contents of the total ($p<0.001$), proximal ($p<0.001$) and distal ($p<0.001$) stomach were greater following the "large" meal when compared to the "small" meal. Although the 50% emptying time was greater with the "large" than the "small" meal in both postures ($p<0.02$), the post-lag emptying rate (g/min) was more rapid with the "large" meal (sitting: "large 1.7 ± 0.2 g/min vs "small" 1.1 ± 0.1 g/min, $p<0.02$; left lateral: "large" 1.8 ± 0.1 g/min vs "small" 1.3 ± 0.04 g/min, $p<0.02$). The retention in the proximal stomach was slightly less ($p<0.05$) in the sitting when compared to the left lateral position for both the "large" and the "small" meal. The magnitude of the postprandial reduction in hunger ($p<0.05$) and increase in fullness ($p<0.05$) was greater with the "large"

meal. We conclude that meal volume has a major effect on gastric emptying and intragastric distribution of a digestible solid meal; in contrast posture has only a minor impact on intragastric meal distribution, and no effect on gastric emptying.

9.2 INTRODUCTION

There is relatively little information about the effects of alterations in meal composition or volume on the rate of gastric emptying. The emphasis of most previous studies has been on gastric emptying of liquids, which has been demonstrated to be affected by propulsive forces generated by intragastric volume and by gravity (Hunt et al 1965, Burn-Murdoch et al 1980, Hunt et al 1985, Anvari et al 1995, Chapter 10), as well as feedback from receptors in the small intestinal lumen (McHugh & Moran 1979, Brener et al 1983, Lin et al 1989). In dogs, it has been suggested that the time taken to grind solid food into small particles, so-called trituration, is the major factor regulating its emptying (Lin et al 1992), implying that gastric emptying of solids, unlike that of liquids, is not "load-dependent" and that digestible solids normally empty from the stomach at a maximum rate (Lin et al 1992). However, this hypothesis has not been tested in humans. In humans, the potential effects of posture and meal volume on gastric emptying of solids has hitherto only been assessed with mixed solid/liquid meals (Moore et al 1984, Moore et al 1988, Collins et al 1996), and it is clear that the presence of liquid may modulate the rate of emptying of a solid meal (Collins et al 1983, Horowitz et al 1989b, Collins et al 1991).

Satiety signals from the gastrointestinal tract, triggered by gastric distension and the interaction of nutrients with small intestinal receptors are important in the regulation of appetite (Guss et al 1994, Read et al 1994, Collins et al 1996, Lavin et al 1996, Phillips et al 1996, Cook et al 1997). There is some evidence that postprandial

appetite may be influenced by posture, an effect which may be mediated by changes in intragastric meal distribution or the rate of gastric emptying (Chapter 10).

The purpose of this study was to evaluate the effects of meal volume and posture on gastric emptying and intragastric distribution of a solid meal and appetite in normal subjects.

9.3 MATERIALS AND METHODS

Eight healthy male volunteers, mean age 24 yrs (range 18 - 34) and mean body mass index (BMI) 23.5 kg/m^2 (20.5 - 27.9 kg/m^2) were studied. All subjects were non-smokers on no medication, and none had a history of gastrointestinal disease nor surgery. Written, informed consent was obtained from each subject and the protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

9.3.1 *Experimental protocol*

Each subject had measurements of gastric emptying and appetite on four days, each of which was separated by 2 - 14 days. Two of the four studies were performed while the subject was lying in the left lateral decubitus ("pylorus up") position, and two while the subject was sitting. In both postures gastric emptying of a "large" and a "small" meal was quantified. The order of the four studies was randomised. The "large" meal (total weight 650 g) consisted of 450 g cooked ground beef with *in vivo* labelled ^{99m}Tc-chicken liver and 200 g tomato sauce ("Dolmio", Master Foods, Wyong, NSW, Australia) and the "small" meal (total weight 217 g) 150 g ground beef with ^{99m}Tc-chicken liver and 67 g sauce. The caloric content of the "large" meal was 1302 kcal, and that of the "small" meal 434 kcal. Each meal was

consumed at 12.00h after an overnight fast (12 hours liquids and 14 hours solids) in front of a scintillation camera (Collins et al 1983). Subjects were asked not to chew before swallowing (in an attempt to standardise particle size) and to consume the meal within 5 minutes. The time for meal consumption was measured. Immediately prior to, and following meal consumption, appetite was assessed using a visual analogue questionnaire (Sepple & Read 1989). Both gastric emptying and appetite were quantified for 240 minutes following ingestion of the test meal.

9.3.2 *Measurement of gastric emptying*

20 MBq (about 5 g) of *in vivo* labelled ^{99m}Tc sulphur colloid-chicken liver (Collins et al 1983) was mixed thoroughly with uncooked ground beef (so that the combined weight was 450 g or 150 g) and then cooked. The tomato sauce (200 g or 67 g) was added after cooking and mixed through the meat.

Scintigraphic data were acquired for 240 minutes at 1 min frames for the first 60 min and at 3 min frames thereafter. Data acquisition commenced immediately after meal consumption. Radionuclide data were corrected for radionuclide decay, gamma ray attenuation and subject movement using established methods (Collins et al 1983, Collins et al 1991, Collins et al 1996). The total stomach region-of-interest was divided into proximal and distal regions, with the proximal region corresponding to the fundus and proximal corpus and the distal region corresponding to the distal corpus and antrum (Collins et al 1991). Emptying curves were derived for the total, proximal and distal stomach regions-of-interest and expressed as percent of isotope retained versus time (Collins et al 1991, Collins et al 1996). From the emptying curves a number of parameters were then calculated for further analysis. For the total stomach these were the lag phase (defined as the time period, in minutes, before any

of the meal entered the proximal small intestine (Collins et al 1983), the amount of isotope remaining in the stomach at 15 minute intervals until 240 minutes, the post-lag linear emptying rate (g/min) (between the end of the lag phase and 180 min), and the 50% emptying time (T50). The content of both the proximal and distal stomach at 15 min intervals until 240 minutes, and the rate of emptying from the proximal stomach (g/min) (between 0 and 180 min) were also calculated (Collins et al 1996).

9.3.3 *Assessment of Appetite*

Hunger and fullness were evaluated by having the subjects mark a previously validated visual analogue scale at -15, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 minutes (Sepple & Read 1989).

9.3.4 *Statistical Analysis*

Data were evaluated using repeated measures ANOVA, the Wilcoxon test and linear regression analysis and are shown as mean values ± SEM. A p value <0.05 was considered significant in all analyses.

9.4 RESULTS

All subjects tolerated the study well and no adverse affects were reported. In 5 of the 32 studies the time for meal consumption was more than five minutes (maximum 9 minutes), and the time taken for consumption of the large meal was greater than that for the small meal in both postures (sitting: "large" 5.4 ± 0.6 min vs "small" 2.3 ± 0.3min, $p<0.05$; left lateral "large" 5.4 ± 0.7 min vs "small" 1.8 ± 0.2 min, $p<0.05$).

9.4.1 *Gastric emptying*

Effect of meal volume

In both postures gastric emptying approximated a linear pattern after an initial lag phase (Figure 9.1). The lag phase was shorter for the "large" meal when compared to the "small" meal (sitting: "large" 13 ± 5 min vs "small" 29 ± 7 min, $p<0.02$; left lateral: "large" 16 ± 3 min vs "small" 24 ± 3 min, $p<0.05$). The T50 was longer with the "large" meal in both postures (sitting: "large" 197 ± 10 min vs "small" 121 ± 19 min, $p<0.02$; left lateral: "large" 202 ± 12 min vs small 133 ± 14, $p<0.02$). In all studies more than 15 g of the meal remained in the stomach at 180 minutes. The post-lag emptying rates were also more rapid with the "large" meal in both postures (sitting: "large" 1.7 ± 0.2 g/min vs "small" 1.1 ± 0.1 g/min, $p<0.02$; left lateral: "large" 1.8 ± 0.1 g/min vs "small" 1.3 ± 0.04 g/min ($p<0.02$).

The retention in both the proximal ($p<0.001$) and distal ($p<0.001$) stomach was greater with the "large" than the "small" meal in both postures throughout the 240 minutes (Figure 9.1). However, as with the total stomach, the rate of emptying (g/min) from the proximal stomach was greater with the "large" meal in both postures ($p<0.001$ for both).

Effect of posture

Posture had no effect on either the lag phase or the post-lag emptying rate. However, posture did slightly, but significantly, alter intragastric distribution, in that for both the "large" and the "small" meal the retention in the proximal stomach was less ($p<0.05$) and the retention in the distal stomach greater ($p<0.05$) in the sitting when compared to the left lateral position (Figure 9.2).

9.4.2 *Appetite*

There was no difference between the four studies in scores for hunger or fullness before meal ingestion. In both postures there was a reduction in hunger ($p<0.001$) and an increase in fullness ($p<0.001$) after both meals. The magnitude of these changes was greater with the "large" than the "small" meal ($p<0.05$ for both) (Figure 9.3); this difference being evident from 15 minutes after meal consumption (ie when very little food had emptied from the stomach) and sustained until 240 min. After the meal, hunger and fullness were inversely related ($r\geq-0.73$, $p<0.05$) at all time points up to 180 min. After ingestion of the "small" meal, hunger was slightly less ($p<0.05$) in the left lateral position when compared to the sitting position. Otherwise, there were no significant effects of posture on hunger or fullness.

9.4.3 *Relationship between appetite and gastric emptying*

There were no significant relationships between scores for either hunger or fullness and the content of the total or proximal stomach. After the "large" meal the score for hunger at 210 min was inversely related to the content of the distal stomach at that time ($r\geq0.72$, $p<0.05$) in both postures.

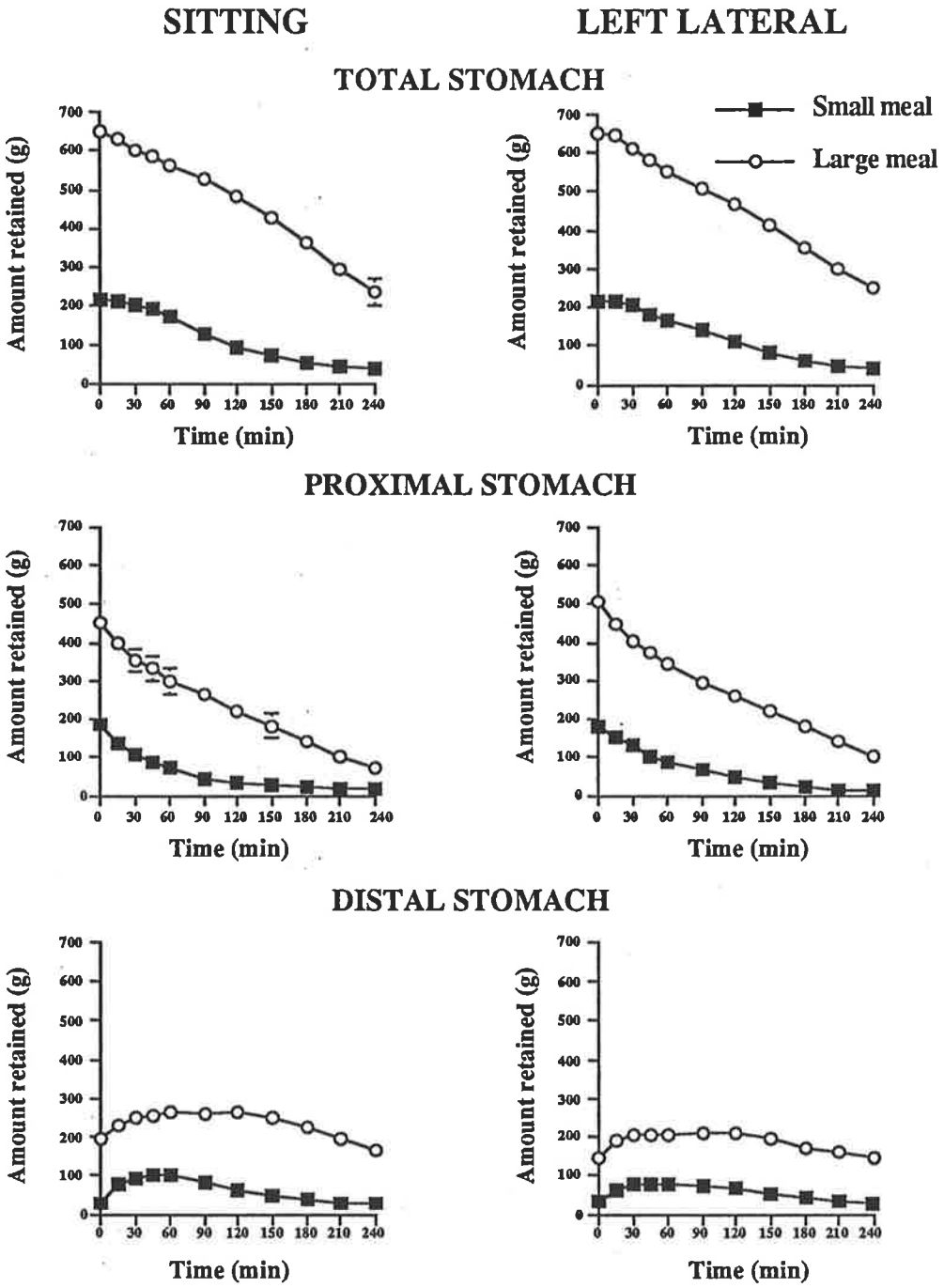

Figure 9.1: Gastric emptying (g) and intragastric distribution of "small" (217 g) and "large" (650 g) meals in the sitting and left lateral positions. Data are mean values ± SEM.

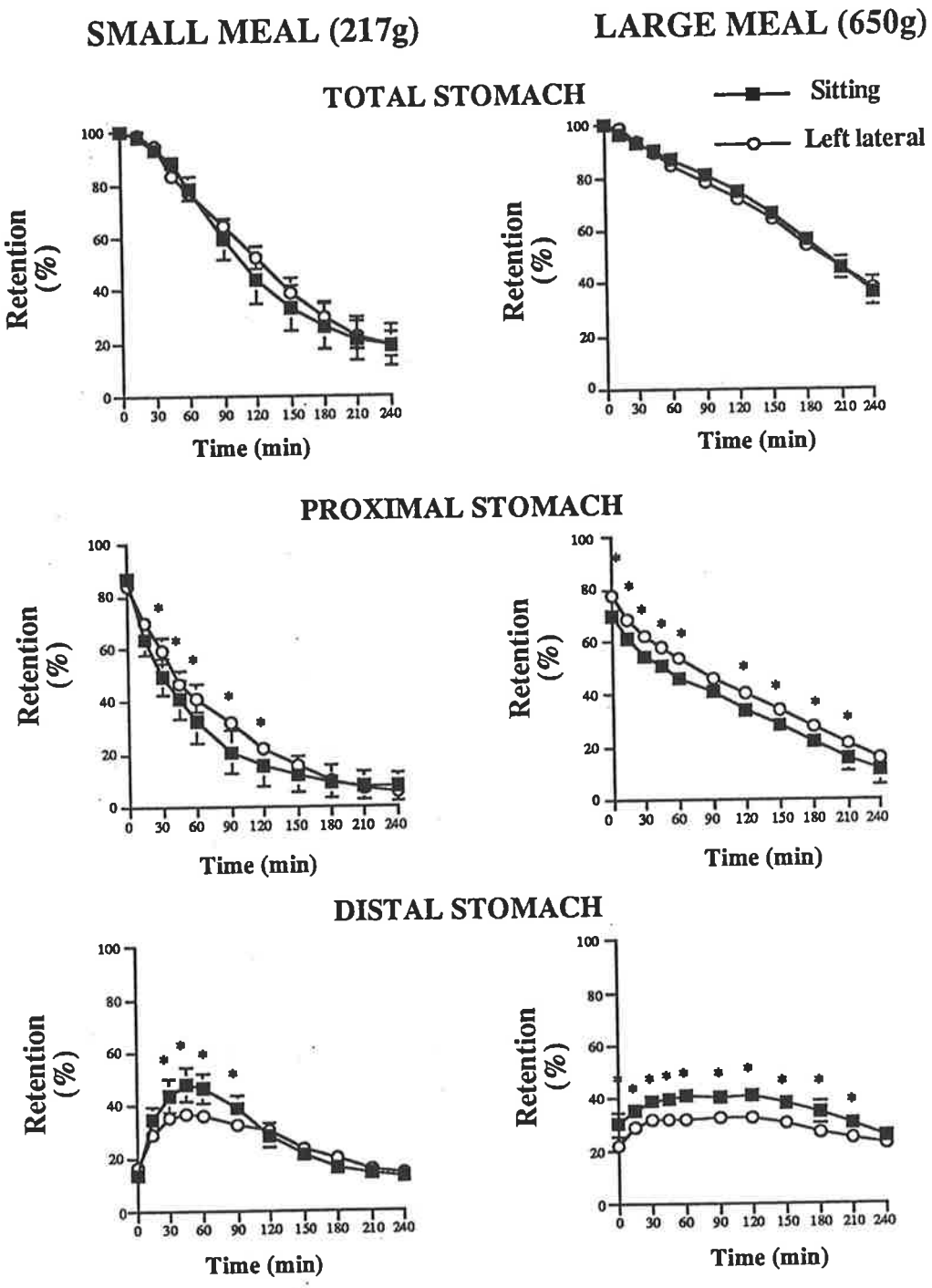

*Figure 9.2: Effect of posture on gastric emptying and intragastric distribution of "small" (217 g) meals and "large" (650 g) meals. Data are mean values ± SEM and are shown as a percentage of maximum. For n=8 subjects, *F>4.0, P<0.05 sitting vs left lateral position.*

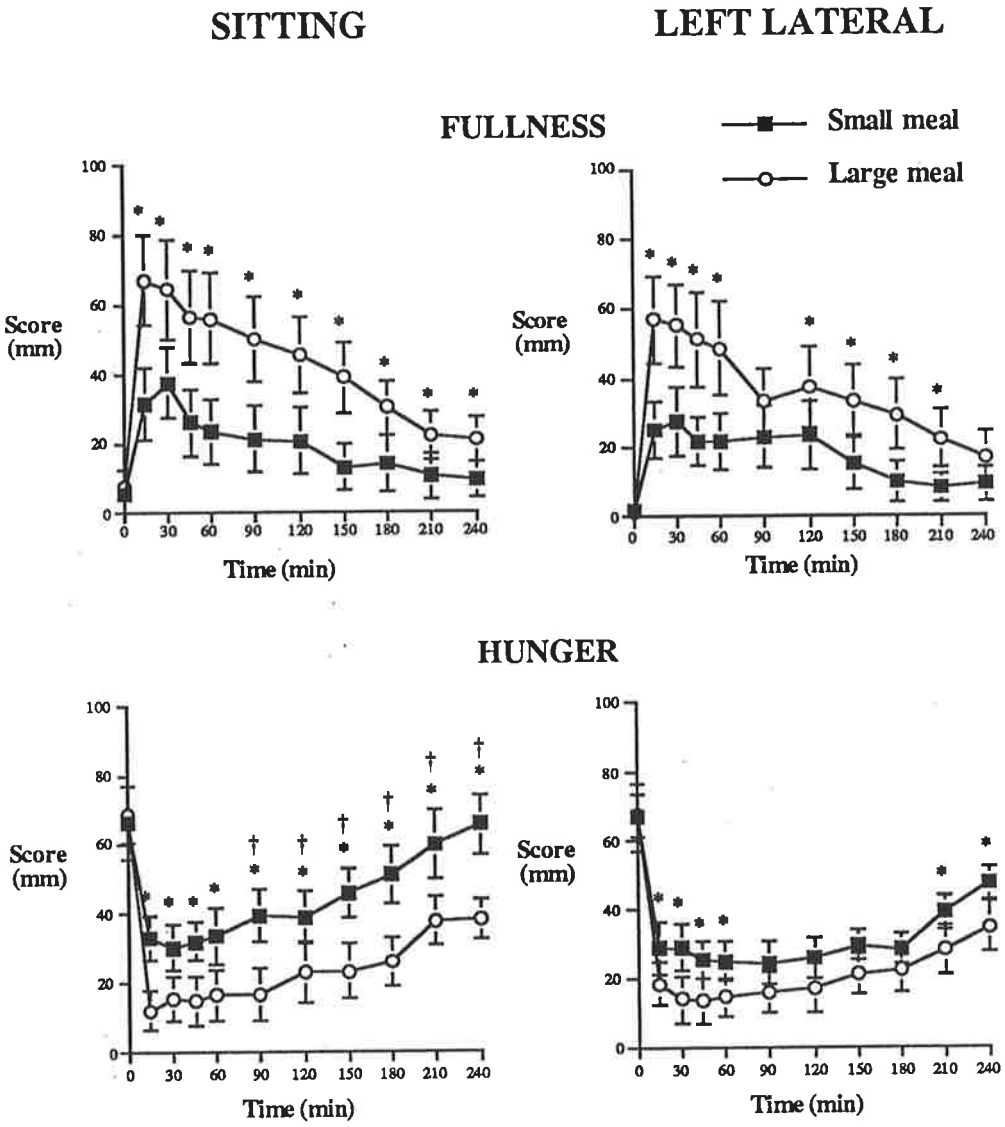

*Figure 9.3: Perceptions of hunger and fullness immediately before and after ingestion of "small" (217 g) and "large" (650 g) meals in the sitting and left lateral positions. Data are mean ± SEM. For n=8 subjects, *F>4.0, P<0.05 "small" vs "large" meal. †F>4.0, P<0.05 sitting vs left lateral position for "small" meal.*

9.5 DISCUSSION

This study establishes for the first time that gastric emptying of a solid meal is influenced by its volume. A three-fold increase in the volume of a solid meal (from 217 g to 650 g) was associated with a reduction in the duration of the lag phase, more rapid emptying from the proximal stomach, and acceleration of the post-lag emptying rate. As a consequence of these changes the rate of energy delivery from the stomach to the small intestine was much faster with the larger meal. In contrast to the effects of volume, posture had only a minor (albeit statistically significant) impact on intragastric meal distribution, and no effect on the rate of gastric emptying. While the demonstration that meal volume was a major determinant of postprandial satiation is predictable, the observation that after ingestion of the large meal, hunger was inversely related to the content of the distal stomach is of interest.

The effect of the volume of a solid meal on its rate of gastric emptying has hitherto not been evaluated in humans. In dogs, Lin et al (1992) reported that the rate of emptying of 10 mm pieces of steak was independent of meal volume in the range 150-600 g, and accordingly suggested that trituration was the rate limiting step for solid emptying. It should, however, be noted that in this study chyme was diverted from the small intestine by a duodenal fistula, thereby eliminating small intestinal feedback. It has been clearly established in humans that increasing the volume of a liquid meal is associated with more rapid emptying (Lin et al 1992), even if the liquid contains nutrients (Hunt et al 1985), indicating that with liquids intragastric volume has the capacity to act as a propulsive force sufficient to overcome feedback from small intestinal chemoreceptors (McHugh et al 1979, Brener et al 1983, Lin et al 1989). In contrast, studies in humans assessing volume dependency with solids have been conducted only using mixed solid/liquid meals. Moore and co-workers assessed the relative influence of weight and caloric content on gastric emptying of a mixed meal using a scintigraphic technique (Moore et al 1984), but interpretation

of their results is difficult, as the major energy component of their meal (oil) was not labelled. Our group has previously reported (Collins et al 1996) that an increase in the volume of the solid component of a mixed solid and liquid meal is associated with more rapid emptying of solids, from both the total and proximal stomach. In this study (Collins et al 1996) the lag phase was longer after the larger meal, confirming that the presence of a nutrient liquid modifies emptying of the solid component of a meal (Collins et al 1983, Horowitz et al 1989b). The mechanisms mediating the observed volume-related acceleration of gastric emptying of solids are uncertain. The amount of solid in the distal stomach was greater with the larger meal in both postures, and it has been suggested that greater antral distension may increase antral contractile activity, leading to more efficient trituration (Moore et al 1984, Horowitz & Dent 1991). The shorter lag phase with the larger meal may be attributable to more efficient antral mixing (Urbain et al 1989). If this is the case the relationship between volume and emptying of a solid meal is likely to be critically dependent on the time required for trituration (Holt et al 1982, Lin et al 1992). It should also be recognised that after the lag phase much of the solid meal has been triturated to small particles and therefore, essentially liquified. This is likely to contribute to the observed effect of meal volume on the post-lag emptying rate.

Our study indicates that posture does not affect gastric emptying of a solid meal. The emphasis of most previous studies of the effects of posture on gastric emptying has related to emptying of liquids (non-nutrient, nutrient and oil) (Hunt et al 1965, Burn-Murdoch et al 1980, Anvari et al 1995, Boulby et al 1997); gastric emptying and intragastric distribution of liquids, semisolids and oil is affected by posture, being slower in the recumbent than the erect position (Hunt et al 1965, Hancock et al 1974, Burn-Murdoch et al 1980, Anvari et al 1995, Boulby et al 1997). The effects of posture on gastric emptying of liquids is likely to relate to changes in

antropyloric motility, as well as passive forces generated by volume and gravity (Anvari et al 1995). Moore and co-workers evaluated the effects of posture on gastric emptying of a meal consisting of beef stew and orange juice (Moore et al 1988). While gastric emptying of the solid component was observed to be slower in the supine when compared to the sitting and standing positions, emptying of the liquid component of the meal was not quantified, and this could account for the observed differences in gastric emptying of solid (Collins et al 1983, Horowitz et al 1989b). This study is therefore the first to evaluate the effects of posture on gastric emptying of a solid meal in the absence of liquid. It was anticipated that emptying of solids may be more rapid in the sitting than the left lateral position, but this proved not to be the case, probably because the observed effects of posture on intragastric distribution of solids were relatively small. It is uncertain why gravity does not have a major effect on intragastric distribution of solids, as it does for liquids (Anvari et al 1995, Chapter 10). Moore et al (1986) have suggested that the so-called "mid-gastric band" may limit movement of solid food from the proximal to the distal stomach. It is also possible that antral tone may play a significant role in regulating intragastric distribution of solids (Collins et al 1991).

Signals from the gastrointestinal tract play a major role in the regulation of appetite (Read et al 1994), but it has not been established whether gastric distension or feedback from small intestinal nutrient receptors is the more important of these mechanisms (Carbonnel 1994, Guss et al 1994, Lavin et al 1996, Phillips et al 1996, Cook et al 1997, Chapter 10, Chapter 11). The potential effects of posture on appetite and gastrointestinal symptoms is of some interest; patients with upper gastrointestinal symptoms frequently report that improvement occurs with standing or sitting. In Chapter 10, after ingestion of an oil/aqueous meal, postprandial hunger in normal subjects is influenced by posture, being less in the left lateral decubitus than the sitting position (Chapter 10). In the current study postprandial

appetite was less after the larger meal in both postures, for at least the first four hours after eating. This difference was apparent soon after ingestion of the meal, indicative of an effect mediated, at least initially, by greater intragastric volume, rather than more rapid gastric emptying. The possibility that the more rapid emptying of the larger meal, and thus greater stimulation of small intestinal nutrient-receptors, contributed to the sustained increase in satiation, cannot however, be excluded. Postprandial hunger was less in the left lateral than the sitting position after ingestion of the small meal, but the magnitude of this difference was small. It is, therefore, likely that the reduction in hunger in the left lateral position after ingestion of an oil/aqueous meal, reported in Chapter 10 relates to the more rapid emptying of oil in this posture. As the number of subjects studied was relatively small, it is somewhat tenuous to draw firm conclusions from any observed correlations. Nevertheless, the inverse relationship between postprandial hunger and the content of the distal stomach is consistent with the concept that antral distension plays a major role in triggering satiation (Chapter 8).

CHAPTER 10

THE EFFECT OF POSTURE ON GASTRIC EMPTYING AND INTRAGASTRIC DISTRIBUTION OF OIL AND AQUEOUS MEAL COMPONENTS AND APPETITE

10.1 SUMMARY

There is relatively little information about gastric processing of fat in humans. In this study the effects of posture on gastric emptying, intragastric distribution and appetite after ingestion of a liquid meal containing oil and aqueous phases, were evaluated.

Eleven volunteers consumed 60 ml ^{99m}Tc-(V)-thiocyanate labelled olive oil (473 kcal) and 290 ml ^{113m}In-labelled soup (32 kcal) on two occasions: while sitting and while lying in the left lateral decubitus position. Feelings of hunger before and after the meal were recorded on a visual analogue scale.

In the sitting position oil emptied from the stomach more slowly ($p<0.01$) than the aqueous phase of the meal, while in the decubitus position oil emptied faster ($p<0.01$) than the aqueous phase. The lag phase for the oil was longer ($p<0.001$) in the sitting position. Although oil was preferentially retained in the proximal stomach when sitting ($p <0.01$) and more oil was retained in the distal stomach in the decubitus position ($p<0.05$), the total amount of oil that emptied from the stomach in the first 180 min was not significantly different between the two postures. The aqueous phase emptied much more slowly ($p<0.01$) in the decubitus position and this was associated with increased retention of the aqueous phase in the proximal stomach ($p<0.01$). At 120 min and 180 min after meal consumption

subjects were less hungry ($p<0.05$) in the decubitus position. In the decubitus position the score for hunger at 120 min and 180 min was related to the retention of oil ($r \geq 0.79$, $p<0.01$), but not to that of the aqueous phase ($r \geq 0.03$, ns) in the total stomach.

These results indicate that after ingestion of an oil/aqueous meal: (i) gravity has a major effect on the duration of the pre-emptying phase and the intragastric distribution and relatively little effect on total stomach emptying of oil, but influences both intragastric distribution and gastric emptying of the aqueous phase of the meal and (ii) postprandial hunger is affected by posture and, in the decubitus position, is inversely related to the amount of oil that has entered the small intestine.

10.2 INTRODUCTION

Although upper gastrointestinal symptoms are reported frequently after the ingestion of fatty foods and gastric emptying is likely to be important in the digestion and absorption of fat, there is relatively little information about gastric processing of fat in humans (Chang et al 1968, Hunt & Knox 1968, Cortot et al 1981, Cortot et al 1982, Jian et al 1982, Meyer et al 1986, Meyer et al 1987, Houghton et al 1990, Lin et al 1990b, Cunningham et al 1991d, Edelbroek et al 1992b). Clinical measurements of gastric emptying are usually performed using small and relatively bland meals (Horowitz et al 1985a) and it has been suggested (Read 1989) that the use of test meals designed to provoke symptoms may demonstrate a higher prevalence of abnormality, particularly in patients with non-ulcer dyspepsia and gastrooesophageal reflux disease.

The intragastric distribution of extracellular fat and the importance of that distribution to gastric emptying and digestion of fat is controversial (Chang et al

1968, Jian et al 1982, Meyer et al 1986, Edelbroek et al 1992b). Extracellular fat empties from the stomach more slowly than low nutrient aqueous liquids (Cortot et al 1981, Cortot et al 1982, Jian et al 1982, Meyer et al 1986, Cunningham et al 1991d). In a recent study (Edelbroek et al 1992b) it was reported that the slower emptying of oil, when compared to the aqueous component of a meal, was associated with greater retention of oil in the proximal stomach. It was also demonstrated that oil emptied from the stomach at a similar rate to that of a simultaneously ingested equicaloric solid meal, but had a different intragastric distribution, so that there was a greater proportion of the oil in the proximal stomach and more of the solid phase in the distal stomach. It is unclear whether the increased retention of oil in the proximal stomach, when compared to both solid and aqueous meal components, reflects the effect of gravity causing "layering" of oil above aqueous meal components (Chang et al 1968), retrograde movement of oil from distal to proximal stomach (Houghton et al 1990, Cunningham et al 1991d, Edelbroek et al 1992b) and/or the physical barrier of a midgastric band (Moore et al 1986, Collins et al 1988, Edelbroek et al 1992b). In an attempt to resolve this issue the effect of posture on gastric emptying and intragastric distribution of simultaneously ingested oil and aqueous meal components has been evaluated.

The factors which influence appetite in humans are controversial and poorly understood. Gastric distension is well recognized as a signal for satiety in animals (Gibbs & Smith 1978) and it has been postulated that more rapid gastric emptying, by reducing gastric distension, would result in increased food intake and a predisposition to obesity (Hunt 1980). Recent studies suggest that postprandial hunger may be more closely related to the extent of small intestinal nutrient exposure than gastric distension (Welch et al 1985, Welch et al 1988, Sepple & Read 1989, Greenberg et al 1990 Greenberg et al 1992). For example, intraduodenal infusion of fat reduces food intake in both animals (Greenberg et al

1990, Greenberg et al 1992) and humans (Welch et al 1988, Sepple & Read 1989, Drewe et al 1992) and in animals this effect is not dependent on retardation of gastric emptying (Greenberg et al 1990). Patients with postprandial upper gastrointestinal symptoms frequently report that improvement occurs with standing, or sitting and limited studies indicate that gravity influences gastric emptying (Burn-Murdoch et al 1980, Gulsrud et al 1980, Tothill et al 1980, Horowitz et al 1982, Moore et al 1988, Anvari et al 1991). Somewhat surprisingly, the effects of posture on appetite have not been examined. Furthermore no studies have evaluated whether postprandial hunger relates to the intragastric distribution of a meal.

10.3 MATERIALS AND METHODS

Paired studies were carried out in 11 healthy volunteers (4 male, 7 female, mean age 21 years, range 18 - 26 years) and mean body weight 66 kg (range 55 - 81 kg). None had a history of gastrointestinal disease, or used medication which could have influenced gastrointestinal motility. Written informed consent was obtained from each subject and the study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

10.3.1 *Experimental protocol*

Each volunteer had measurements of gastric emptying performed on two separate days in different postures; one with the subject sitting and the other while the subject was lying in the left lateral decubitus "pylorus-up" position. The order of the two studies was randomized and they were separated by an interval of between 3 and 14 days. In female subjects gastric emptying measurements were performed during the follicular phase of the menstrual cycle. The test meal was consumed

within two minutes at 10:00 am after an overnight fast (14 h for solids and 12 h for liquids) in front of a scintillation camera and consisted of a mixture of 60 ml olive oil (Faulding Pty Ltd., South Australia), labelled with 20 MBq ^{99m}Tc-(V)-thiocyanate and 290 ml low nutrient beef consomme soup (Campbells Soups Pty Ltd.; Australia), labelled with 20 MBq ^{113m}In-diethylenetriamine-pentaacetic acid (DTPA), heated to 45^{o}C immediately prior to consumption (Cunningham et al 1991d, Edelbroek et al 1992b). The oil was mixed gently with the soup immediately before and during consumption of the meal. The caloric content of the oil-soup mixture (7 g protein, 52 g fat) was 505 kcal, of which 473 kcal were contained in the oil, and its caloric density was 1.44 kcal/ml (Edelbroek et al 1992b). Subjective feelings of hunger and fullness were recorded on a validated visual analogue scale administered immediately before and at 15, 75, 120 and 180 min after ingestion of the meal (Sepple & Read 1989).

10.3.2 *Measurement of gastric emptying*

Preparation of radioisotopic markers

Olive oil was labelled with 20 MBq ^{99m}Tc-(V)-thiocyanate using a previously described method (Cunningham et al 1991d, Edelbroek et al 1992b). The stability of the labelled oil after incubation with gastric juice and dilute hydrochloric acid at 37^{o}C has been demonstrated with less than 8% of the radioactivtiy eluting into the aqueous phase over a 3 hour period (Cunningham et al 1991d). The labelled olive oil (20 ml) was mixed with non-labelled oil to a volume of 60 ml prior to consumption. ^{113m}In-diethylenetriamine-pentaacetic acid (DTPA) was prepared according to a standard method (Heading et al 1971).

Data acquisition and analysis

In each study data were acquired for at least 180 min, commencing immediately before ingestion of the liquid meal (Edelbroek et al 1992). Radionuclide data were corrected for subject movement, radionuclide decay and Compton scatter, using previously described methods (Collins et al 1983). Correction for radionuclide gamma ray attenuation was done using factors derived from a lateral image of the stomach (Collins et al 1983). The total stomach region-of-interest was divided into proximal and distal regions, with the proximal region corresponding to the fundus and proximal corpus and the distal region representing the distal corpus and antrum (Collins et al 1988). Identical regions-of-interest were used for studies performed in the sitting and decubitus postures. Emptying curves (expressed as the percentage retention of isotope versus time) were derived for total stomach, proximal stomach and distal stomach regions-of-interest. From the emptying curves several parameters were derived for subsequent statistical analysis. For the total stomach these were the lag phase before any isotope entered the duodenum and the amount of isotope remaining in the stomach at 60, 120 and 180 min. The lag phase was determined visually by the frame preceding that in which activity appeared in the proximal small intestine (Edelbroek et al 1992B). The 50% emptying time for the total stomach could not be used as a parameter because some subjects did not reach 50% emptying for either the oil or aqueous phases during the study period. For the proximal and distal stomach the amount of isotope remaining at 60, 120 and 180 min were derived (Edelbroek et al 1992b). Retrograde movement of oil or aqueous phases from the distal into the proximal stomach was defined as a nonsustained rise in proximal stomach counts of $\geq$ 10% associated with a fall in distal stomach counts of $\geq$ 10% (Edelbroek et al 1992b).

10.3.3 *Assessment of appetite*

Subjective ratings of various symptoms including hunger, fullness, nausea, indigestion and dizziness were assessed by marking line analogues which were 100 mm long. Complete details of the questionnaire used are given in a previous publication (Sepple & Read 1989). As an example, hunger was graded according to the following scheme : 0 = not hungry at all, 2 cm = slightly hungry, 5 cm = moderately hungry, 8 cm = very hungry and 10 cm = extremely hungry.

10.3.4 *Statistical analysis*

Data were evaluated using Student's paired t-test (as data conformed to a normal distribution), using Bonferoni's correction for multiple comparisons and are shown as mean values ± S.E.M. Gastric emptying curves show the retention of isotope at 10, 20, 40, 60, 90, 120, 150 and 180 min (Edelbroek et al 1992b). The relationships between gastric emptying and both the intragastric distribution of oil and aqueous meal components and subjective ratings of hunger were evaluated using linear regression analysis. A p value of < 0.05 was considered significant in all analyses.

10.4 RESULTS

All subjects tolerated the study well and there were no untoward events. No subject experienced nausea. Analysis of intragastric distribution was not performed in one study (sitting posture) due to a computer malfunction.

10.4.1 *Gastric emptying of oil and aqueous phases*

Total stomach

In the sitting position oil emptied much more slowly than the aqueous phase of the meal ($p<0.01$). The lag phase was longer for oil than aqueous phase (44.3 ± 4.7 min vs 7.6 ± 2.5 min, $p<0.01$). Emptying of the aqueous phase approximated a monoexponential function, while that of the oil phase approximated a linear pattern after the lag phase. About 70% of the aqueous phase had emptied from the stomach before the oil started to empty (Figure 10.1a).

In contrast, in the decubitus position the aqueous phase emptied more slowly than oil ($p<0.01$) and the lag phase was much longer for the aqueous phase than oil (160.9 ± 26.5 min vs 16.7 ± 4.8 min, $p<0.01$). The emptying phase of both aqueous and oil components approximated a linear pattern (Figure 10.1a).

When emptying of oil and aqueous phases in the two postures were compared, the lag phase for oil was longer ($p<0.001$) in the sitting position, but after this time there was no significant difference in emptying of oil between the two postures. At 60 min there was a non-significant trend for greater retention of oil in the sitting position, $p=0.076$). The lag phase was longer ($p<0.001$) (Figure 10.2) and the aqueous phase emptied much more slowly ($p<0.001$) in the decubitus than the sitting position.

There was no significant difference between the two postures in the total number of calories which had entered the duodenum at 180 min (258 ± 30 kcal in the sitting position and 219 ± 22 kcal in the decubitus position). Similarly, there was no significant difference at this time in the calories emptied in the oil phase (238 ± 27 kcal vs 214 ± 21 kcal, NS).

Intragastric distribution

In the sitting position there was more oil in the proximal stomach when compared to the aqueous phase ($p<0.01$), while in the decubitus position more ($p<0.05$) of the aqueous phase was present in the proximal stomach (Figures 10.1b and 10.3). In all studies there was evidence of a "midgastric band" - a transverse band of reduced isotope activity separating proximal and distal stomach (Moore et al 1986, Collins et al 1988). In 8 of the 10 studies performed in the sitting position there was evidence of retrograde movement of oil from the distal to the proximal stomach on at least one occasion with a rise in proximal stomach counts associated with a fall in distal stomach counts between 70 and 150 minutes (Edelbroek et al 1992b). The latter was not apparent for the aqueous phase. In the decubitus position retrograde movement of oil was evident in only 1 of 11 studies. Retrograde movement of the aqueous phase was again not apparent.

To establish that differences in intragastric distribution between oil and aqueous components were not due to variations in rates of emptying, the ratio of the amount of isotope in the proximal stomach to that in the distal stomach at 180 min was calculated for both aqueous and oil phases. For the oil these ratios were 10.3 ± 0.67 (sitting) and 2.0 ± 0.40 (decubitus) and for the aqueous phase 1.2 ± 0.23 (sitting) and 4.1 ± 0.98 (decubitus). Analysis confirmed that in the sitting position a greater proportion of oil than aqueous phase was retained in the proximal stomach ($p<0.02$) and that in the decubitus position more oil than aqueous was retained in the distal stomach ($p<0.01$). Similarly, a greater proportion of the aqueous phase was retained in the proximal stomach in the decubitus position, when compared to the sitting position ($p<0.02$).

10.4.2 *Relationship between gastric emptying and intragastric distribution*

In the sitting position total stomach emptying of oil was related to emptying from the proximal stomach. The relationships between total stomach and proximal stomach retention at 60 and 180 min were r=0.83 and r=0.88 ($p<0.01$ for both). There was no significant relationship between retention of oil in the total and distal stomach (r=0.38 and r=0.31 respectively; NS). In the decubitus position total stomach emptying of oil was related to the retention in the distal stomach (r=0.82 and r=0.88, $p<0.01$), but not to that in the proximal stomach (r=-0.17 and r=0.45; NS).

In the sitting position the retention of the aqueous phase in the total stomach at 60 min was related to retention in both the proximal (r=0.88, $p<0.01$) and distal (r=0.68, $p<0.05$) stomach at this time. In the lateral decubitus position total stomach retention of the aqueous phase at 60 min was related to retention in the distal (r=0.70, $p<0.01$), but not the proximal (r=-0.04, NS) stomach.

10.4.3 *Hunger and fullness*

Before consumption of the meal, there was no difference in hunger between the two postures and at 15 min hunger had decreased to a similar extent in the sitting ($p<0.02$) and decubitus ($p<0.01$) positions. At 120 and 180 min hunger was less in the decubitus position ($p<0.05$ for both) (Figure 10.4a). At 180 min the score for hunger was not different from baseline in the sitting position ($p=0.3$), while the decrease was sustained in the decubitus position ($p<0.01$).

Fullness increased after the meal in both the sitting ($p<0.02$) and decubitus ($p<0.05$) positions. There was no significant difference between the two postures,

although from 75 min mean values were higher in the decubitus position (Figure 10.4b).

10.4.4 *Relationship between hunger and gastric emptying*

In the sitting position there was no significant relationship between the score for hunger at 120 or 180 min and the retention of oil, or aqueous phases of the meal in either the total, proximal or distal stomach. In contrast, in the decubitus position the score for hunger at 120 min was related to the retention of oil ($r=0.77$, $p<0.01$), but not the aqueous phase ($r=0.13$, NS) in the total stomach. The score for hunger at 180 min was also related to the retention of oil in the total ($r=0.79$, $p<0.01$) and the distal stomach ($r=0.81$, $p<0.01$) but not to the retention of the aqueous phase in the total stomach ($r=0.03$, NS) (Figure 10.5).

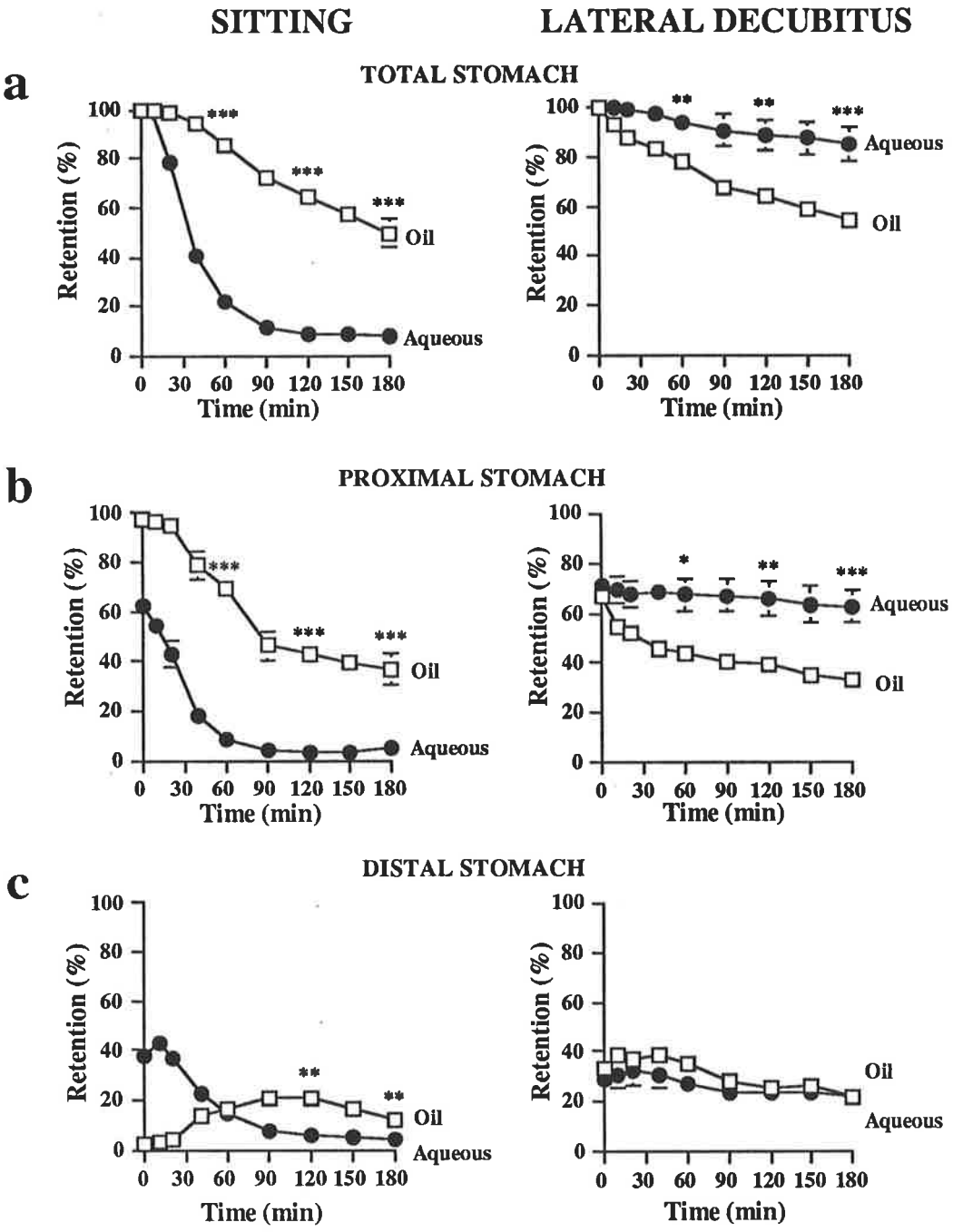

*Figure 10.1: Comparison of gastric emptying for oil and aqueous phases of the meal in the sitting and lateral decubitus positions for the (a) total, (b) proximal and (c) distal stomach. Data are mean values ± SEM. *p<0.05, **p<0.01, ***p<0.001.*

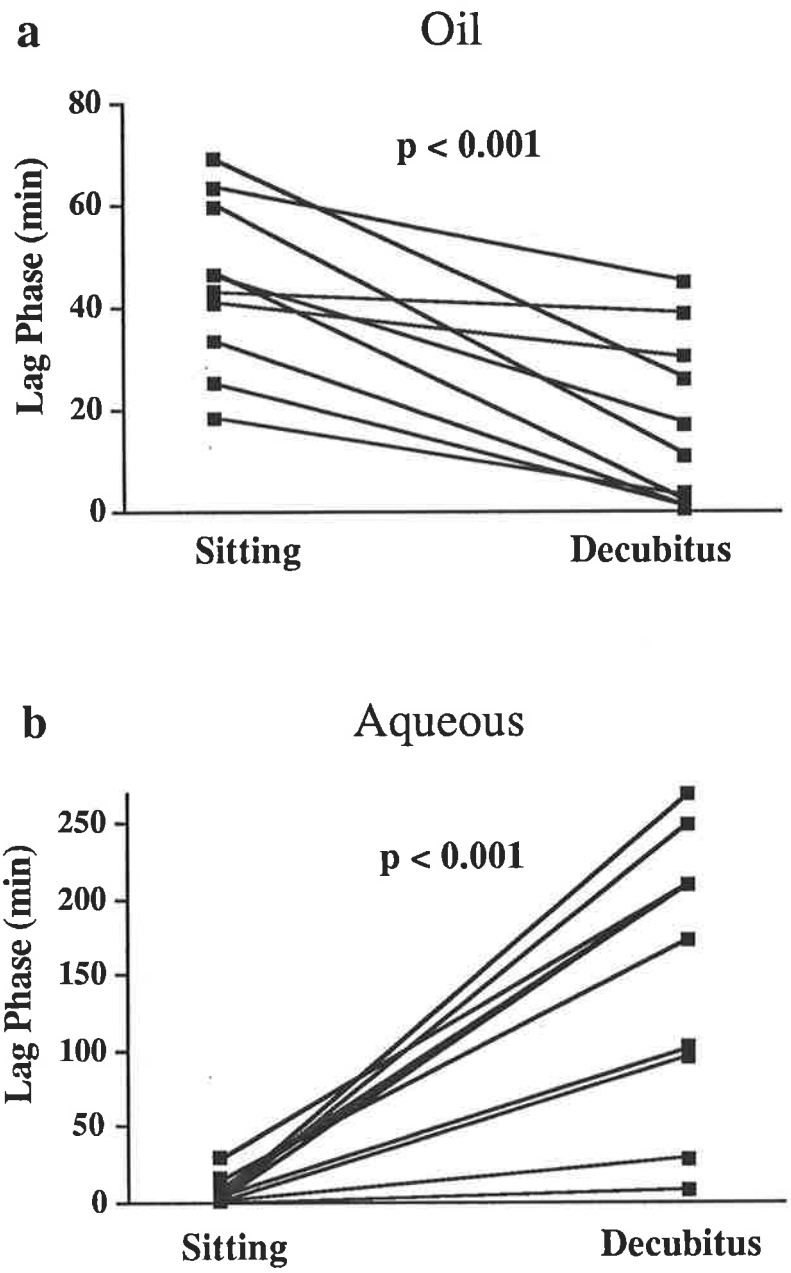

Figure 10.2: Effect of posture on the lag phase for (a) oil and (b) aqueous meal components.

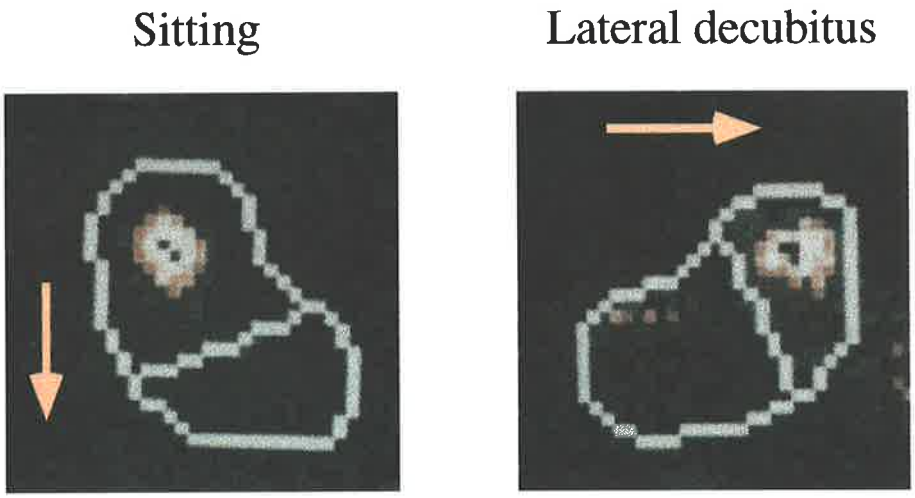

Figure 10.3: Scintigraphic images showing the abdominal distribution of oil in one subject 60 mintes after meal ingestion. The total stomach region-of-interest is divided into proximal and distal regions. In the sitting position more oil is retained in the proximal stomach, while in the lateral decubitus position oil is retained preferentially in the distal stomach. The direction of gravity is indicated by the arrows.

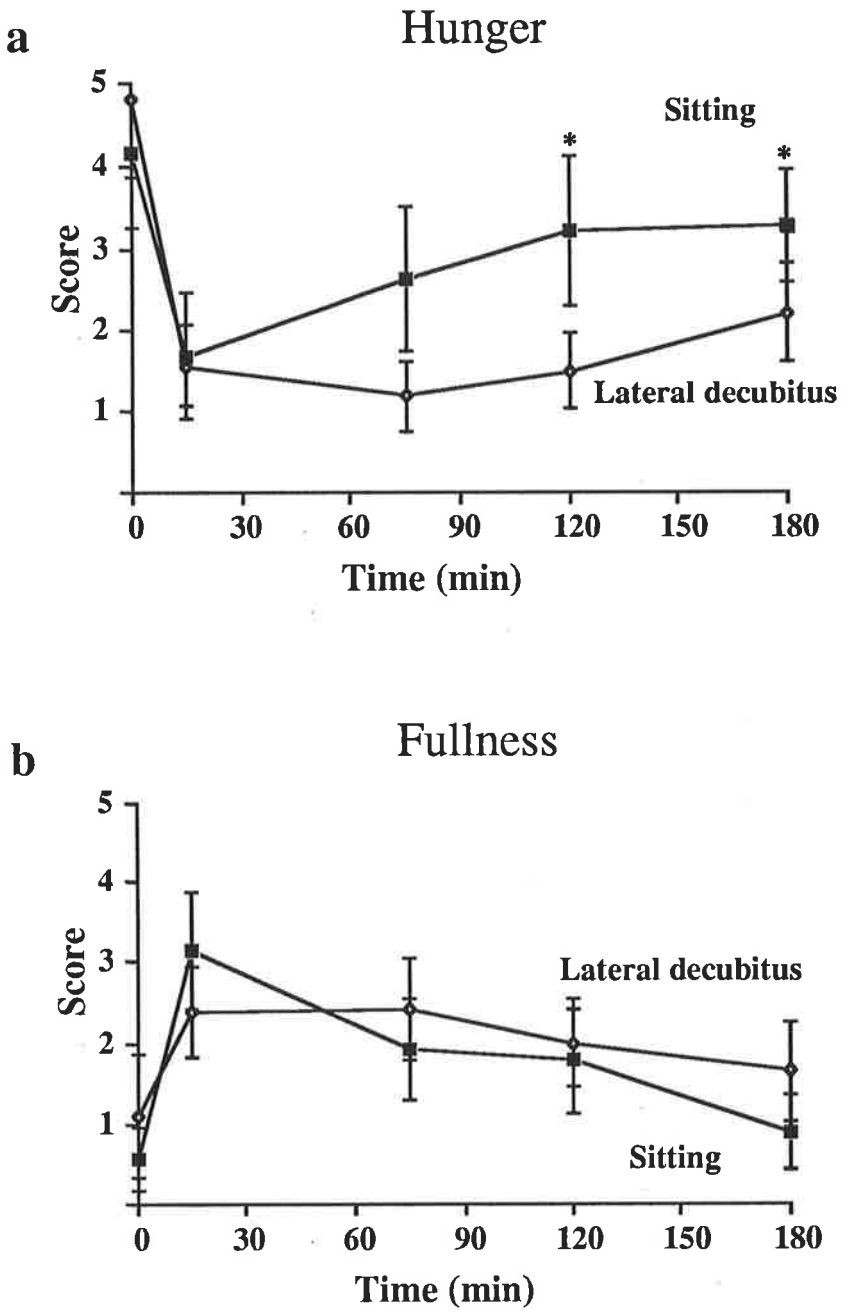

Figure 10.4: Scores for (a) hunger and (b) fullness in the sitting and lateral decubitus positions. Data are mean values ± SEM.

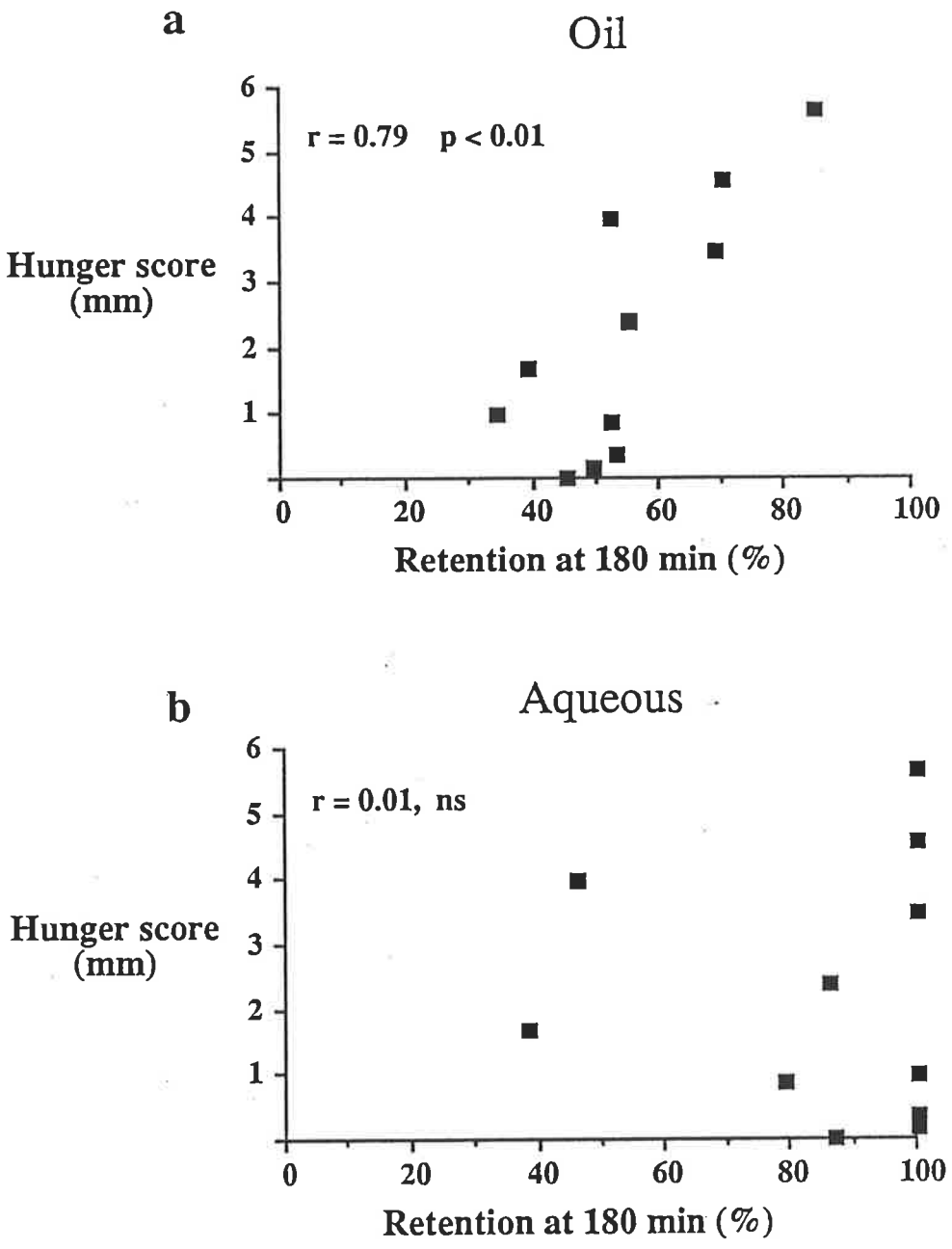

Figure 10.5: Relationships between hunger at 180 minutes and gastric emptying of (a) oil and (b) aqueous phases in the lateral decubitus position.

10.5 DISCUSSION

The results of this study indicate that after ingestion of a meal containing oil and aqueous components: (i) gravity has a major effect on the pre-emptying phase and intragastric distribution, but has relatively little effect on total stomach emptying of the oil phase (ii) gravity has a major effect on both intragastric distribution and gastric emptying of the aqueous phase (iii) postprandial hunger is affected by posture and (iv) in the lateral decubitus position, hunger is inversely related to the rate of gastric emptying of oil.

10.5.1 *Gastric emptying and intragastric distribution of extracellular fat*

While extracellular fat empties from the stomach slower than low nutrient aqueous liquids (Chang et al 1968, Hunt & Knox 1968, Cortot et al 1981, Cortot et al 1982, Jian et al 1982, Meyer et al 1986, Cunningham et al 1991d, Edelbroek et al 1992b), the mechanisms responsible for this have been hitherto poorly understood. In particular, it is controversial whether the slower gastric emptying of fat is determined mainly by its physical characteristics, or its chemical composition (Meyer et al 1986). Our observations strongly suggest that the difference in intragastric distribution of non-emulsified oil compared to aqueous liquids in both the sitting and lateral decubitus positions are caused mainly by "layering" due to gravity and that the major determinant of the rate of emptying of oil from the stomach is the interaction of its digestion products with receptors in the small intestinal lumen.

Chang et al were the first to suggest that gravity had a major influence on gastric emptying of oil in humans by causing "layering" on top of the aqueous phase (Chang et al 1968). While the results of this study strongly support this concept

i.e. oil was preferentially retained in the proximal stomach when sitting and in the distal stomach in the decubitus position, their observations were based on an aspiration technique, which could not discriminate between the content of the proximal and distal stomach. A further limitation was that gastric emptying was only evaluated at one time point, 30 minutes after meal ingestion. Apparent layering of oil above aqueous meal components has also been observed in animals (Duke et al 1989). More recently Jian et al reported in a scintigraphic study that the delay in gastric emptying of extracellular fat compared to aqueous liquids occurred in the apparent absence of layering (Jian et al 1982). However, this latter observation is likely to reflect the relatively small amount of fat (10 g butter) included in their test meal, which may have been emulsified, and the less than optimal radioisotopic marker (^{75}Se) used to label fat. It has previously been reported that retrograde movement of oil, but not the aqueous phase from distal into the proximal stomach occurs after ingestion of an oil/aqueous meal in the sitting position – a finding confirmed in the present study (Houghton et al 1990, Edelbroek et al 1992b). However, as retrograde movement appears to occur infrequently in the decubitus position (perhaps because the presence of the aqueous phase in the proximal stomach acted as a physical barrier to retrograde movement because of its higher density), it does not appear to be a major factor contributing to the intragastric distribution of oil. In previous studies a midgastric band (a region of reduced isotope activity) which may be important in the intragastric distribution of meals has been observed (Moore et al 1986, Collins et al 1988, Edelbroek et al 1992b). However, the demonstrated effects of gravity on the intragastric distribution of oil and aqueous meal components suggest that it is not an important mechanism in the retention of oil in the proximal stomach when sitting.

The results of a number of studies suggest that the rate of gastric emptying influences the digestion and absorption of fat (Cortot et al 1981, Cortot et al 1982,

Meyer et al 1986). Meyer et al reported that extracellular fat empties from the stomach predominantly as an oil phase (Meyer et al 1986). Because digestion of fat commences in the stomach (Moreau et al 1988), malabsorption may reflect decreased intragastric digestion, as well as an excessive rate of delivery of fat into the small intestine (Long & Weiss 1974). In patients with pancreatic insufficiency hydrolysis of fat by gastric lipase may be of major importance to optimal digestion of fat (Long & Weiss 1974, Meyer et al 1994a). The extent of intragastric lipolysis is presumably dependent on the amount of fat and its physical form (emulsified or non-emulsified). Emulsified fats are likely to be subject to significant intragastric lipolysis. The position of the fat within the stomach may also be important, as gastric lipase appears to be secreted exclusively by the fundic mucosa in humans (Melone & Mei 1991). Hunt and Knox proposed that gastric emptying of extracellular fat is regulated predominantly by the interaction of its digestion products with small intestinal luminal receptors (Hunt & Knox 1968) and this has been supported by subsequent studies (Cortot et al 1981, Cortot et al 1982, Lin et al 1990b, Edelbroek et al 1992b). For example, Cortot et al demonstrated that gastric emptying of the non-hydrolysable fat, sucrose polyester, is similar to that of a low nutrient aqueous meal (Cortot et al 1981) and that when digestible fats and aqueous liquids are ingested in an homogenized form, they empty from the stomach at similar rates (Cortot et al 1979). The observation in this study that despite differences in intragastric distribution both the total amount of calories emptied from the stomach in the two meals in the first 180 min and the individual emptying rates of oil in the two postures were similar, is consistent with this hypothesis, although the faster initial emptying of oil in the decubitus position indicates that factors other than small intestinal receptors may be important. There is evidence that dietary modifications may modify both the sensitivity of small intestinal nutrient receptors and the activity of gastric lipase. An increased dietary fat intake is associated with more rapid gastric emptying of fat in humans (Cunningham et al 1991d) and

increased levels of gastric lipase in animals (Borel et al 1991). The latter response may contribute to more efficient digestion and absorption of fat.

Small intestinal luminal receptors, sensitive to the digestion products of fats, are therefore likely to be of major importance in triggering the motor mechanisms regulating gastric emptying of fat. Infusion of lipid into the small intestine is known to be associated with stimulation of phasic pressure waves isolated to the pylorus (Heddle et al 1988a, Fone et al 1990b) suppression of antral pressure waves (Heddle et al 1988a) and electrical spike activity (Fone et al 1990b), relaxation of the proximal stomach (Azpiroz & Malagelada 1985) and retardation of gastric emptying (Welch et al 1988, Heddle et al 1989). Recent animal studies suggest that there are two types of vagal intestinal receptors which are sensitive to lipids – one sensitive to long-chain lipids and the other to short-chain lipids and glycerol (Melone& Mei 1991). It is likely that the products of lipolysis which trigger initial feedback inhibition of gastric emptying are normally formed within the stomach. However, while it is possible that reduced intragastric lipolysis may have contributed to the initially faster emptying rate of oil in the decubitus position, this is likely to primarily reflect the presence of oil in the distal, rather than in the proximal stomach due to the effect of gravity. Layering of oil above the aqueous phase may be facilitated by the inhibition of antral motility resulting from the presence of lipid in the small intestine (Heddle et al 1988a, Fone et al 1990b).

10.5.2 *Effect of gravity on gastric emptying*

There is relatively little information about the effects of posture on gastric emptying and routine radioisotopic measurements of gastric emptying are performed in the sitting, standing, lying and semirecumbent positions (Burn-Murdoch et al 1980, Tothill et al 1980, Moore et al 1986, Smout et al 1987, Read 1989). The effects of

gravity on intragastric distribution of meals have not been examined previously. It is well recognised that gastric drainage procedures are characteristically associated with very rapid initial emptying of non-nutrient and nutrient containing liquid meals, when these are consumed in the non-recumbent position and that this may be associated with symptoms of the early dumping syndrome (Gulsrud et al 1980, Horowitz et al 1982, Smout et al 1987). In the intact stomach gravity has been reported to increase gastric emptying of non-nutrient liquids, possibly by causing an increase in the number of temporally associated antropyloric pressure waves (Anvari et al 1991) the tight control on nutrient emptying exerted by small intestinal receptors (Burn-Murdoch et al 1980). Moore et al reported that gastric emptying of a solid meal is slower in the lying when compared to the erect position (Moore et al 1988), implying that gravity can assist fundic contraction in priming the antral mill, but did not discriminate between effects on the lag phase and the emptying phase. Our observations indicate that the effect of gravity on gastric emptying and intragastric distribution of a meal in the intact stomach is critically dependent on the composition of that meal. This observation is potentially relevant to the absorption of oral pharmaceuticals (Nimmo et al 1976, Horowitz et al 1989b), blood glucose homeostasis (Welch et al 1987) and the evaluation of pharmacological agents on gastric emptying (Horowitz & Dent 1991). The profound delay in gastric emptying of the aqueous phase of the meal in the decubitus when compared to the sitting position occurred presumably because the early emptying of the oil phase from the distal stomach triggered motor mechanisms associated with retardation of gastric emptying.

10.5.3 *Relationship between hunger and gastric emptying*

The regulation of appetite is a complex process involving a variety of central and peripheral mechanisms (Morley et al 1989). This study provides the first evidence

that postprandial hunger may be influenced by posture. Although the test meal was somewhat unusual, containing discrete lipid and aqueous components, the observation that hunger was reduced in the decubitus, when compared to the sitting position may be clinically important, particularly in relation to the treatment of gastrointestinal symptoms associated with gastroparesis and optimisation of nutritional status in patients with anorexia or nausea. Postprandial intragastric volume was larger in the decubitus position because the aqueous component of the meal emptied more slowly and it is therefore possible that greater gastric distension contributed to the difference in hunger between the two postures (Bergmann et al 1992). This concept is supported by the observations that hunger decreased in the decubitus posture at 15 minutes, before any of the meal (aqueous or oil phase) had emptied from the stomach, that the magnitude of the decrease at this time was similar in the two postures and that differences in hunger were only apparent from 120 min. It is possible that the reduction in hunger soon after a meal may be triggered by receptors in the gastric fundus or antrum, although our results suggest that this response is not dependent on the distribution of nutrients within the stomach. The strong inverse relationship between hunger and the rate of emptying of oil in the decubitus position also indicates that a major factor contributing to postprandial satiety is the extent of small intestinal nutrient exposure, as has been suggested (Sepple & Read 1989). In humans and animals, small intestinal infusions of fat decrease food intake by acting at a preabsorptive site of action (Welch et al 1985, Welch et al 1988, Sepple & Read 1989, Greenberg et al 1990, Drewe et al 1992, Greenberg et al 1992). Inhibition of food intake during small intestinal infusion of fats also occurs in animals with gastric fistulae (Greenberg et al 1990) indicating that this effect is independent of slowing of gastric emptying and a consequent prolongation of gastric distension. Stimulation of vagal efferents (Yox et al 1991a, Yox et al 1991b) and release of cholecystokinin (Greenberg et al 1989, Gregory et al 1989, Peikin 1989) may be important in mediating effects of

intraduodenal fat on satiety. The fact that a relationship between gastric emptying and hunger was not evident in the sitting position suggests that stimulation of small intestinal receptors and gastric distension may have additive effects to decrease hunger.

CHAPTER 11

GASTRIC EMPTYING OF OIL AND AQUEOUS MEAL COMPONENTS IN PANCREATIC INSUFFICIENCY - EFFECTS OF POSTURE AND ON APPETITE

11.1 SUMMARY

The aims of this study were to evaluate the effects of posture on gastric emptying, intragastric distribution and satiation after a meal containing oil and aqueous phases in patients with exocrine pancreatic insufficiency. Five patients with cystic fibrosis (CF) consumed 60 ml ^{99m}Tc-(V)-thiocyanate olive oil and 290 ml ^{113m}In-DTPA soup while sitting and while lying in the left lateral decubitus position. Hunger and fullness before and after the meal were recorded. Results were compared to those obtained in 11 normal volunteers.

In both postures emptying of oil was faster ($p<0.01$) in the CF patients. Emptying of the aqueous phase was faster ($p<0.01$) in the CF patients in the decubitus position. In the normal subjects there was no overall difference in emptying of oil between the two postures, whereas emptying of the aqueous phase was delayed ($p<0.01$) in the decubitus position. In the CF patients emptying of oil was faster ($p<0.01$) in the decubitus position and emptying of the aqueous phase was only slightly faster ($p<0.05$) in the sitting position. In both postures there was greater retention ($p<0.05$) of oil in the proximal stomach in the normal subjects than the CF patients. Hunger decreased ($p<0.05$) after the meal in the control subjects, but there was no change in CF patients.

These results indicate that in CF patients with pancreatic exocrine insufficiency: (i) gastric emptying of non-homogenized fat is faster than normal (ii) gravity affects gastric emptying of oil and (iii) effects of a fatty meal on hunger are reduced.

11.2 INTRODUCTION

There is considerable evidence that gastric emptying is an important factor in the digestion and absorption of dietary fat (Long & Weiss 1974, Cavell 1981, Cortot et al 1982, Meyer et al 1986, Meyer et al 1994a, Meyer et al 1994b, Meyer et al 1994c). The rate of gastric emptying of fat is known to be dependent on its physical composition (unemulsified, homogenized or associated with solid food) (Chang et al 1968, Hunt & Knox 1968, Cortot et al 1979, Cortot et al 1982, Jian et al 1982, Houghton et al 1990, Lin et al 1990b, Edelbroek et al 1992b). In Chapter 10 it was reported that after ingestion of a meal containing 60 ml olive oil and 290 ml low nutrient soup in normal volunteers, gravity has a major effect on intragastric distribution, but relatively little effect on the rate of gastric emptying of the oil (Chapter 10). The slow emptying of oil when compared to the aqueous phase in the erect position was consistent with the marked layering of oil to the top of the water contents, away from the pylorus (Chang et al 1968, Edelbroek et al 1992b); but the equally slow emptying of oil from the lateral decubitus position could not be simply explained by intragastric positioning, since the oil was nearest to the pyloric outlet when the subjects assumed this posture (Chapter 10). Thus, it seemed that the gastric emptying of oil was controlled by a complex interplay between intragastric layering (Chang et al 1968, Edelbroek et al 1992b) and feedback inhibition from the small intestine (Cortot et al 1979, Cortot et al 1981, Lin et al 1990b).

Gastric emptying of fat is inhibited by lipolytic products reaching small intestinal sensors (Hunt & Knox 1968, Cortot et al 1981, Welch et al 1985, Lin et al 1990, Meyer et al 1994a). For example, Cortot et al observed that digestible corn oil emptied more slowly from the human stomach than water, but a non-digestible oil, sucrose polyester, emptied as rapidly as a low nutrient aqueous meal (Cortot et al 1981). Meyer et al demonstrated that canine gastric emptying of oil was accelerated specifically by inhibition of lipase (Meyer et al 1994a). Limited clinical studies (Long & Weiss 1974, Roillet et al 1980, Smith et al 1990) indicate that fat empties abnormally rapidly in patients who have exocrine insufficiency of the pancreas, most likely as a result of diminished lipolysis and feedback inhibition from lipolytic products in the small intestine. Thus, a study of gastric emptying of oil from the erect and left lateral decubitus positions in patients who have pancreatic insufficiency, when compared to emptying in normal subjects, might clarify to what extent small intestinal feedback inhibition influences the posturally determined emptying of oil.

In the previous study reported in Chapter 10 it was also reported that in normal subjects, postprandial hunger was affected by posture and, in the decubitus position, was inversely related to the rate of emptying of the oil, suggesting that signals from the small intestine were important in the aetiology of satiation.

The effect of posture on gastric emptying, intragastric distribution and appetite after ingestion of meal containing oil and aqueous phases in patients with exocrine pancreatic insufficiency due to cystic fibrosis has now been evaluated and compared to the results obtained in normal subjects (Chapter 10).

11.3 MATERIALS AND METHODS

Paired studies were carried out in 5 patients with cystic fibrosis (CF), (3 male, 2 female) with a mean age of 25 yr (range 19-39) and a mean body weight of 53 kg (range 50-68). Patients were not selected on the basis of gastrointestinal symptoms. All had steatorrhea (elevated 3 day faecal fat excretion off pancreatic enzyme supplements) and had been taking pancreatic enzyme supplements for a number of years. Pulmonary function tests performed just before participation in the study showed a mean forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) of 66.4% (range 54-88). No subject had a history of gastrointestinal disease unrelated to cystic fibrosis, or had a constant requirement for medication that could affect gastrointestinal motility. No patient had diabetes mellitus.

Results were compared to those obtained previously as reported in Chapter 10, ie. 11 healthy volunteers (4 male, 7 female; mean age 21 years; range 18-26 and mean body weight 66 kg (range 55-81 kg). There was no significant difference in age or body weight between the normal subjects and the patients with CF. Written, informed consent was obtained from each subject and the study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

11.3.1 *Experimental protocol*

Each subject had measurements of gastric empting performed on two separate days in different postures; one while sitting and the other while lying in the left lateral decubitus, "pylorus-up" position. The order of the two studies was randomised and they were separated by an interval of between 3 and 14 days. The test meal was consumed at 10.00 am after an overnight fast (14 h for solids and 12 h for liquids) while in front of a scintillation camera and consisted of a mixture of

60 ml olive oil (Faulding Pty Ltd, South Australia), labelled with 20 MBq ^{99m}Tc-(V)-thiocyanate and 290 ml low nutrient beef consomme soup (Campbells Soups Pty Ltd, Australia), labelled with 20 MBq ^{113m}In-diethylenetriamine-pentaacetic acid (DTPA), heated to 45°C immediately prior to consumption (Cunningham et al 1991d). The oil was mixed gently with the soup immediately before and during consumption of the meal. Pancreatic enzyme supplements were ceased 14 h before the consumption of each meal. The energy content of the oil-soup mixture (7 g protein, 52 g fat) was 505 kcal, of which 473 kcal were contained in the oil. Subjective feelings of hunger and fullness were recorded on a validated visual analogue scale (Sepple et al 1989), administered immediately before and at 15, 30, 60, 120, 150 and 180 min after ingestion of the meal in the patients with cystic fibrosis, and before the meal and at 15, 75, 120 and 180 min in the normal subjects.

11.3.2 *Measurement of gastric emptying*

Olive oil was labelled with ^{99m}Tc-(V)-thiocyanate using a previously described method (Cunningham et al 1991d). ^{113m}In-diethylenetriamine pentaacetic acid (DTPA) was prepared according to a standard method. In each study, data were acquired for at least 120 min, or until <5% of activity remained in the stomach (whichever came first), commencing immediately before complete ingestion of the liquid meal. Radionuclide data were corrected for subject movement, radionuclide decay and Compton scatter, using previously described methods (Collins et al 1983, Collins et al 1988). Radionuclide gamma ray attenuation was corrected using factors derived from a lateral image of the stomach (Collins et al 1983). In both the decubitus and sitting positions, the total stomach region-of-interest was divided into proximal and distal regions, with the proximal region corresponding to the fundus and proximal corpus and the distal region

representing the distal corpus and antrum (Collins et al 1988). Emptying curves, expressed as the percentage of isotope retention versus time, were derived for total stomach, proximal stomach and distal stomach regions-of-interest. From these curves for the total stomach, the lag phase before any isotope entered the duodenum, the amount of isotope remaining in the stomach at 10, 20, 30, 40, 60, 90 and 120 min were derived for statistical analysis. The amounts emptied in the first 30 min (0-30 min) and second 30 min periods (31-60 min) were also evaluated for both oil and aqueous phases. For the proximal and distal stomach, the amounts of isotope remaining in the stomach at 10, 20, 30, 40, 60 and 120 min were derived. The 50% emptying time for the proximal stomach was also calculated.

11.3.3 *Assessment of appetite*

Subjective ratings of various symptoms including hunger and fullness were assessed by marking line analogues which were 100 mm in length. Details of the questionnaire used are given in a previous publication (Sepple & Read 1989).

11.3.4 *Statistical analysis*

Data were evaluated using repeated measured analysis of variance and are shown as mean values ± SEM. Gastric emptying curves show the retention of isotope at 10, 20, 30, 40, 60, 90 and 120 min. A p value < 0.05 was considered significant in all analyses.

11.4 RESULTS

All subjects tolerated the study well and there were no untoward effects.

11.4.1. *Gastric emptying*

Normal subjects compared with CF patients in each posture

In the normal subjects, emptying of oil in both postures approximated a linear pattern after an initial lag phase. In CF patients emptying of oil was non-linear in the lateral decubitus position - a short lag phase was followed by a more rapid emptying phase and subsequently by a slower rate of emptying (Figure 11.1). In CF patients, emptying of the aqueous phase approximated a monoexponential pattern in both postures (Figure 11.1). In the normal subjects emptying of the aqueous phase approximated a monoexponential pattern in the sitting position, but a linear pattern in the decubitus position.

The lag phase for oil was shorter in the CF group when compared to normals in the sitting position (13.6 ± 5.3 min vs 43.3 ±4 .7 min, $p<0.05$), but not significantly in the decubitus position (3.8 ± 1.8 min vs 16.7 ± 4.8 min $p=0.22$). In the sitting position, the lag phase for the aqueous phase was not different between CF patients and normals (1.8 ± 0.8 min vs 7.6 ± .5 min, $p=0.1$), but was much shorter in the CF patients in the decubitus position (2.6 ± 0.7 min vs 160.9 ± 26.5 min, $p<0.005$). In both postures emptying of oil was much faster in the CF patients than the normal subjects with less retention of oil at 120 min ($p<0.01$) (Figures 11.1 and 11.2). In CF patients the amount of oil that emptied in the decubitus position in the first 30 min was greater than that which emptied between 31-60 min (41.4 ± 6.8% vs 19.8 ± 6.2%, $p<0.05$), whereas there was no significant difference in the sitting position (20.8 ± 9.4% vs 16.8 ±3 .8%, NS). In contrast, in the control subjects there was a trend for less oil to be emptied from the stomach between 0-30 min, when compared to 31-60 min in the sitting, but not the decubitus position (sitting 3.0 ± 2.8% vs 11.7 ± 4.7%, $p=0.2$; decubitus 12.4 ± 3.6% vs 9.4 ± 4.9%, $p=0.7$). There was relatively little difference in gastric emptying of the aqueous phase between the normal subjects and patients with CF

in the sitting position, although emptying was faster ($p<0.01$) in the CF group. However, emptying of the aqueous phase was much faster in the CF patients than the control subjects in the decubitus position ($p<0.01$) (Figure 11.1). The amount of the aqueous phase that emptied from the total stomach between 0-30 min compared to 31-60 min was greater in the sitting position in CF patients ($69 \pm 6.8\%$ vs $19.2 \pm 5.0\%$, $p<0.05$) reflecting in part the shorter lag phase, but not in the normal volunteers ($38.3 \pm 6.4\%$ vs $39.5 \pm 6.1\%$, NS). In the decubitus position there was no difference in total stomach emptying rates between 0-30 min compared to 31-60 min for either CF patients ($43.4 \pm 6.3\%$ vs $25 \pm 7.1\%$, NS), or normal volunteers ($0.9 \pm 0.9\%$ vs $5.3 \pm 4.5\%$, NS).

There was no significant relationship between gastric emptying of either oil or aqueous meal components and body weight in the normal or CF groups.

Effects of posture in normals and CF patients

In the normal subjects the lag phase for the oil was longer in the sitting compared to the lateral decubitus position (44.3 ± 4.7 min vs 16.7 ± 4.8 min, $p<0.001$), but after this time there was no significant difference in emptying of oil between the two postures. In the CF patients, the lag phase for the oil was also longer in the sitting than the decubitus position (18.0 ± 4.4 min vs 3.8 ± 1.8 min, $p<0.05$). However, after this time the rate of emptying of oil was slower ($p<0.01$) in the sitting position (e.g. retention at 40 min, $74.0 \pm 8.7\%$ vs $44.6 \pm 12.2\%$, $p<0.01$) (Figure 11.1).

In the normal subjects the lag phase for the soup was much shorter (7.6 ± 2.5 min vs 160.9 ± 26.5 min, $p<0.01$) and the rate of emptying much faster ($p<0.01$) in the sitting when compared to the decubitus position. In contrast, there was no effect of posture on the lag phase for the aqueous phase of the meal in the CF patients

(1.8 ± 0.8 min vs 2.6 ± 0.7 min, NS), but after this time emptying of aqueous phase was slightly faster ($p<0.05$) in the sitting position (e.g. retention at 40 min, 29.0 ± 5.9% vs 46.6 ± 6.6%, $p<0.05$). In the CF patients the 50% emptying time for oil was longer than for the aqueous phase in the sitting position ($p<0.05$), but not in the decubitus position.

11.4.2 *Intragastric distribution*

In both postures, there was greater retention ($p<0.01$) of oil in the proximal stomach in the normal subjects when compared to CF patients ie oil moved more rapidly into the distal stomach in the CF patients (Figures 11.3 and 11.4). Emptying of the aqueous phase from the proximal stomach was also slower ($p<0.01$) in the normal subjects than the CF patients, particularly in the decubitus position (Figure 11.3). In both normal subjects and CF patients there was relatively greater retention of oil in the proximal stomach ($p<0.05$) in the sitting position and greater retention of the aqueous phase in the proximal stomach ($p<0.05$) in the decubitus position (Figures 11.3 and 11.4).

11.4.3 *Hunger and fullness*

Before the meal there was no significant difference in hunger between the two groups in either posture. In the normal subjects hunger decreased after the meal in both postures ($p<0.05$), but there was no significant change in the CF patients. At 120 min the score for hunger was greater ($p<0.05$) in the CF patients than the control subjects in both postures (Figure 11.5). As reported previously in Chapter 10 in the control subjects, there was no significant relationship between the score for hunger at 120 min and the retention of either oil or aqueous phases in the stomach, whereas in the decubitus position the score for hunger at 120 min was

related to the retention of oil ($r=0.77$, $p<0.01$), but not the aqueous meal ($r=0.13$, NS) in the total stomach. In the CF patients there was no significant relationship between the score for hunger at 120 min and gastric emptying of oil or aqueous phases in either posture, although there was a non-significant trend ($r=0.62$, NS) in the decubitus position for hunger to be related to the retention of oil. There was no difference in fullness between the two groups in either posture before the meal. After the meal, fullness increased ($p<0.05$) in the normal subjects, whereas the mean increase from baseline was not statistically significant in the CF patients. There was no significant difference in the score for fullness between the two groups at any time although mean values were higher in the normal subjects in the decubitus position.

In the normal volunteers postprandial hunger was less ($p<0.05$) in the decubitus position (Chapter 10). In the CF patients there was no significant difference in hunger or fullness between the two postures, although hunger tended to be less in the decubitus position at 120 min ($p=0.053$).

TOTAL STOMACH

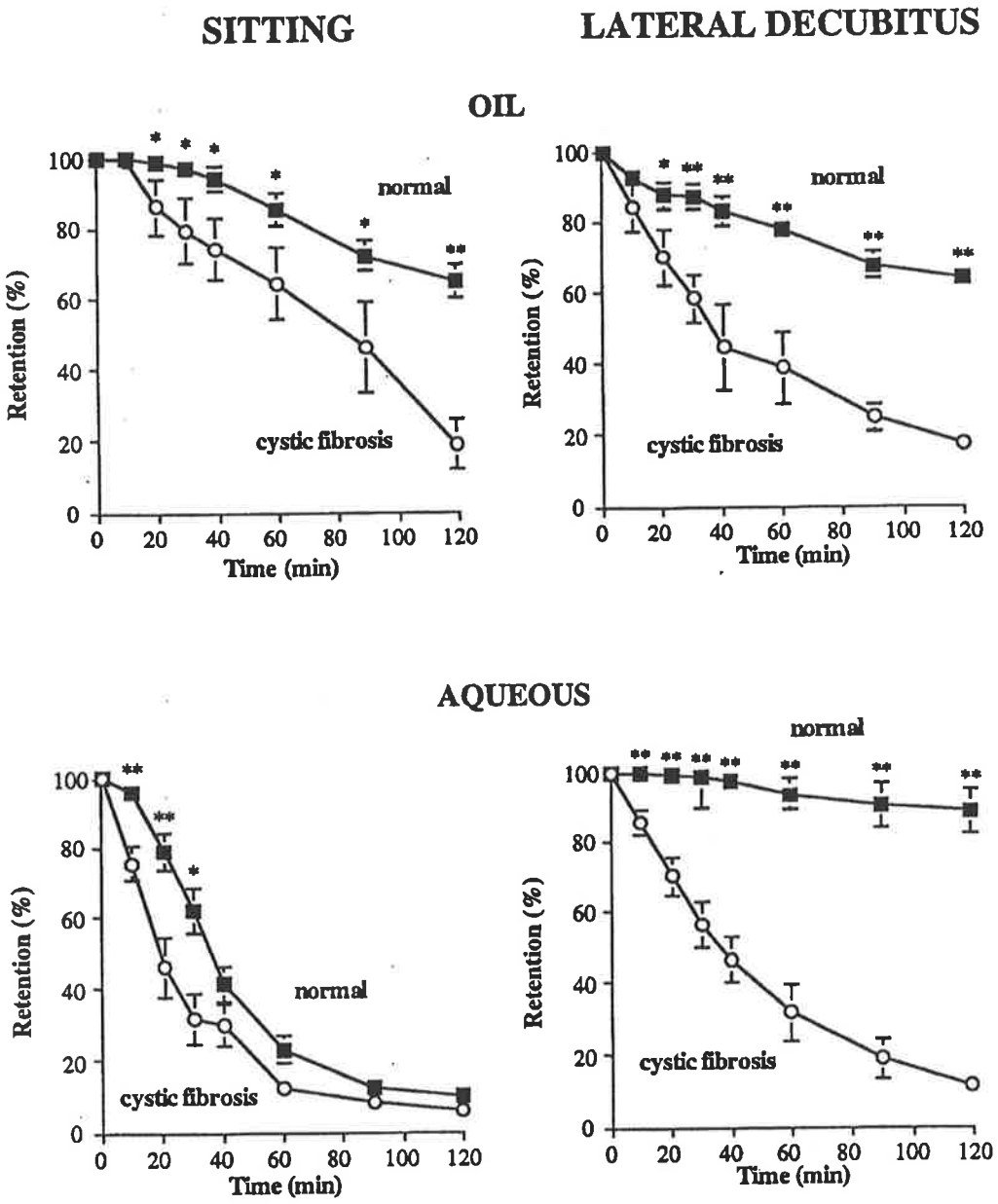

*Figure 11.1: Gastric emptying of the oil and aqueous phases of the meal in the sitting and lateral decubitus positions from the total stomach in patients with cystic fibrosis and normal volunteers. Data are mean ± SEM. *p<0.05, **p<0.01 between cystic fibrosis and normal volunteers.*

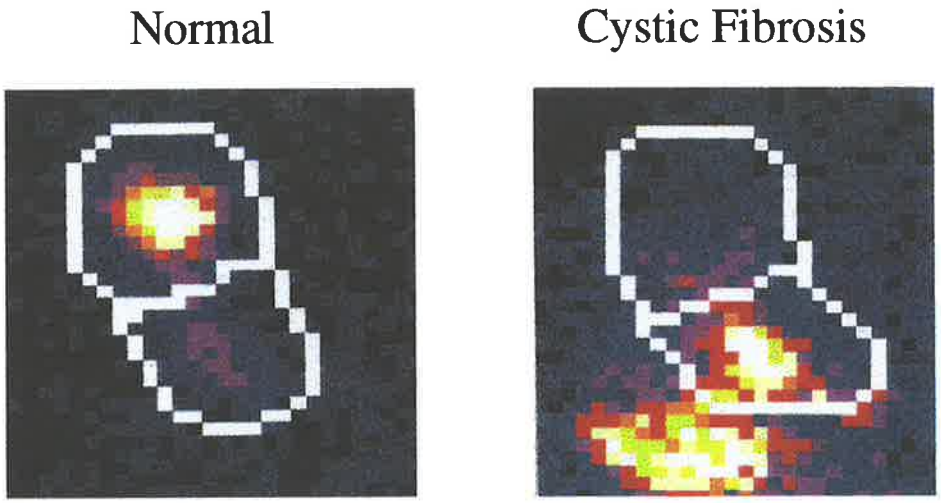

Figure 11.2: Scintigraphic images in a normal volunteer and a patient with cystic fibrosis in the sitting position at 60 min showing the oil phase of the meal. The total stoamch region is divided into proximal and distal regions. In the normal subject most of the oil is in the proximal stomach while in the cystic fibrosis patient the majority of the oil has emptied from the stomach with the remainder in the distal stomach.

PROXIMAL STOMACH

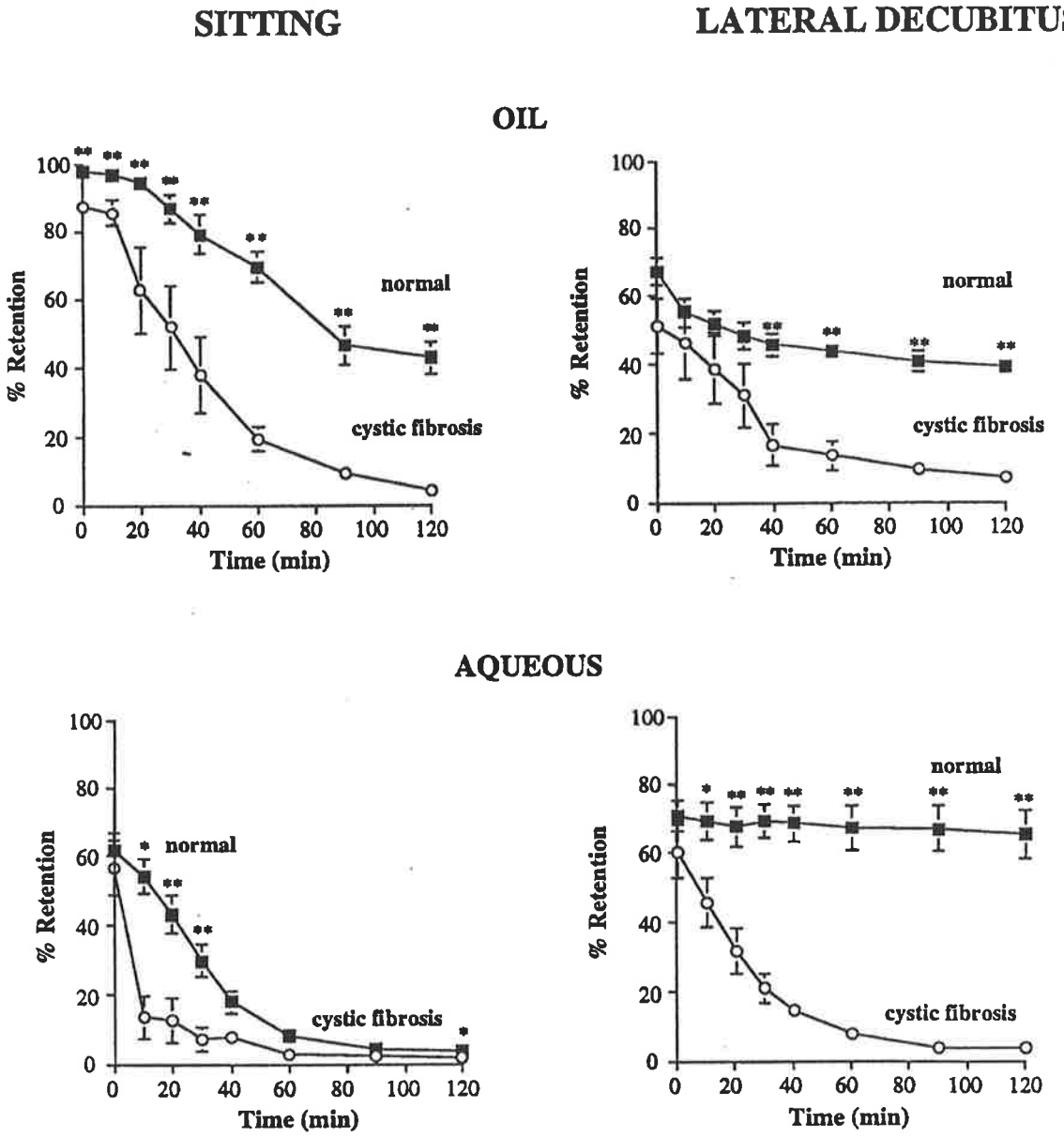

*Figure 11.3: Gastric emptying of the oil and aqueous phases of the meal in the sitting and lateral decubitus positions from the proximal stomach in patients with cystic fibrosis and normal volunteers. Data are mean ± SEM. *p<0.05, **p<0.01 between cystic fibrosis and normal volunteers.*

DISTAL STOMACH

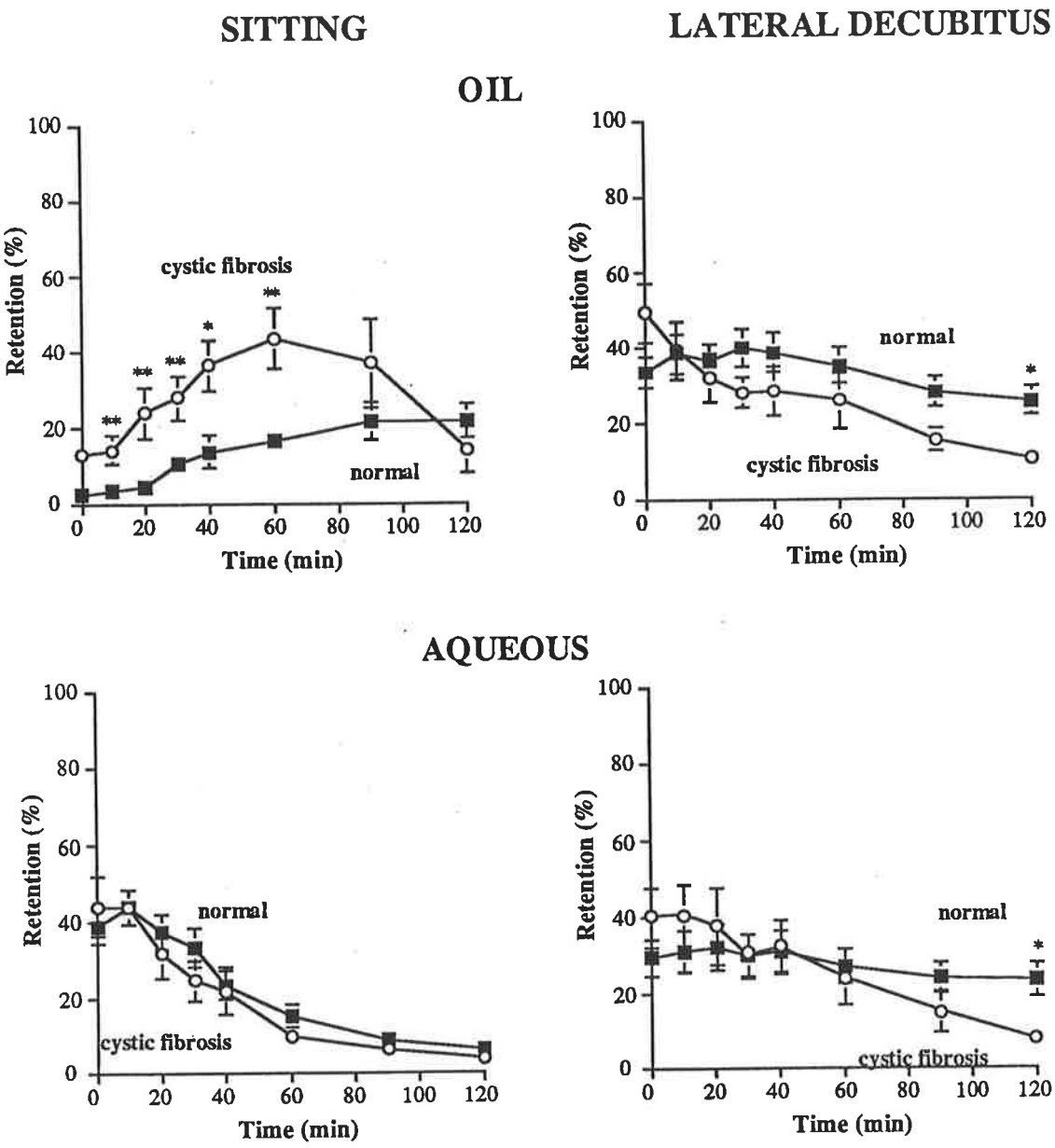

*Figure 11.4: Gastric emptying of oil and aqueous phases of the meal in the sitting and lateral decubitus positions from the distal stomach in patients with cystic fibrosis and normal volunteers. Data are mean values ± SEM. *p<0.05, **p<0.01 between cystic fibrosis and normal volunteers.*

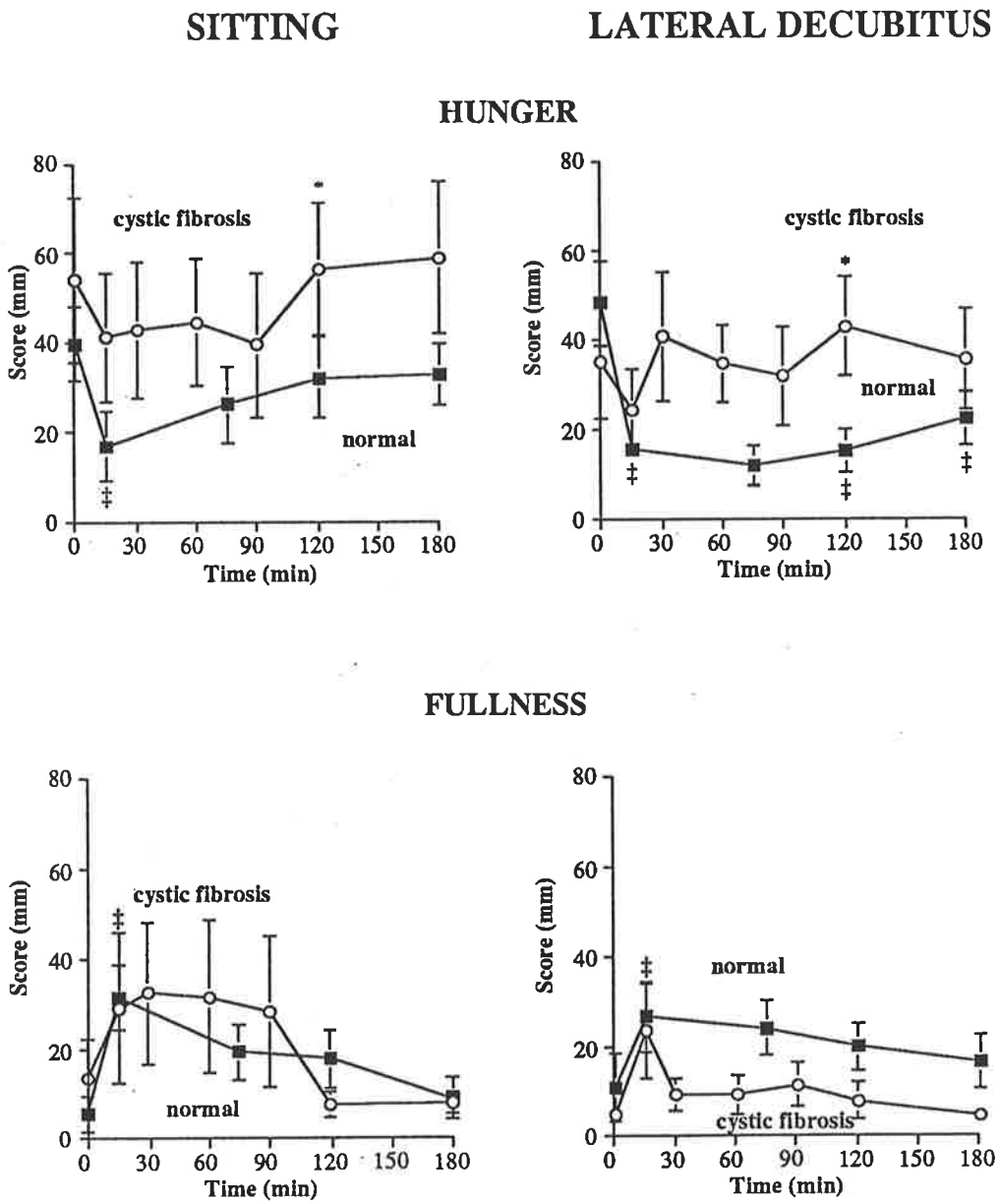

*Figure 11.5: Scores for (a) hunger and (b) fullness in the sitting and left lateral decubitus positions in patients with cystic fibrosis and normal volunteers. Data are mean values ± SEM. *p<0.05 between cystic fibrosis patients and normal volunteers; ‡p<0.05 compared to baseline.*

11.5 DISCUSSION

Because of limited availability of patient volunteers, we studied only a small number of patients with CF; yet differences of gastric emptying between patient volunteers and normal subjects were clear. Our results indicate that in patients with CF and exocrine insufficiency of the pancreas: (i) gastric emptying of non-homogenised fat is much faster than in normal subjects in both the sitting and decubitus ("pylorus up") position; (ii) gravity has a major effect on gastric emptying of both oil and aqueous phases of an oil/aqueous meal; and (iii) the effects of this fatty meal on hunger are less than in normal subjects.

In both body positions, oil and water each emptied faster in CF patients than in normals. Evidence that CF may directly cause disordered motility is not convincing (Hyman 1986). Therefore, the faster emptying overall in our CF patients undoubtedly reflected diminished feedback inhibition of gastric emptying (Hunt & Knox 1968, Cortot et al 1981, Welch et al 1985, Lin et al 1990b, Meyer et al 1994a). Nevertheless, previous studies of gastric emptying in patients with CF have yielded conflicting results. For example, both Long and Weiss and Cavell reported that milk emptied more rapidly in CF patients (Long & Weiss 1974, Cavell 1981), whereas Smith and co-workers found no difference in gastric emptying of orange squash (mainly carbohydrate) (Smith et al 1990). Two factors may have contributed to these discrepancies. First, gastric emptying of fat is likely to be profoundly affected by variations in the severity of pancreatic insufficiency. In dogs, Meyer observed a cube-root relation between the rate of duodenal entry of lipase and inhibition of gastric emptying of oil, so that emptying of a large oil load was slowed considerably when lipase was supplied at rates as low as 10% of normal when compared to its complete absence (Meyer et al 1994a). Second, the uninhibited speed of gastric emptying of oil is likely to vary directly with the amount of oil ingested. In dogs, the effect of even lower

grade pancreatic insufficiency on gastric emptying is more easily observed when, as here, large loads of oil are given in the test meal (Meyer et al 1994a).

In the normal subjects, in whom intestinal feedback inhibition from lipolytic products was fully intact, oil emptied at similarly slow rates (when compared to the aqueous phase) whether from the sitting or decubitus position; while water emptied much more slowly from the decubitus than from the sitting position. By contrast, in the CF patients, in whom feedback inhibition from lipolytic products was expected to be considerably diminished, oil emptied much more rapidly from the decubitus ("pylorus up") position than from the sitting posture; water emptied rapidly from both positions, though significantly faster from the sitting than from the decubitus position. These contrasts between normal and CF patients indicate that feedback inhibition greatly modified the effects of posture and gravity on gastric emptying of oil and of water in the normal subjects.

From previous studies (Hunt et al 1965, Chang et al 1968), it would be expected that oil would empty faster from the "pylorus up" (decubitus) position because of the oil floating in this position toward the pyloric outlet and that, conversely, water would empty faster from the sitting than from the decubitus position because of the decubitus positioning of water away from the pylorus, toward the cardia. In the CF subjects, the effects of gravity on both the layering of water and oil and on the time courses of gastric emptying of each phase was fully observed. Although oil and water layered somewhat similarly in the normal subjects, the expected effects of posture on gastric emptying were not fully realised. There was, as expected (Chang et al 1968), a slower initial emptying of oil from the sitting compared to the decubitus position; but throughout most of the time-course, the oil emptied at similar rates from both the decubitus and sitting positions. The observations are consistent with the idea that feedback by lipolytic

products in the small intestine of the normal subjects stimulated motor mechanisms (Azpiroz & Malagelada 1985, Heddle et al 1988a, Heddle et al 1989, Fone et al 1990b, Drewe et al 1992) which held the outflow of oil to a more constant rate and that, except for the initial period in which lipolytic products were just beginning to be released in the small intestine, this inhibition obscured the effects of gravity on emptying of oil. The late slowing of gastric emptying of oil in the CF patients may reflect hydrolysis of oil by gastric lipase (Moreau et al 1988) as well as a reduction in propulsive forces as a result of decreased intragastric volume. Two further comparisons between the normal and CF subjects are also consistent with modulation of gravitational effects by strong intestinal feedback. In both normal and CF subjects the aqueous phase emptied faster, as expected, from the sitting than from the decubitus position, but the positional effects were much greater in the normal than in the CF subjects. - The normal subjects probably had a more intense feedback inhibition than the CF subjects from lipolysis of the oil that emptied rapidly from the "pylorus up" position in the initial postcibal period; and thus, feedback slowed further the emptying of water, accentuating the effects of gravity and body position on water outflow. Although body position and thus gravity clearly affected the intragastric distributions of oil and water in both the normal and CF patients, the confinement of oil to the top of the stomach during the period of observation was less marked in the CF than in the normal subjects. This last observation is similar to that in dogs in which layering of unemulsified oil to the top of gastric contents was significantly less when all pancreatic enzymes were excluded from duodenum than when they were fully present (Meyer et al 1994a) and indicates that even the intragastric distribution of oil arises from a mix of passive, gravitational forces and active contractions of the stomach.

In the study of Hunt et al, the effects of gravity on emptying of homogeneous, aqueous meals also demonstrated a complex interplay between passive gravitational forces and active control of gastric emptying by small intestinal feedback (Hunt et al 1965). With water, which does not elicit intestinal feedback, the effects of gravity were readily observed; that is, gastric emptying of water was fastest from the erect "head up" position, slowest from the "head down" position, and intermediate from the horizontal position. With solutions of glucose, which empty more slowly than water because small intestinal feedback mechanisms limit the rate of intestinal entry, emptying was similarly slow from the sitting and horizontal postures and barely less rapid from the head down position. Thus, the effects of gravity, so evident with water, were modulated by pronounced small intestinal feedback inhibition from the glucose. In this study a similar masking by intestinal feedback of the effects of gravity on the gastric emptying of oil in normal subjects, an effect that was unable to be unmasked by studying CF subjects in whom feedback mechanims were diminished. However, this meal was biphasic and nonhomogeneous, in contrast to Hunt and co-worker's glucose meals (Hunt et al 1965). In this study, oil was the main nutrient in the meal that provoked intestinal feedback; and it emptied independently of water, yet affected the outflow of the separately emptied water phase.

This mix of passive gravitational and active controls on the gastric emptying of fat is further complicated by the distributions of fat within ingested foods. Fat confined to the matrix of solid foods does not float freely within the gastric contents and empties predominantly with the solid food phase (Meyer et al 1986). Its emptying within this phase is even more potently inhibited by intestinal feedback than is the emptying of free oil (Meyer et al 1994a). Fat distributed homogeneously in aqueous emulsions will empty initially like the water phase, until the emulsion breaks apart and the fat floats to the top of the gastric contents

(Meyer et al 1994a). The studies performed in Chapter 10 and Chapter 11 indicate that the initial emptying of unemulsified oil is determined by its intragastric position. Both in normal and CF subjects, positioning the fat nearer to the pylorus by assumption of the decubitus posture sped its initial emptying. However, even in the erect position, the proximity of unemulsified oil to the pylorus, and thus its initial speed of emptying, may be influenced by the size of the aqueous phase of the meal. Feeding unemulsified oil to dogs (Meyer et al 1994a) or normal humans (Meyer, independent, unpublished observations) in meals in which there was no water phase resulted in an initially rapid emptying for 20-30 min without a lag phase. By contrast, feeding unemulsified oil as globules within a large aqueous ("soup") phase in the present experiments resulted in a slow, initial emptying from the erect posture in which the oil was separated from the pylorus by a large, aqueous phase underneath it. The emptying of fat therefore lagged until most of the underlying aqueous phase had emptied. These behaviors were also modified by feedback inhibition by lipolytic products in the small intestine and thus differed in detail in pancreatic insufficiency, but not in principle. Finally, even the intensity of feedback on gastric emptying of fat fluctuates and appears to adapt to prior intakes of dietary fat (Cunningham et al 1991d). Reduced feedback inhibition from small intestinal receptors as a result of increased intestinal exposure to non-hydrolysed fat may therefore also contribute to more rapid emptying of fat in pancreatic insufficiency. Thus, gastric emptying of fat is extremely complex.

How fat empties from the stomach is very important in the manifestations and treatment of pancreatic insufficiency. The amount of fat which is undigested and unabsorbed at any rate of pancreatic secretion of lipase is determined by how fast fat substrate enters the duodenum. Thus, ingestion of large amounts of oil in a meal devoid of a large aqueous phase, or ingestion of large volumes of aqueous

emulsions of fat will promote rapid emptying of fat and thus accentuate steatorrhea even in patients who have borderline pancreatic insufficiency. The timing of duodenal delivery of exogenous lipase relative to the time-course of gastric emptying of fat substrate will also greatly affect the success of treatment of steatorrhea with exogenous pancreatic enzymes. While it seems probable that optimal pancreatic enzyme replacement would result in abolition of the effects of posture on gastric emptying of oil in patients with pancreatic insufficiency, this issue warrants formal evaluation.

The regulation of appetite is a complex process which involves both central and peripheral mechanisms (Welch et al 1988, Morley et al 1989, Greenberg et al 1990, Greenberg et al 1992). Postprandial hunger is influenced by both intragastric volume (Bergmann et al 1992) and the extent (and possibly the site) of small intestinal exposure to nutrients (Welch et al 1988, Sepple & Read 1989). In humans and animals, small intestinal infusion of fats inhibits food intake (Welch et al 1985, Welch et al 1988, Greenberg et al 1990) and this effect is not dependent on slowing of gastric emptying (Greenberg et al 1990). Stimulation of vagal efferents (Yox et al 1991) and release of cholecystokinin (Greenberg et al 1989, Gregory et al 1989) may contribute to the effects of intraduodenal fat on satiation. We found in the CF patients that there was no change in either hunger or fullness after the meal, in contrast to the normal subjects. While more rapid gastric emptying may have contributed to reduced satiation in the CF patients, it is also possible that lipolysis may be required for the intestinal stimulation of satiation by fat. Information about the effects of pancreatic insufficiency on cholecystokinin release after ingestion of fat is inconsistent (Abdello et al 1989, Masclee et al 1989), but Masclee et al have reported that the plasma cholecystokinin response to intraduodenal fat is reduced in patients with pancreatic insufficiency, and that this is normalised by the addition of pancreatic

enzymes (Masclee et al 1989). The observations that in the normal subjects postprandial hunger was related to the retention of oil in the stomach in the decubitus posture, whereas in the CF patients there was no significant relationship, may also reflect the small number of CF patients that were studied.

CHAPTER 12

EFFECTS OF CISAPRIDE ON GASTRIC EMPTYING OF OIL AND AQUEOUS MEAL COMPONENTS, HUNGER AND FULLNESS

12.1 SUMMARY

To evaluate the effects of cisapride on gastric emptying of extracellular fat and hunger and fullness, 10 volunteers consumed a meal consisting of 60 ml ^{99m}Tc-V-thiocyanate labelled olive oil and 290 ml ^{113m}In labelled soup after taking cisapride (10 mg qid p.o.) and placebo, each for four days, in randomised, double-blind fashion. Gastric emptying was quantified scintigraphically. Hunger and fullness before and after the meal were evaluated using visual analogue scales. Cisapride accelerated gastric emptying of oil and aqueous components by reducing the lag phase (20.3 ± 7.0 min vs 40.7 ± 4.1 min ($p<0.05$) for oil and 4.1 ± 2.5 min vs 10.0 ± 3.1 min ($p<0.05$) for aqueous). Cisapride had no effect on the post-lag emptying rate of oil. Treatment with cisapride was associated with reduced retention of oil in the proximal stomach ($p<0.05$). Subjects were more hungry before ingestion of the meal on cisapride (6.7 ± 0.9 vs 3.9 ± 0.7, $p<0.001$). The scores for hunger at 120 and 180 min were inversely related to gastric emptying of oil on both cisapride ($r>-0.62$, $p<0.05$) and placebo ($r>-0.86$, $p<0.001$). Fullness increased after the meal on placebo ($p<0.01$), but not cisapride and postprandial fullness was less on cisapride at (30 min; 0.4 ± 0.3 vs 3.3 ± 1.0, $p<0.05$). On placebo, but not cisapride, the score for fullness at 15 min was inversely related to emptying of the aqueous phase ($r=-0.68$, $p<0.05$).

These results indicate that in normal volunteers after ingestion of an oil/aqueous meal: (i) postprandial hunger is inversely related to gastric emptying of oil, while fullness is inversely related to gastric emptying of the aqueous phase (ii) cisapride affects the intragastric distribution and accelerates gastric emptying of both oil and aqueous meal components and (iii) cisapride increases preprandial hunger and reduces postprandial fullness.

12.2 INTRODUCTION

Disordered gastric emptying, particularly delayed emptying, occurs frequently and may be associated with gastrointestinal symptoms such as nausea, abdominal pain and vomiting (Horowitz & Dent 1991). In normal subjects gastric (Stacher et al 1990, Stacher et al 1991) and small intestinal (Heddle et al 1989) administration of fat retard gastric emptying. In patients who suffer from unexplained upper abdominal symptoms, the latter may be exacerbated by intake of high fat meals and in patients with non-ulcer dyspepsia, delay in gastric emptying is more commonly observed with nutrient rich (high fat) than with bland meals (Houghton et al 1993). The intragastric distribution of fatty meals is also frequently abnormal in patients with non-ulcer dyspepsia (Mangnall et al 1994).

The most effective therapeutic approach to the treatment of symptomatic gastroparesis is the use of drugs designed to increase the rate of gastric emptying (Horowitz & Dent 1991) and cisapride is arguably the gastrokinetic drug of first choice (Wiseman & Faulds 1994). Cisapride has been shown to abolish the slowing of gastric emptying induced by giving fat immediately before a meal in normal subjects (Stacher et al 1990, Stacher et al 1991), but the effects of cisapride or other prokinetic agents on gastric emptying of fat have not yet been evaluated. Recent studies indicate that gastric emptying of extracellular fat is influenced by

both its intragastric distribution, and feedback from receptors in the small intestine (Cortot et al 1982, Meyer et al 1986, Chapter 10, Chapter 11). There is evidence that in therapeutic doses cisapride does not have the capacity to overcome small intestinal feedback regulation of normal gastric emptying (Wiseman & Faulds 1994), but the effects of cisapride on intragastric meal distribution have not been assessed.

While cisapride accelerates gastric emptying and relieves symptoms in most forms of gastroparesis, there is a poor relationship between the magnitude of the improvements in emptying and symptoms (Wiseman & Faulds 1994), suggesting that factors unrelated to normalisation of gastric emptying may contribute to the beneficial effects of cisapride on symptoms. The controls of appetite in humans are poorly understood, but it is clear that signals from the gastrointestinal tract are important (Morley 1989). Gastric distension is well recognised as a signal for satiety (Bergmann et al 1992), and recent studies suggest that postprandial hunger is also related to the extent of small intestinal nutrient exposure (Welch et al 1988, Chapter 10). Cisapride is devoid of antidopaminergic and central antiemetic properties and psychological effects (Stacher et al 1987b, Wiseman & Faulds 1994). Perhaps because of these reasons the effects of cisapride on appetite have not been formally evaluated.

A specific radioisotopic marker of extracellular fat has been used in this study to evaluate the effects of cisapride on gastric emptying and intragastric distribution of oil and aqueous meal components and appetite in normal subjects.

12.3 MATERIALS AND METHODS

Ten healthy volunteers (1 male, 9 female), mean age 22 years (range 18 - 28) and mean body weight 67.2 kg (range 39.6 - 98.4) had two measurements of gastric emptying, hunger and fullness, once after taking cisapride and the other after taking placebo. None of the subjects had a history of gastrointestinal disease or was taking medication known to influence gastrointestinal motility. Written informed consent was obtained from each subject and the study was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

12.3.1 *Experimental protocol*

Each of the volunteers had measurements of gastric emptying, hunger and fullness on two separate days after receiving cisapride (10 mg qid) or placebo, both administered as tablets in random, double-blind, crossover fashion. Cisapride and placebo tablets were identical in appearance and taste. For four days before each of the two study days each subject took one tablet four times a day (before meals). After the first study day, each subject entered a drug-free "washout" phase of 7 to 10 days and then received the alternate medication in identical fashion. The last tablet was taken about two hours prior to the gastric emptying study. Remaining tablets were returned on each of the study days. The test meal was consumed within five minutes at about 10.00 am after an overnight fast (14 hours for solids and 12 hours for liquids) with the subject seated in front of a scintillation camera (Chapter 10, Chapter 11). The meal comprised 60 ml olive oil (Faulding Pty Ltd, South Australia) labelled with 20 MBq ^{99m}Tc-(V)-thiocyanate and 290 ml of low-nutrient beef consomme soup (Campbell's Soup Pty Ltd, Australia) labelled with 20 MBq ^{113m}In-diethylenetriamine-pentaacetic acid (DTPA). The meal was heated to 45^{o}C immediately prior to ingestion (Chapter 10, Chapter 11) and the oil was mixed gently with the soup immediately before and during consumption. The

caloric content of the oil-soup mixture (7 g protein, 52 g fat) was 505 kcal (of which 473 kcal were contained in the oil). Feelings of hunger and fullness were recorded on a validated visual analogue scale administered immediately before and at 15, 30, 60, 90, 120, 150, 180, 210 and 240 minutes after ingestion of the test meal (Sepple & Read 1989, Chapter 10, Chapter 11).

12.3.2 *Measurement of gastric emptying*

The preparation of the test meal has been described previously (Cunningham et al 1991d). Radionuclide data for both isotopes, were acquired on computer for at least 180 minutes in each of the studies, starting immediately after ingestion of the liquid meal and were subsequently corrected for subject movement, Compton scatter, radionuclide gamma ray attenuation and radionuclide decay (Collins et al 1983). Correction for attenuation was done using factors derived from a lateral image of the stomach (Collins et al 1983). A region-of-interest (ROI) was drawn around the total stomach, which was then divided into proximal and distal regions - the proximal region corresponding to the fundus and proximal corpus and the distal region representing the distal corpus and antrum (Collins et al 1988). Gastric emptying curves for total, proximal and distal stomach (expressed as % retention over time) were derived (Chapter 10, Chapter 11) and several parameters were obtained from these curves for subsequent statistical analysis. For the total stomach these were the lag phase, before any of the oil or aqueous components started to empty from the stomach, and the amount of the oil and aqueous meal components which remained in the stomach at 15, 30, 60, 120 and 180 minutes (Chapter 10, Chapter 11). The lag phase was determined visually by the frame preceding that in which activity was seen in the proximal small intestine (Collins et al 1983). For the oil component of the meal the rate of emptying, expressed as %/min between the end of the lag phase and 180 min, was also calculated (Cunningham et al 1991d,

Collins et al 1983). The 50% emptying time (T50) for the total stomach was derived for the aqueous, but not the oil phase, as in some subjects the T50 for oil was not reached during the study period. For the proximal and distal stomach, the retention of isotope at 15, 30, 60, 120 and 180 minutes (expressed as a percentage of the maximum counts in the total stomach) was calculated. The 50% emptying time for the proximal stomach (PT50) and the maximum content of the distal stomach were also derived (Chapter 10, Chapter 11). The maximum content of the distal stomach was defined as the maximum counts in the distal stomach following meal ingestion (Chapter 10, Chapter 11). Retrograde movement of oil or aqueous phases from the distal into the proximal stomach was defined as a rise in proximal stomach counts ≥ 10% associated with a fall in distal stomach counts of > 10% (Cunningham et al 1991d). The number of episodes of retrograde movement in each subject was counted.

12.3.3 *Assessment of Hunger and Fullness*

Subjective ratings of various sensations including hunger and fullness, were assessed by marking line analogues 100 mm long. Full details of this questionnaire have been published previously (Sepple & Read 1989).

12.3.4 *Statistical Analysis*

Data were evaluated using repeated measures analysis of variance (ANOVA) and are shown as mean values ± SEM. The factors for which the ANOVA's accounted included treatment (cisapride or placebo), time after meal ingestion, sequence (order), meal component (oil or aqueous) and region of the stomach (total, proximal, distal). Gastric emptying curves show the retention of isotope at 0, 15, 30, 60, 120 and 180 min. The relationships between gastric emptying and

intragastric distribution of both oil and aqueous meal components and subjective ratings of hunger and fullness were evaluated using linear regression analysis. A *p* value of <0.05 was used to indicate statistical significance in all analyses.

12.4 RESULTS

All 10 subjects tolerated the study well and, as assessed by tablet counts, complied with medication. Six subjects reported adverse effects including nausea (2 subjects), headache (2 subjects) and more frequent bowel actions (5 subjects) while taking cisapride. In all cases these symptoms were mild and disappeared within a week after taking the last tablet. One subject had a mild headache while taking placebo, but no other adverse effects were reported. The effect of cisapride on the sensation of fullness was analysed using the first period data only, as there was an order effect.

12.4.1 *Gastric Emptying of Oil and Aqueous Phases*

Total Stomach

Oil Component

Emptying of oil approximated a linear pattern after an initial lag phase (Cunningham 1991d). When subjects were taking cisapride, the lag phase was shorter (20.3 ± 7.0 min vs 40.7 ± 4.1 min; $p<0.05$) and the retention of oil in the stomach at 30 min was less (84.4 ± 5.4% vs 98.6 ± 1.2%; $p<0.05$) (Figure 12.1) than placebo. There was no effect of cisapride on the emptying rate of oil after the lag phase (0.30 ± 0.04%/min vs 0.29 ± 0.04%/min; NS).

Aqueous Component

Emptying of the aqueous component from the stomach approximated a monoexponential function after a short lag phase. The latter was shorter after cisapride (4.1 ± 2.5 min vs 10.0 ± 3.1 min; $p<0.05$) compared to placebo. The amount of the aqueous component remaining in the stomach at 15 min and 30 min were less ($p<0.05$) on cisapride (Figure 12.1). There was a non-significant trend for the T50 to be shorter on cisapride (28.7 ± 6.0 min vs 50.8 ± 9.2 min; $p=0.076$).

Intragastric Meal Distribution

During treatment with both cisapride and placebo there was more of the oil than the aqueous component retained in the proximal stomach ($p<0.001$) and in all studies there was evidence of a "midgastric band" - a band of decreased activity separating the proximal and distal stomach (Chapter 10, Chapter 11). Retrograde movement of the oil from the distal to the proximal stomach in the 180 min after ingestion of the meal was evident in all subjects, on both cisapride and placebo. There was a non-significant trend for a greater number of episodes of retrograde movement per subject in those taking cisapride (3.5 ± 0.65 vs 2.4 ± 0.58; $p=0.063$). Retrograde movement of the aqueous phase from distal to proximal stomach was not evident in any study.

Oil Component

On cisapride there was less oil in the proximal stomach at 15 and 30 min ($p<0.05$ for both) and at 15 min there was more oil in the distal stomach ($p<0.05$) (Figure 12.1) when compared to placebo. There was no effect of cisapride on either the proximal stomach T50 (117.4 ± 27.9 min vs 145.1 ± 32.5 min; NS) or the maximum content of the distal stomach (44.9 ± 5.1% vs 40.4 ± 6.4%; NS).

Aqueous Component

On cisapride there was less of the aqueous meal component in the proximal stomach at 15 min and 30 min ($p<0.05$) and the proximal stomach T50 was shorter (5.9 ± 2.5 min vs 14.3 ± 5.3 min; $p<0.05$) compared to placebo. There was no significant difference in the retention of the aqueous component in the distal stomach or the maximum content of the distal stomach (55.0 ± 5.8% vs 51.5 ± 6.2%; NS) between cisapride and placebo (Figure 12.1).

12.4.2 *Relationships between retention in the total, proximal and distal stomach*

Oil Component

There were significant relationships between the amounts of oil in the proximal and total stomach at 120 min on both cisapride ($r=0.61$, $p<0.05$) and placebo ($r=0.74$, $p<0.01$). There was a significant inverse relationship between total stomach and distal stomach content at 30 min on placebo ($r=-0.80$, $p<0.01$) but not cisapride ($r=-0.08$; NS).

Aqueous Component

There was a significant linear relationship between the amount of the aqueous component in the proximal stomach at 30 min and the total stomach T50 on cisapride ($r=0.86$, $p<0.001$), but not placebo ($r=0.32$, NS).

12.4.3 *Hunger and Fullness*

Hunger

Before ingestion of the meal the score for hunger was higher ($p<0.001$) when subjects were taking cisapride (Figure 12.2). There was a decrease in hunger 15

min after the meal on both cisapride ($p<0.0001$) and placebo ($p<0.05$) and no significant difference between the two groups.

Fullness

Fullness increased 15 min after the meal when subjects had taken placebo ($p<0.001$) but not significantly on cisapride ($p=0.59$; NS). The scores for fullness were lower on cisapride than placebo at 15 min, 30 min and 90 min ($p<0.05$ for all) (Figure 12.3).

12.4.4 *Relationship between hunger and fullness and gastric emptying*

Oil Component

At both 120 and 180 min hunger, was directly related to the retention of oil in the stomach on both placebo ($r\geq0.86$, $p<0.001$) and cisapride ($r\geq0.62$, $p<0.05$) (Figure 12.4) ie. subjects were less hungry when more of the oil had emptied from the stomach. There were no significant relationships between fullness and gastric emptying of oil on either cisapride or placebo.

Aqueous Component

On placebo the score for fullness at 15 min was directly related to both the lag phase ($r=0.65$, $p<0.05$) and the retention at 30 min ($r=0.68$, $p<0.05$) i.e. subjects felt more full when gastric emptying of the aqueous phase was slower. In subjects taking cisapride there was no significant relationship between fullness and gastric emptying.

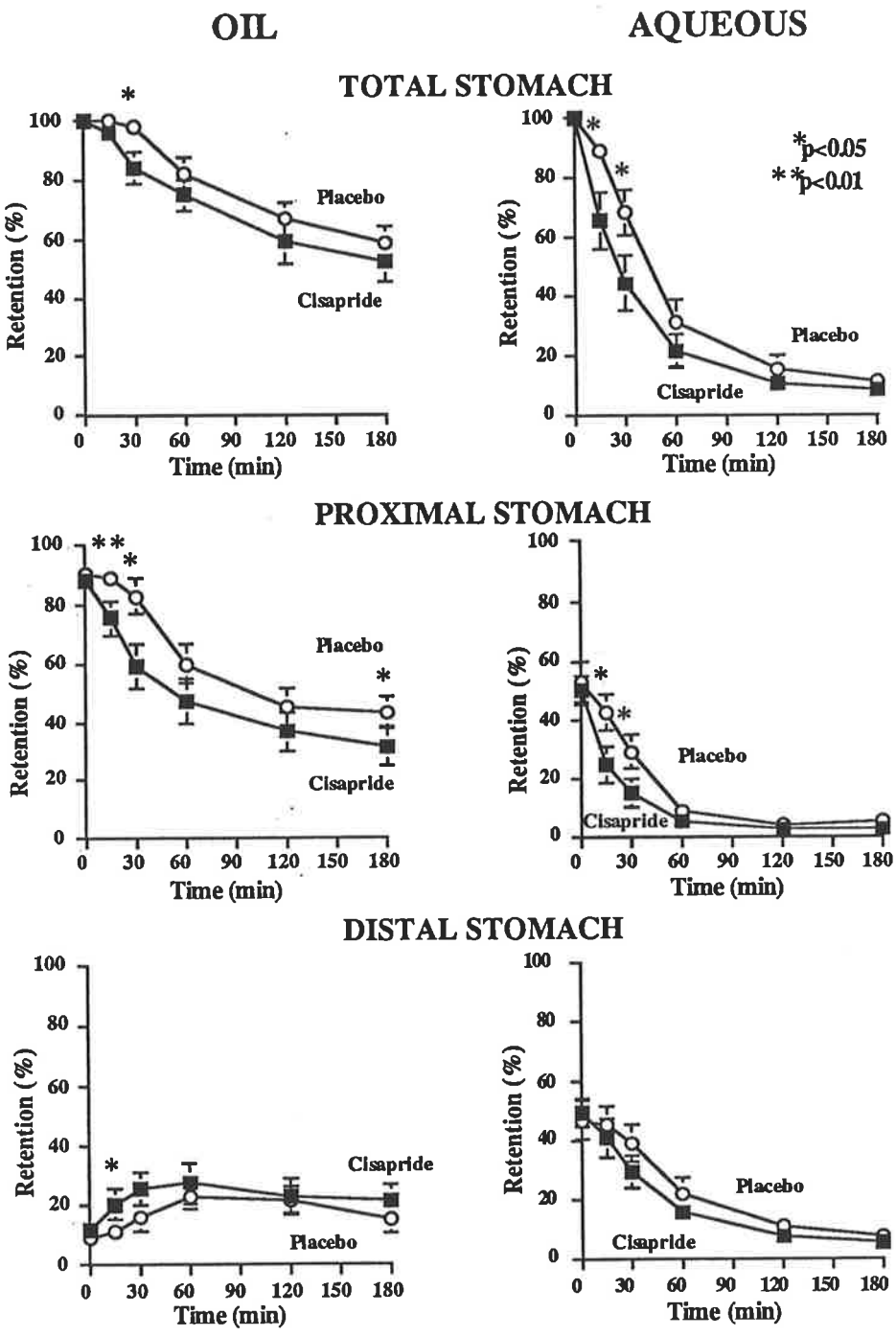

Figure 12.1: Retention of oil and aqueous meal components in total, proximal and distal stomach regions-of-interest. Data are mean values ± SEM.

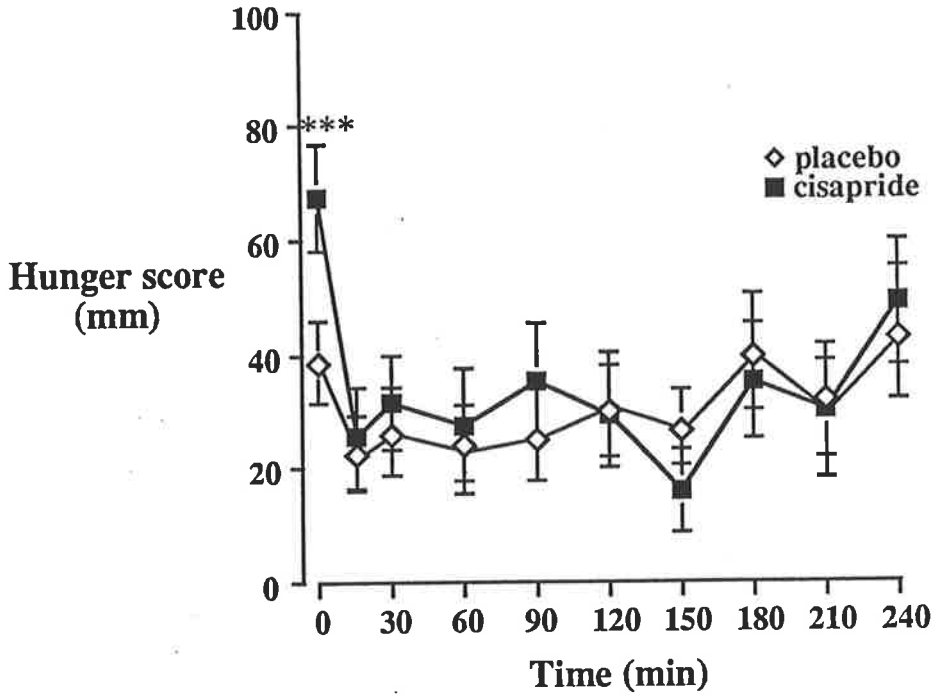

*Figure 12.2: Scores for hunger before and after meal ingestion. Data are mean values ± SEM. ***p<0.001 placebo vs cisapride*

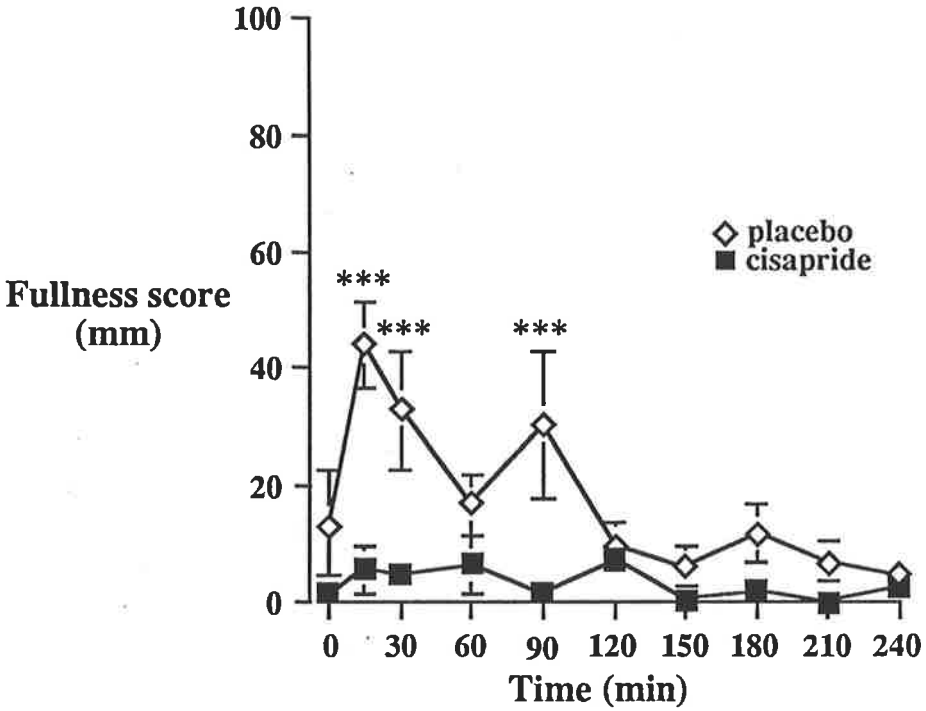

*Figure 12.3: Scores for fullness before and after meal ingestion for the first test day. Data are mean values ± SEM. ***p<0.001 placebo vs cisapride*

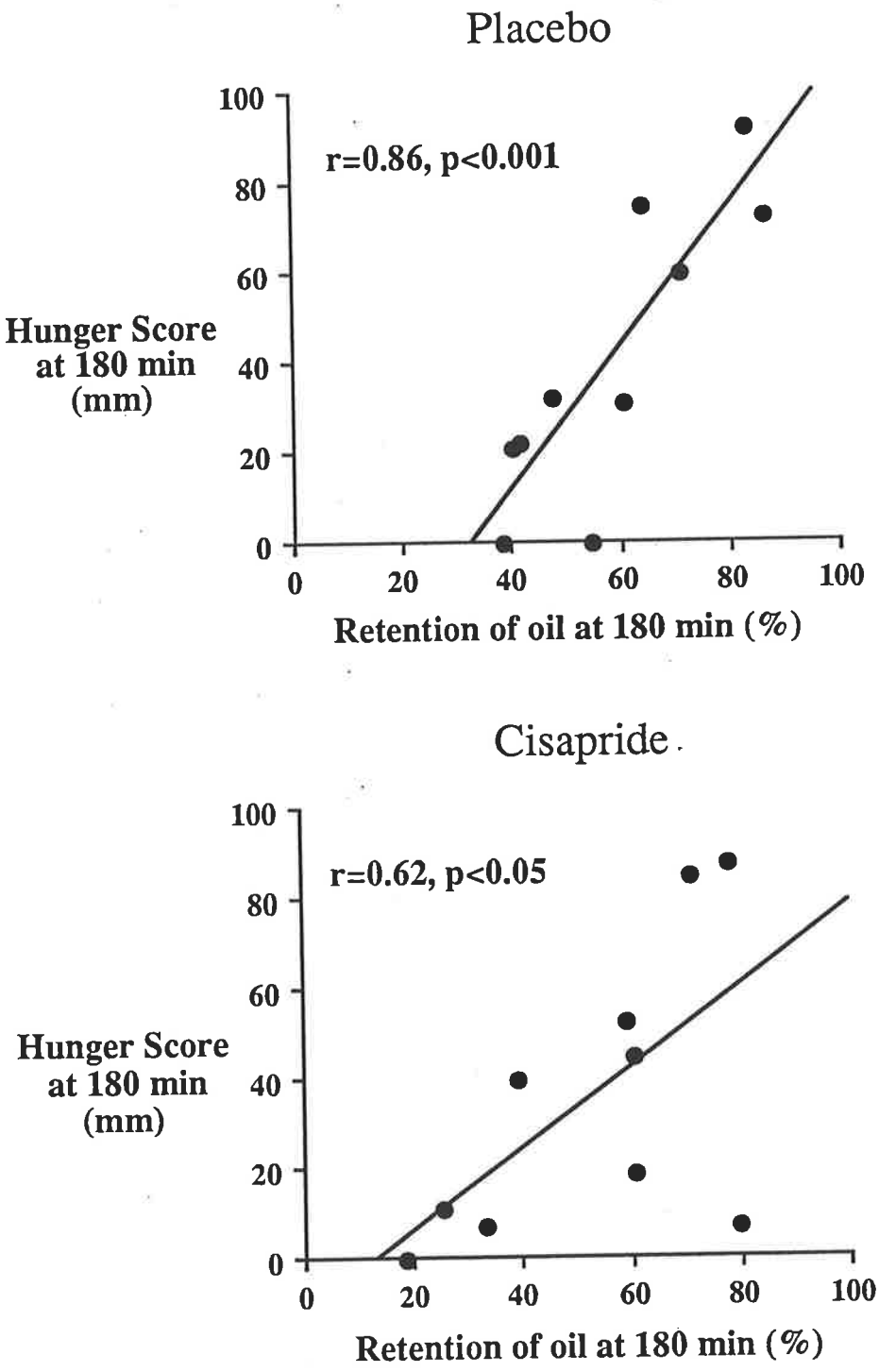

Figure 12.4: Relationship between the score for hunger at 180 min and the amount of oil remaining in the stomach at 180 min on placebo and cisapride.

12.5 DISCUSSION

Our results show that in normal subjects, after ingestion of a meal comprising oil and aqueous components (i) cisapride affects the intragastric distribution of the oil component and accelerates gastric emptying of both oil and aqueous meal components, (ii) postprandial hunger is inversely related to gastric emptying of oil, while fullness is inversely related to gastric emptying of the aqueous phase and (iii) cisapride increases preprandial hunger and reduces postprandial fullness.

It is well known that gastric emptying of high fat meals is slower than that of low nutrient meals. At body temperature the majority of extracellular fat is in the oil phase. The intragastric distribution of oil is influenced by the composition and volume of other meal components and posture (Cortot et al 1982, Meyer et al 1986, Chapter 10). For example, because of its lower density, oil will float towards the gastric outlet in the decubitus position and away from it in the sitting position (Chapter 10). However, the major factor regulating gastric emptying of oil in normal subjects is the interaction of lipolytic products with receptors in the small intestinal lumen (Cortot et al 1982, Meyer et al 1986). As a result of diminished small intestinal feedback, gastric emptying of oil is faster than normal in patients with pancreatic insufficiency (Chapter 11). Our observation that gastric emptying of oil was accelerated by cisapride is consistent with previous studies (Stacher et al 1990, Stacher et al 1991). Stacher et al reported that the retardation of gastric emptying of a semisolid meal by giving a fat preload to normal subjects was abolished by both intravenous (Stacher et al 1990) and rectal (Stacher et al 1991) administration of cisapride, while in dogs, Janisch et al found that gastric emptying of a barium meal containing 20 ml olive oil was also accelerated by cisapride (Janisch et al 1987). It should, however, be recognised that the magnitude of the increase in gastric emptying of oil induced by cisapride that was observed in this study was small and reflected a reduction in the duration of the lag phase, with no

significant change in the post-lag emptying rate. This latter observation is compatible with the concept that cisapride, at least in doses used therapeutically, does not overcome the physiological feedback mechanisms which regulate gastric emptying of nutrient-containing meals in normal subjects (Wiseman & Faulds 1994). In particular, cisapride has little or no effect on normal gastric emptying of solid meals (Wiseman & Faulds 1994). The reduction in the lag phase for oil and aqueous components of the meal by cisapride probably reflects the more rapid movement of oil from the proximal to the distal stomach.

A number of studies have evaluated the motor mechanisms responsible for the modest increase in gastric emptying caused by cisapride in normal subjects (Rezende-Filho et al 1989, Fraser et al 1993b, Wiseman & Faulds 1994) and the more marked acceleration in patients with gastroparesis (Schuurkes et al 1983, Fraser et al 1994). The rate of gastric emptying is dependent on the relationships between contractions generated by the proximal stomach, antrum, pylorus and proximal small intestine, so that no motor mechanism should be considered to exert the dominant control, either propulsive or retardant over normal gastric emptying (Horowitz & Dent 1994). Cisapride has been shown to affect antral and pyloric motility, including the organisation of antral pressure waves, in both normal subjects and patients with gastroparesis (Fraser et al 1993b, Fraser et al 1994, Wiseman & Faulds 1994). The observation that the retention of both oil and aqueous phases in the proximal stomach was less on cisapride suggests that cisapride also affects proximal stomach motility (Maddern et al 1991). Gastric emptying is predominantly pulsatile, rather than continuous, and there is considerable variation in the characteristics of flow pulses (volume and frequency) from one contraction cycle to the next (Malbert et al 1992, Malbert & Mathis 1994). This variability appears to result mainly from changes in the temporal and spatial patterning of tone and active lumen occlusion in different regions of the stomach

and small intestine (Horowitz & Dent 1994). Therefore, while we found that cisapride had no effect on the overall emptying rate of oil or aqueous phases, we cannot exclude changes in the characteristics of individual flow pulses (Malbert et al 1992).

Although the mechanisms responsible for the regulation of appetite in human are complex it is clear that signals from the gastrointestinal tract influence both satiety and satiation. Because our test meal comprised discretely labelled oil and aqueous components and the aqueous phase had a low nutrient content, the relationships between hunger and fullness and gastric emptying could be more fully evaluated than in previous studies. The observation that postprandial hunger in normal subjects is inversely related to gastric emptying of oil is consistent with the previous study described in Chapter 10 and indicates that interaction with small intestinal receptors (perhaps via the subsequent stimulation of vagal efferents and/or release of cholecystokinin) contributes to the effects of fat on satiation (Welch et al 1988, Gregory et al 1989, Yox et al 1991a). The results of the previous study in patients with pancreatic insufficiency (Chapter 11) suggest that lipolysis may be required for small intestinal inhibition of hunger by fat. The observation that postprandial fullness was related to the amount of the aqueous phase in the stomach is novel but consistent with the study described in Chapter 10 and compatible with the concept that gastric distension leads to satiety (Bergmann et al 1992), as the aqueous phase comprised the majority of the volume of our test meal. The intragastric mechanisms triggering satiety are uncertain. It is, however, of interest that patients with non-ulcer dyspepsia have, as a group, a wider gastric antrum than normal, both fasting and postprandially (Hausken et al 1992). The latter has been postulated to result from disordered proximal stomach motor function, with secondary effects on antral distension.

The observations that cisapride increased preprandial hunger and reduced postprandial fullness are novel, and because of their potential major clinical relevance require confirmation. An evaluation of hunger was included in the study of Stacher et al. (Stacher et al 1987b) but the results were not given. Presumably no effect of cisapride on appetite was detected. However, in an unpublished study, an improvement in appetite was observed in patients after partial gastrectomy treated with cisapride (Tomita et al). Current understanding of the aetiology of gastrointestinal symptoms in patients with gastroparesis and the factors responsible for symptomatic improvement resulting from prokinetic therapy is limited, but it is clear that neither can be totally attributed to the rate of gastric emptying per se (Horowitz & Dent 1991, Wiseman & Faulds 1994). While the mechanisms mediating the effects of cisapride on fullness are uncertain it seems unlikely that the reduction in fullness on cisapride compared to placebo is accounted for by a decrease in intragastric volume, as the overall acceleration of gastric emptying by cisapride was modest. More plausible alternatives are that effects of cisapride on proximal stomach or antral tone, or intragastric meal distribution, perhaps by leading to changes in afferent sensory feedback, are important. These issues warrant exploration in future studies.

CHAPTER 13

RELATIONSHIPS BETWEEN GASTRIC EMPTYING, INTRAGASTRIC MEAL DISTRIBUTION AND BLOOD GLUCOSE CONCENTRATIONS IN DIABETES MELLITUS

13.1 SUMMARY

To evaluate the prevalence of disordered intragastric meal distribution and the relationships between gastric emptying, intragastric distribution, glycaemic control and gastrointestinal symptoms 86 patients with diabetes mellitus had measurements of gastric emptying and intragastric distribution of a radioisotopically labelled solid/liquid meal (100 g beef and 150 ml 10% dextrose), glycaemic control (plasma glucose concentrations), upper gastrointestinal symptoms (questionnaire) and autonomic nerve function (cardiovascular reflexes). Results were compared to those obtained in 20 normal volunteers. Solid ($p<0.001$) and liquid ($p<0.02$) gastric emptying were delayed in the diabetic patients, and correlated weakly ($r=0.42$, $p<0.001$). Intragastric meal distribution was also often abnormal with increased retention of both solid and liquid in the proximal stomach ($p<0.05$) and increased retention of solid ($p<0.05$), but not liquid in the distal stomach. In all patients with increased retention of solid in the proximal stomach, emptying from the total stomach was delayed. Symptoms and autonomic nerve dysfunction correlated weakly with gastric emptying of solid ($r\geq0.32$, $p<0.01$), but not liquid ($r>0.11$, NS). Gastric emptying of liquid was slower ($p<0.01$) in those subjects who had a mean plasma glucose >15 mmol/L during the gastric emptying measurement, when compared to the remainder of the group. In those patients with a mean plasma glucose ≤15 mmol/L there was a direct relationship ($r=0.70$,

$p<0.001$) between the rate of liquid emptying and the postprandial rise in glucose. We conclude that in patients with diabetes mellitus: there is a poor relationship between solid and liquid gastric emptying, intragastric meal distribution is frequently abnormal but measurement of this is of little clinical relevance and interpretation of the results of gastric emptying measurements should take into account both meal composition and plasma glucose concentrations.

13.2 INTRODUCTION

The recent application of scintigraphic techniques has demonstrated that disordered gastric emptying, particularly delayed emptying, occurs frequently in patients with diabetes mellitus (Loo et al 1984, Horowitz et al 1986a, Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991). Abnormal gastric motor function may have a major impact on the management of diabetic patients by causing upper gastrointestinal symptoms, impaired oral drug absorption, and contributing to poor control of blood glucose concentrations (Horowitz & Fraser 1994). There is a relatively poor relationship between delay in gastric emptying in patients with diabetes and the presence or absence of upper gastrointestinal symptoms, such as nausea and vomiting (Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991). Gastrointestinal symptoms may theoretically relate to abnormal intragastric distribution of ingesta, rather than delay in total stomach emptying, as has been suggested to be the case in patients with non ulcer dyspepsia (Troncon et al 1994). Although there is some evidence that intragastric distribution of a solid meal is often abnormal in patients with diabetes mellitus (Urbain et al 1993), the prevalence of abnormal intragastric distribution of solid and liquid meal components and the relationship between intragastric distribution and gastrointestinal symptoms has not been evaluated. Nor is it clear whether an analysis of intragastric meal distribution

increases the ability of radionuclide methods to detect disordered gastric motility in diabetic patients.

There is inadequate information about the impact of gastric emptying on glycaemic control in diabetic patients. The relationship between gastric emptying and blood glucose concentrations is likely to be complex. While the majority of studies which have evaluated gastric motility in diabetes have not monitored (let alone stabilised) blood glucose concentrations during measurements (Camilleri & Malagelada 1984, Achem-Karam et al 1985, Keshavarzian et al 1987, Wegener et al 1990, Phillips et al 1993) and assumed that delayed gastric emptying reflects irreversible autonomic neuropathy (Feldman & Schiller 1983), recent studies have demonstrated that gastric emptying is slowed during hyperglycaemia (Fraser et al 1990) and accelerated during hypoglycaemia (Schwarcz et al 1993) i.e. the blood glucose concentration, either directly or indirectly, influences gastric motility. By contrast, in normal subjects it has been established that there is a direct relationship between the rate of gastric emptying and the magnitude of the rise in plasma glucose after an oral glucose load (Horowitz et al 1993) i.e. in this situation gastric emptying "drives" the blood glucose response to oral carbohydrate.

We have sought to shed further light on the above issues by evaluating gastric emptying and intragastric distribution of a mixed solid/liquid meal, gastrointestinal symptoms, glycaemic control and autonomic nerve function in a large cohort of patients with diabetes mellitus.

13.3 MATERIALS AND METHODS

Studies were carried out in 86 patients with diabetes mellitus (66 IDDM, 20 NIDDM). The 40 male and 46 female patients had a median age of 46 yr (range 18-

77), a median body mass index (BMI) of 24.7 (range 19.9-35.9) and a median body weight of 71 kg (range 46-102). The patients were randomly selected by two endocrinologists (MH, PEH) from ambulant outpatients who were being treated for diabetes mellitus of at least one year's known duration (median 14.5 yr (range 1-49)) at the Royal Adelaide Hospital. Some of the patients were included in previous reports (Horowitz et al 1986a, Horowitz et al 1991). Patients taking any medication known to affect gastrointestinal motility, apart from insulin or oral hypoglycaemic drugs, were excluded. No subject had a history of upper gastrointestinal surgery or peptic ulcer disease. The plasma creatinine concentration was required to be within the normal range (0.05-0.12 mmol/l) in all patients. Gastric emptying results were compared to those obtained in 20 normal volunteers (19 male, 1 female), median age 36 yr (range 18-63), median body weight 68 kg (range 57-92) and median BMI 22.1 (range 18.0-27.2). None of the control subjects was taking medication that could have influenced gastrointestinal motility, had gastrointestinal symptoms, or a history of gastrointestinal disease. Median body mass index ($p<0.05$) and age ($p<0.05$) were greater in the patients than in the control subjects. Age ($p<0.01$) and BMI ($p<0.01$) were greater in the NIDDM than IDDM patients, while the duration of diabetes was longer in the IDDM group.

13.3.1 *Experimental protocol*

Each diabetic patient was evaluated for gastrointestinal symptoms and underwent objective assessments for autonomic neuropathy, peripheral neuropathy and retinopathy in addition to measurements of gastric emptying and intragastric distribution of a mixed solid and liquid meal and glycaemic control. On the study day smoking was prohibited and none of the patients took oral hypoglycaemic drugs until after the completion of the gastric emptying measurement. On the morning of the test the IDDM patients administered their usual dose of insulin,

usually about 20 minutes before consumption of the test meal. Written informed consent was obtained from all subjects and the study was approved by the Ethics Committee of the Royal Adelaide Hospital.

13.3.2 *Assessment of gastrointestinal symptoms*

Upper gastrointestinal symptoms were assessed by questionnaire (Horowitz et al 1987, Horowitz et al 1991). "Gastric" and "oesophageal" symptoms, including anorexia, nausea, early satiety, distension, vomiting, abdominal pain, dysphagia, heartburn and acid regurgitation, were graded as 0=none, 1=mild, 2=moderate, 3=severe. The frequency and consistency of bowel actions and the presence or absence of nocturnal diarrhea and fecal incontinence were also assessed (Horowitz et al 1991).

13.3.3 *Assessment of autonomic neuropathy, peripheral neuropathy and retinopathy*

Autonomic nerve function was assessed by standardised cardiovascular reflex tests (Ewing & Clarke 1982, Horowitz et al 1991). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the immediate heart rate response to standing ("30:15" ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. The result of each of these tests was scored as 0=normal, 1=borderline or 2=abnormal. A total score of ≥3 was taken to indicate definite autonomic nerve damage (Horowitz et al 1986a). Retinopathy was graded as none (0), background (1) or proliferative (2) on the basis of a recent ophthalmological assessment, which often included fluorescein angiography. Peripheral neuropathy was diagnosed clinically

when absent ankle reflexes were associated with either sensory or motor changes (Horowitz et al 1986a).

13.3.4 *Assessment of glycaemic control*

Venous blood samples (5 ml) were taken from an indwelling cannula for subsequent measurement of plasma glucose using a hexokinase technique. Samples were taken immediately before meal ingestion and then at 30, 60, 90 and 120 min. The changes in plasma glucose from immediately before ingestion of the meal were calculated. Haemoglobin A_{1c} (HbA_{1c}) was measured using the initial venous sample and the results expressed as a percentage. The range in normal subjects is 3.5%-6.0%.

13.3.5 *Measurement of gastric emptying*

Details of this dual isotope test which measures total, proximal and distal stomach emptying of solid and liquid meal components simultaneously have been reported (Collins et al 1983). The solid component of the meal comprised chicken liver labelled in vivo with 37-55 MBq of ^{99m}Tc-sulphur colloid added to 100g minced beef which was subsequently grilled. The caloric content of the solid meal (25g protein, 21g fat) was about 270 kcal. The liquid component of the meal was 150 ml of 10% dextrose labelled with 25-37 MBq of ^{113m}Indium diethylene triaminepentaacetic acid (^{113m}In-DTPA) i.e. approximately 60 kcal. The test meal was consumed at approximately 10.00 h after an overnight fast (15 h solid, 10 h liquid). Subjects ate the minced beef over a 5 min period and then drank the liquid within 30 seconds. Each study was performed in the sitting position with the gamma camera positioned posteriorly. Data were acquired in "dynamic" mode for at least 120 min, with 1 min frames for the first hour and 3 min frames

subsequently. Time zero was defined as the time of meal completion. Radionuclide data were corrected for subject movement, Compton scatter and radionuclide decay using previously described methods (Collins et al 1983). Correction for gamma ray attenuation was done using factors derived from a lateral image of the stomach (Collins et al 1983). A region-of-interest was drawn around the total stomach, which was subsequently divided into proximal and distal regions - the proximal region corresponding to the fundus and proximal corpus and the distal region representing the antrum and distal corpus (Collins et al 1988). Gastric emptying curves for total, proximal and distal stomach (representing % retention over time) were derived. From the curves several parameters were obtained for subsequent statistical analysis. For the solid component these were the amounts remaining in the total, proximal and distal stomach at 60 and 100 min, expressed as a percentage of maximum counts. For the total stomach the lag phase, before any of the meal had left the stomach, and the slope of the emptying phase between the end of the lag phase and 100 min were calculated (Horowitz et al 1991). The lag phase was determined visually by the frame preceding that in which activity was first seen in the proximal small intestine (Collins et al 1983). The 50% emptying time (T50) for the proximal stomach and the maximum content of the distal stomach (Dmax) were also derived (Collins et al 1991). The T50 of the solid component from the total stomach was not used as in many patients the T50 was not reached in the study period. For the liquid component, the amounts remaining in the total, proximal and distal stomach at 10 and 30 min after meal completion were calculated. For the total and proximal stomach the T50 and for the distal stomach, the maximum retention were also obtained (Collins et al 1991).

13.3.6 *Statistical analysis*

Gastric emptying and intragastric distribution were considered to be abnormal when values were outside the range obtained in the control group. Data are shown as median values and ranges and were evaluated using the Mann-Whitney U-test and linear regression analysis. A p value <0.05 was considered significant.

13.4 RESULTS

All subjects tolerated the study well and none became hypoglycaemic. In one patient the plasma glucose results were lost.

13.4.1 *Gastrointestinal symptoms , diabetic complications and glycaemic control*

The median score for upper gastrointestinal symptoms was 2 (0-15). Eight patients suffered from constipation (<two bowel actions/week), six from diarrhoea and seven from faecal incontinence. 36 (42%) of the diabetic patients had autonomic neuropathy (total score ≥ 3) and 36 (42%) had peripheral neuropathy. 31 (36%) of the diabetic patients had no retinopathy, 26 (30%) had background retinopathy and 29 (34%) had proliferative retinopathy. The median HbA_{1c} in the diabetic patients was 9.3% (3.6-16.0%). Five patients were within the normal range (3.5-6.0%), 36 patients were in the range 6.1% - 9.0%, 33 patients were in the range 9.1%-12.0% and 12 patients had values >12.0%. In 37 (43%) of the diabetics mean plasma glucose during the gastric emptying measurement was ≤15mmol/L. There was a significant ($r>0.22$, $p<0.05$) relationship between HbA_{1c} and plasma glucose at all time intervals. When patients were divided into those who had a mean plasma glucose ≤ 15 mmol/L (37 patients) or > 15 mmol/L (48 patients), HbA_{1c} was

related to mean plasma glucose in the latter ($r=0.39$, $p<0.01$) but not the former ($r=0.005$, NS) group.

When the diabetic patients were divided into the two subgroups (IDDM and NIDDM), there was no difference in mean plasma glucose concentrations 17 mmol/L (5.2 - 29.7) vs 13.7 mmol/L (7.7 - 22.5). 26 of the 65 IDDM patients had a mean plasma glucose $\leq$15 mmo/L and 11 of the 20 NIDDM patients. There was also no significant relationship between either the duration of diabetes or other diabetic complications and the mean plasma glucose in either group.

13.4.2 *Gastric emptying*

Total stomach

There was a significant delay in gastric emptying of both solid and liquid components of the meal in the diabetic patients. For the solid meal, both the lag phase (35 min (7 - 100)) vs (24 min (3 - 63)) $p<0.05$) and the retention at 100 min ($p<0.001$) were delayed (Figure 13.1). The retention of the solid meal at 100 min was increased in 49 (57%) patients and decreased in 2. There was a significant relationship between the duration of the lag phase and the retention of the solid meal at 100 minutes ($r=0.55$, $p<0.001$). There was no significant difference (0.68%/min (0.12 - 1.45) vs 0.75%/min (0.6 - 1.22), $p=0.12$) in the slope of the solid emptying phase between the diabetic and control groups. There was no significant difference between IDDM and NIDDM patients in the retention of the solid meal at 100 min (56% (0 - 100) vs 60% (28 - 83)).

The retention of liquid at 10 min was not significantly different between the diabetic and control groups (82% (38 - 100) vs 79% (53 - 94, $p=0.21$) but the retention at 30 min (52% (14 - 100) vs 44% (25 - 64), $p<0.05$) was increased in 29 (34%) of

the patients. The liquid T50 was delayed in 23 (28%) and more rapid in 3 (3%) of the diabetics (Figure 13.1). There was a significant relationship between rates of solid and liquid emptying ($r=0.42$, $p<0.01$). As assessed by the retention of solid at 100 minutes and the T_{50} for liquid, 16 (19%) patients had a delay in both solid and liquid emptying, 7 (8%) had normal solid but delayed liquid emptying and 30 (35%) had normal liquid but delayed solid emptying (Figure 13.2) i.e. in 62% either solid and/or liquid gastric emptying was delayed.

Intragastric distribution

Intragastric meal distribution was frequently abnormal. For the solid component both the proximal stomach retention at 100 min ($p<0.05$) and the proximal stomach T50 (40 min (4 - 120) vs 26 min (6 - 65) $p<0.05$) were delayed. The proximal stomach retention at 100 min was greater than normal in 15 (17%) patients (Figure 13.3). The proximal T50 for the liquid component was also delayed ($p<0.005$) with 28 (33%) of patients having values greater than the normal range (Figure 13.3). The retention of solid in the distal stomach at 100 min ($p<0.02$) (Figure 13.4) and Dmax (54% (20-89) vs 46% (2-71), $p<0.05$) were both greater in the diabetics. The retention in the distal stomach at 100 min was increased in 23 (27%) of the diabetics. There was no significant difference between the control subjects and patients in the retention of liquid in the distal stomach at either 10 min (40% (9 - 65) vs 42% (18 -65) ns) or 30 min (25% (6 - 44) vs 28% (6 - 64); NS) (Figure 13.4). For the solid meal there was an inverse relationship between the proximal stomach T50 and both the retention in the distal stomach at 100 min ($r=-0.35$, $p<0.001$) and Dmax ($r=-0.45$, $p<0.0001$). There was also a significant relationship between the proximal stomach T50 and Dmax for the liquid meal ($r=0.27$, $p<0.05$).

13.4.3 *Relationships between total stomach emptying and intragastric distribution*

There was a relationship between the lag phase and the retention of the solid meal in the proximal stomach at 100 min ($r=0.53$, $p<0.001$). At 100 min there were significant relationships between the retention of the solid meal in the total and both the proximal ($r=0.70$, $p<0.0001$) and distal stomach ($r=0.62$, $p<0.0001$) (Figures 13.5 and 13.6). There was also a relationship between retention of solid in the total stomach at 100 min and solid Dmax ($r=0.35$, $p<0.001$). At 100 min both total and proximal stomach emptying were delayed in 15 (17%) of the patients. 32 (37%) had normal proximal stomach, but delayed total stomach, emptying. In all patients with normal total stomach emptying the retention in the proximal stomach was also normal (Figure 13.5). At 100 min total and distal stomach emptying of solids were both delayed in 21 (24%) of the patients. 25 (29%) had normal retention in the distal stomach, but delayed total stomach emptying and in 2 patients there was normal total stomach emptying, but marginally increased retention in the distal stomach (Figure 13.6).

There were significant relationships between the total stomach T50 for liquid and both the proximal stomach T50 ($r=0.48$, $p<0.001$) (Figure 13.5), the retention in the distal stomach at 30 min ($r=0.71$, $p<0.001$) (Figure 13.6) and Dmax ($r=0.27$, $p<0.05$) For the total and proximal stomach the T50 for liquid was delayed in 12 (14%) patients. 9 (10%) had delayed total stomach, but normal proximal stomach emptying and 15 (17%) with normal total stomach emptying had delayed emptying from the proximal stomach. In 3 subjects delayed emptying from the total stomach was associated with normal proximal stomach emptying (Figure 13.5). At 30 min both total and distal stomach emptying were delayed for liquid in 10 (12%) diabetic patients. 16 (19%) had delayed total stomach emptying but normal retention in the distal stomach. None of the patients with normal total stomach emptying of liquid

had abnormal retention in the distal stomach. 3 (3%) of the patients with normal distal stomach retention had delayed emptying of liquid from the total stomach (Figure 13.6).

13.4.4 *Relationship between diabetic complications, gastrointestinal symptoms and gastric emptying*

Gastrointestinal symptoms ($r=0.26$, $p<0.05$), retinopathy ($r=0.47$, $p<0.001$) and peripheral neuropathy ($r=0.38$, $p<0.001$) were all related to the duration of known diabetes. The score for autonomic nerve dysfunction was related to age ($r=0.28$, $p<0.01$), but not the duration of diabetes ($r=0.18$, NS). There were significant relationships between solid (lag phase, retention at 100 min, but not the post-lag emptying phase or liquid, gastric emptying and the scores for autonomic nerve function ($r>0.35$, $p<0.001$), peripheral neuropathy ($r>0.31$, $p<0.01$) and gastrointestinal symptoms ($r>0.32$, $p<0.01$). The retention of solid in the distal ($r=0.22$, $p<0.05$), but not the proximal stomach ($r=0.20$, $p<0.1$), at 100 min was also related to the score for gastrointestinal symptoms. The retention of solid in the proximal ($r=0.31$, $p<0.005$), but not in the distal stomach ($r=0.15$, NS), at 100 min was related to the score for autonomic nerve dysfunction. There was no significant relationship between intragastric distribution of liquid and gastrointestinal symptoms.

13.4.5 *Relationships between plasma glucose concentrations, gastric emptying and gastrointestinal symptoms*

Liquid, but not solid, emptying from the total ($p<0.05$) and proximal ($p<0.01$) stomach was slower in those patients with a mean plasma glucose > 15 mmol/l when compared to those with a mean glucose ≤15 mmol/L. (Table 13.1). The

retention of liquid in the distal stomach at 30 min was not different between these two groups. In those patients with a mean plasma glucose ≤ 15 mmol/l there was a strong inverse relationship between liquid (T50), but not solid, emptying and the change in plasma glucose from baseline at both 30 min ($r=-0.70$, $p<0.001$) and 60 min ($r=0.53$, $p<0.001$) (Figure 13.7). Similarly, the plasma glucose at 30 min was inversely related to the retention of the liquid in both the total ($r=-0.41$, $p<0.01$) and proximal ($r=-0.32$, $p<0.05$) stomach, but not to solid emptying. Similar correlations were evident in IDDM and NIDDM subgroups with significant relationships between the liquid T50 and the rise in plasma glucose from baseline at 30 min, ($r=0.25$, $p<0.05$ and $r=0.71$, $p<0.001$ repectively). In patients with a mean plasma glucose >15 mmol/L there was no significant relationship between gastric emptying and either the change in plasma glucose from baseline or the absolute plasma glucose concentration (Figure 13.7). Gastrointestinal symptoms were related to solid ($r=0.38$, $p<0.05$), but not liquid ($r=0.30$, NS), emptying in patients whose mean plasma glucose was ≤ 15 mmol/l. Similarly, in those patients with mean plasma glucose levels > 15 mmol/l, symptoms were related to solid ($r=0.28$, $p<0.05$), but not liquid ($r=0.004$, NS), emptying.

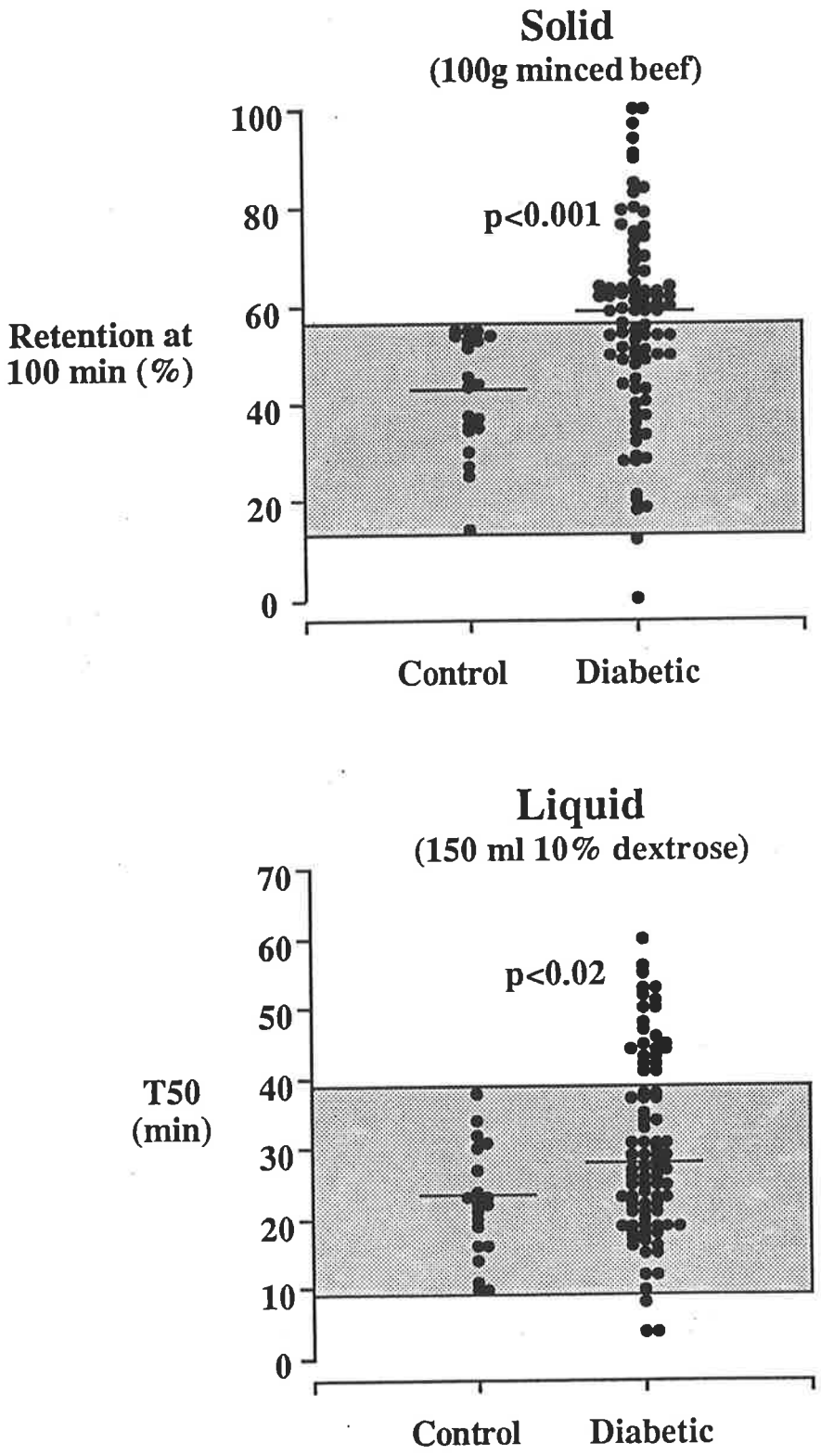

Figure 13.1: Gastric emptying of solid(% retention at 100 min) and liquid (T50) in normal subjects and patients with diabetes mellitus. The horizontal lines represent median values.

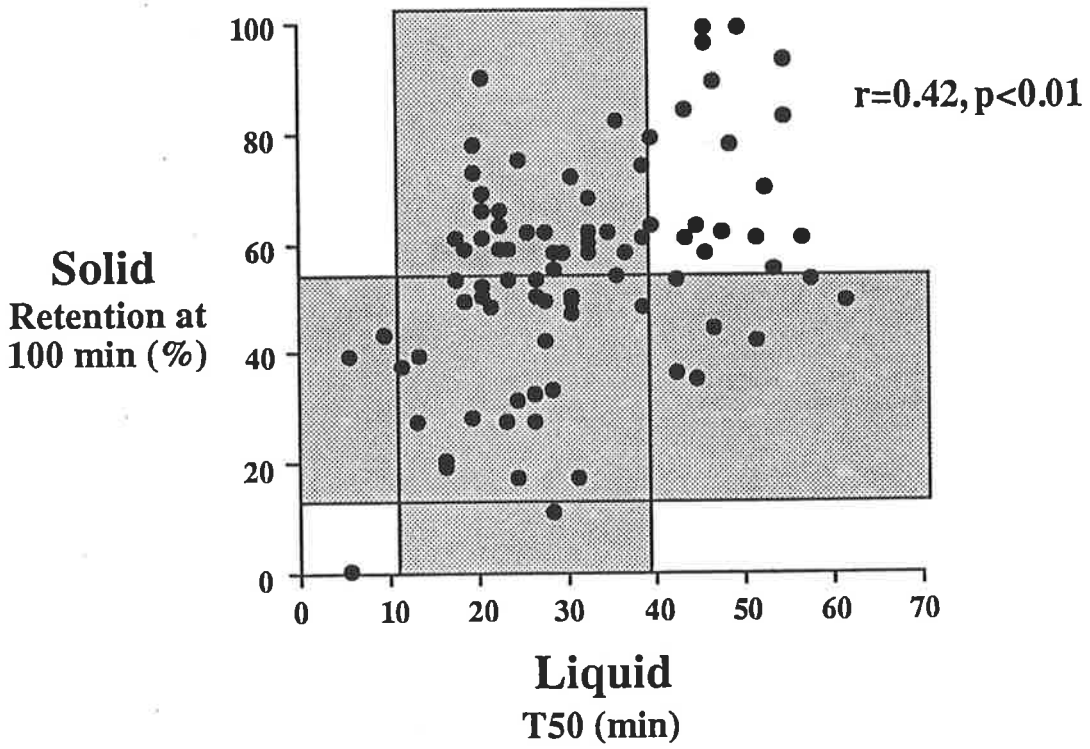

Figure 13.2: Relationship between solid (% retention at 100 min) and liquid (T50) gastric emptying in the diabetic patients. The ranges in normal subjects are shown in the shaded areas.

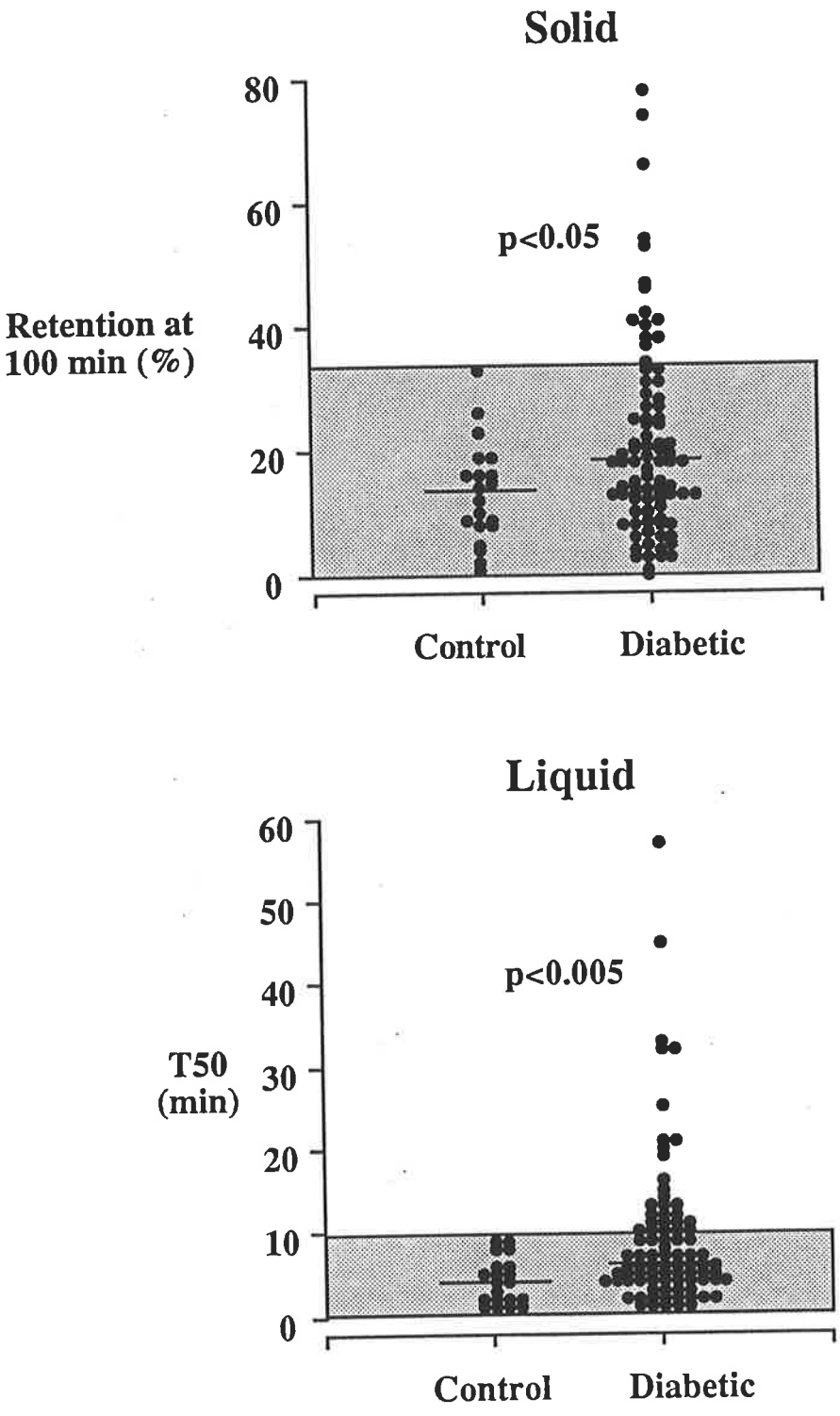

Figure 13.3: Proximal stomach emptying of solid (% retention at 100 min) and liquid (T50) in normal subjects and patients with diabetes mellitus. The horizontal lines represent median values.

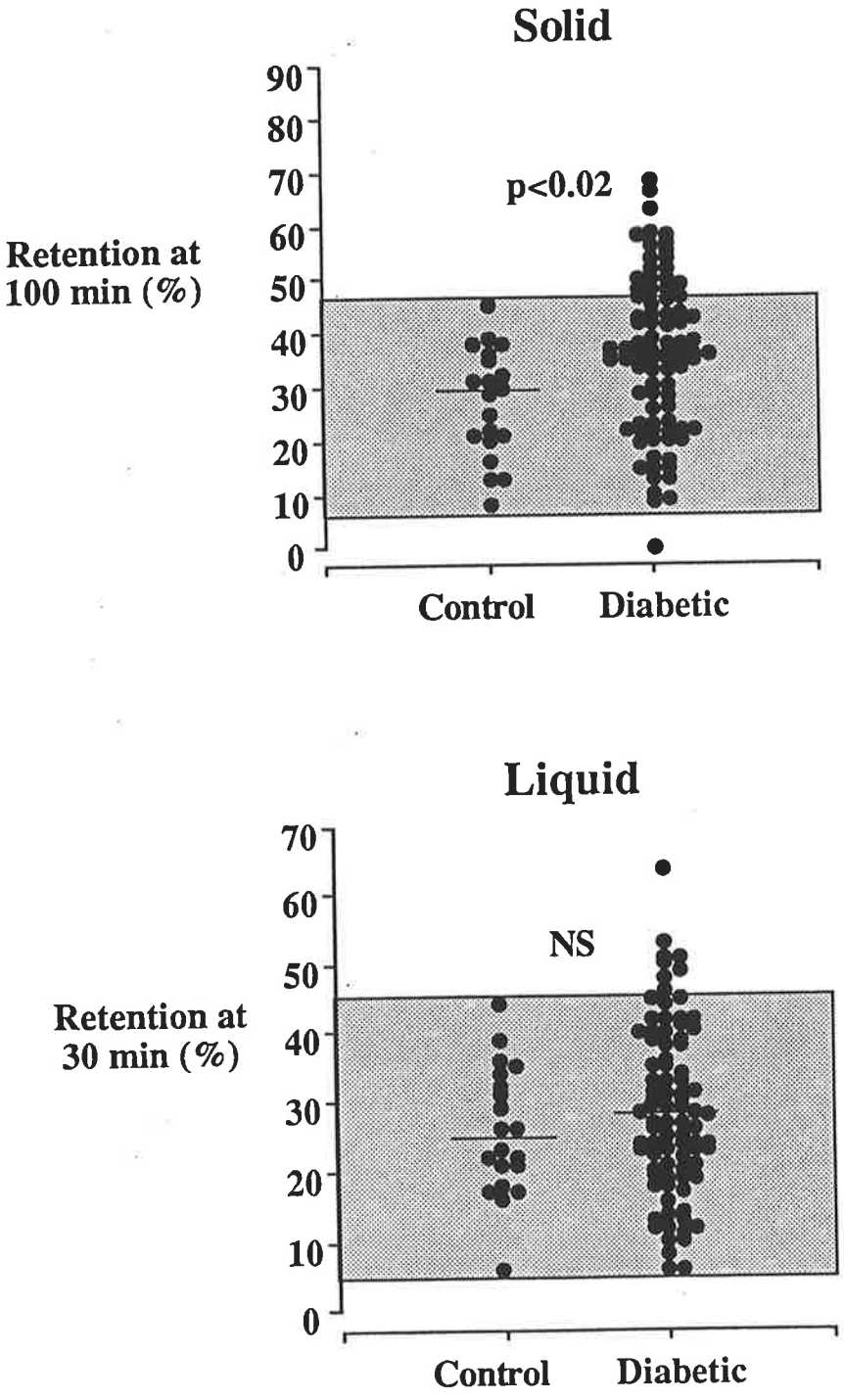

Figure 13.4: Distal stomach retention of solid (% retention at 100 min) and liquid (% retention at 30 min) in normal subjects and patients with diabetes mellitus. The horizontal lines represent median values.

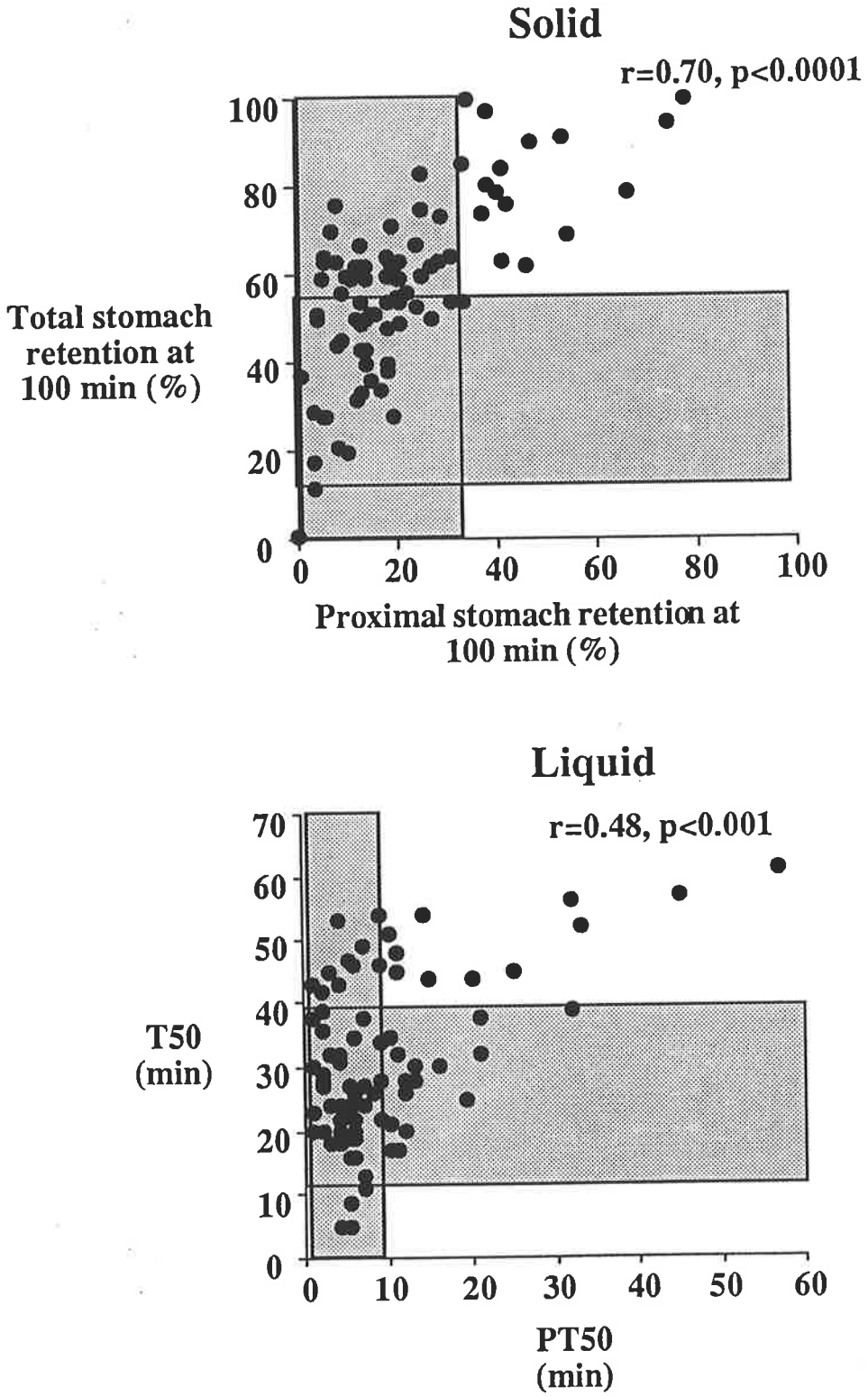

Figure 13.5: Relationship between the retention in the total and proximal stomach for the solid (% retention at 100 min) and the liquid (T50) meal in the diabetic patients. The ranges in normal subjects are shown in the shaded area.

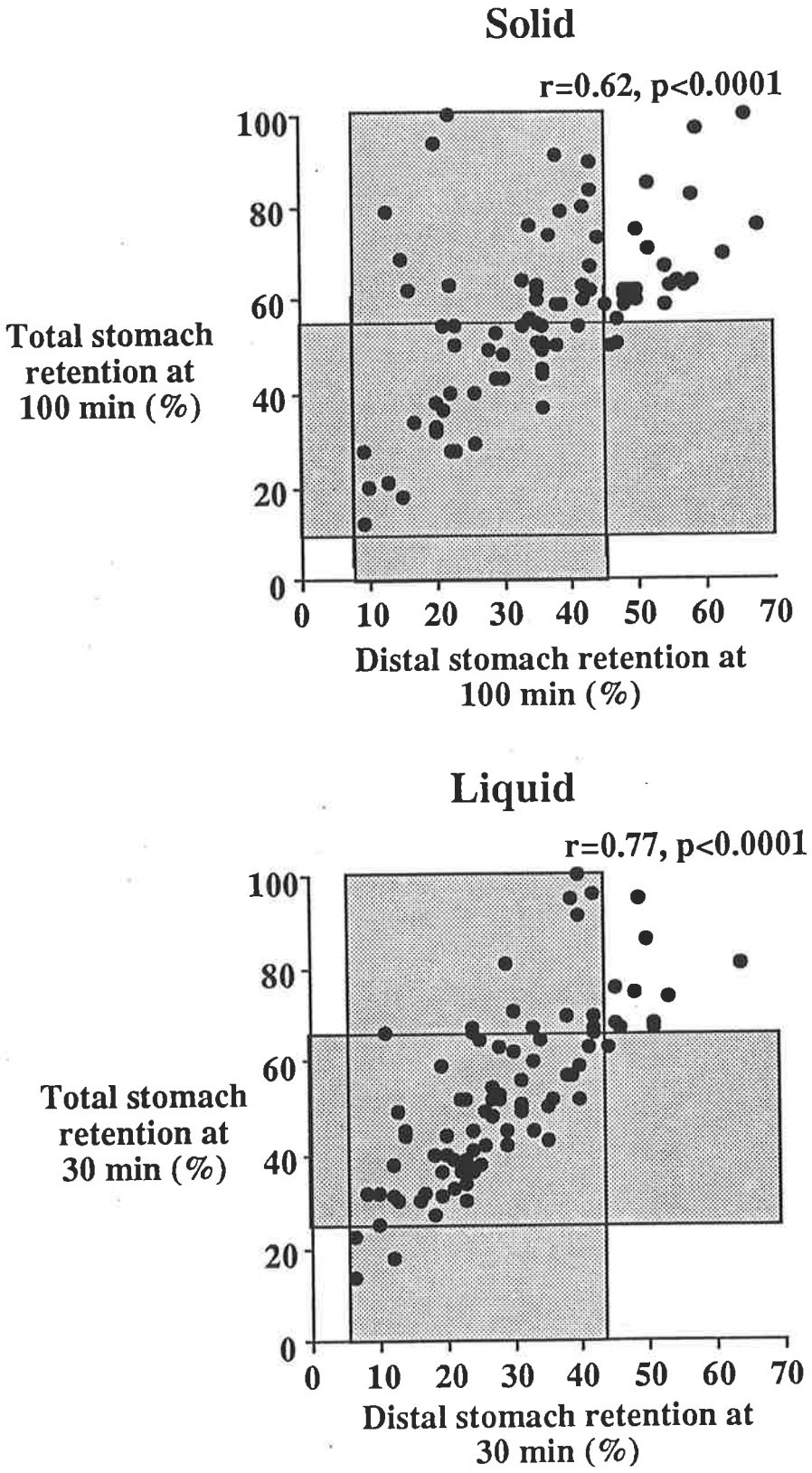

Figure 13.6: Relationship between the retention in the total and distal stomach for the solid (% retention at 100 min) and liquid (% retention at 30 min) meal in the diabetic patients. The ranges in normal subjects are shown in the shaded areas.

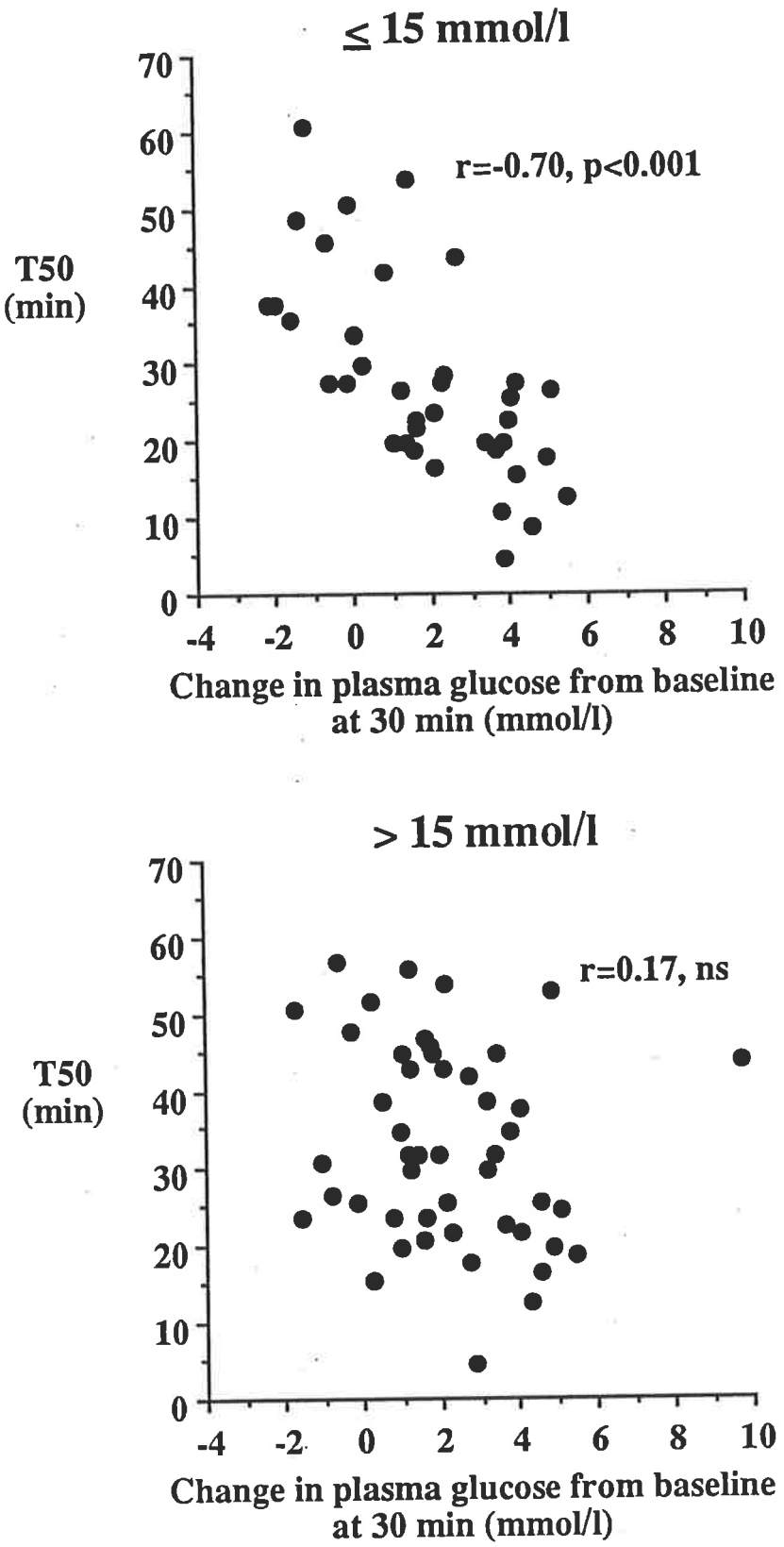

Figure 13.7: Relationship between the change in plasma glucose from baseline at 30 minutes and gastric emptying of liquid (T50) in diabetic patients divided into those with a mean plasma glucose concentration during the gastric emptying measurement ≤15 mmol/L or >15 mmol/L.

Table 13.1: Gastric emptying in 85 patients with diabetes mellitus divided into those with a mean blood glucose concentration during the gastric emptying study ≤ 15mmol/l or > 15 mmol/l. Data are median values and ranges in parentheses

	≤ 15 mmol/l	> 15 mmol/l	P
number of subjects	37	48	
Total Stomach Emptying			
Solid retention at 100 min	(%)59 (0-100)	59 (18-100)	NS
Solid lag phase (min)	33 (9-100)	38 (7-100)	NS
Slope of solid G.E. (%/min)	0.72 (0.12-1.26)	0.67 (0.33-1.45)	NS
Liquid retention at 30 min (%)	45 (14-95)	58 (18-100)	<0.01
Liquid 50% emptying time (min)	27 (5-61)	32 (5-57)	<0.05
Proximal Stomach Retention			
Solid retention at 100 min (%)	16 (0-78)	20 (1-74)	NS
Liquid retention at 30 min (%)	18 (7-56)	25 (6-60)	<0.01
Liquid T50 (min)	6 (1-57)	7 (1-45)	<0.05
Distal Stomach Retention			
Solid retention at 100 min (%)	36 (0-68)	35 (13-66)	NS
Liquid retention at 30 min (%)	28 (6-53)	27 (10-64)	NS

13.5 DISCUSSION

Our results indicate in patients with diabetes mellitus that: (i) there is a relatively weak relationship between gastric emptying of solid and nutrient-containing liquid meal components, (ii) evaluation of intragastric meal distribution does not have a major impact on the ability of radionuclide techniques to detect disordered gastric motility or predict gastrointestinal symptoms and (iii) the relationship between gastric emptying and blood glucose concentrations may be direct or inverse, depending on the blood glucose concentration.

Scintigraphic measurement of gastric emptying is at present the most precise and clinically applicable method to evaluate gastric motility in diabetics (Horowitz & Fraser 1994, Lartigue et al 1994). This study has confirmed that gastric emptying is abnormal in more than 50% of cases and that there is a poor relationship between emptying of solids and liquids (Wegener et al 1990, Horowitz et al 1991). The latter observation indicates the need to use a test meal containing discretely labelled solid and nutrient liquid components when gastric emptying is evaluated in patients with diabetes. The diabetic and control groups in this study were not ideally matched, but it is unlikely that the differences in age, body weight and sex influenced the observations (Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991). In particular, with the same methodology as this study there is no significant difference in gastric emptying between males and females (Horowitz et al 1984a, Horowitz et al 1985b). The suggestion that disordered gastric motility in patients with diabetes predominantly affects gastric emptying of solids (Loo et al 1984, Wright et al 1985) probably reflects the use of non-nutrient liquids, such as water, in the test meal, which do not stimulate mechanisms which retard gastric emptying.

The demonstration that the intragastric distribution of solid and liquid components is frequently abnormal in patients with diabetes is not unexpected. Urbain et al reported, in a relatively small cohort of patients with diabetes, that the retention of a solid meal in the proximal stomach was increased, consistent with the observations from this study (Urbain et al 1993). In this study, in virtually all cases, abnormal intragastric distribution of solids was associated with delay in emptying from the total stomach. In contrast, evaluation of the retention of liquid in the proximal (but not the distal) stomach increased the detection of disordered gastric motility in that increased retention of liquid in the proximal stomach was associated with normal emptying from the total stomach in 17% of patients. It should be recognised that measurement of the retention of isotope in the distal stomach has limitations in that it is influenced by the rate of emptying into the small intestine, as well as filling from the proximal stomach.

The mechanical dysfunctions leading to delayed gastric emptying in patients with diabetes are poorly understood. The rate of gastric emptying is related to the relationship between contractions generated by the fundus, antrum, pylorus and proximal small intestine (Horowitz & Dent 1991). It is now clear that the gastric motor abnormalities in diabetic gastroparesis are widespread, may reflect the blood glucose concentration and do not just involve the antrum (Camilleri & Malagelada 1984, Oliveira et al 1984, Achem-Karam et al 1985, Tack et al 1992, Fraser et al 1993c). Because no studies have measured motor events in the proximal stomach, antrum, pylorus and duodenum simultaneously with transpyloric flow, there is considerable uncertainty about the relative contribution of regional abnormalities of motor function to disordered gastric emptying. It is therefore difficult to speculate on the aetiology of the poor relationship between gastric emptying of solid and nutrient liquid meal components in diabetic patients. Solid food is normally ground into small particles (< 1mm in size) before entering the small intestine and the time

taken for trituration appears to be a major rate limiting step, so that solids can be considered to empty from the stomach at "maximum" rates (Lin et al 1992). In contrast, feedback from small intestinal luminal receptors is the major factor regulating gastric emptying of nutrient-containing liquids and triturated solids (Hunt et al 1985, Horowitz et al 1993). It is of interest that gastric emptying of solid, but not liquid was related to the severity of cardiovascular autonomic nerve dysfunction, albeit weakly, suggesting that "irreversible" autonomic neuropathy may affect the grinding function of the antrum. This concept is supported by the observation that the severity of autonomic nerve dysfunction was related to the duration of the lag phase for the solid meal, but not post-lag emptying rate or gastric emptying of liquid.

In diabetes the aetiology of upper gastrointestinal symptoms, which are presumed to result primarily from disordered gastrointestinal motility, is poorly understood. Despite the frequent occurrence of gastrointestinal symptoms, both total stomach emptying and intragastric meal distribution correlated weakly with symptom severity and only for the solid component of the meal. This observation is not surprising (Loo et al 1984, Horowitz et al 1986a, Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991) and inevitably leads to the conclusion that abnormal gastric emptying and intragastric meal distribution should be regarded as markers of gastroduodenal motor abnormality, rather than the direct cause of symptoms. In considering the etiology of symptoms abnormal gastric myoelectrical activity (Koch et al 1989), disordered esophageal and intestinal motility (Wegener et al 1990, Horowitz et al 1991), psychiatric dysfunction (Clouse & Lustman 1989) and abnormal sensory feedback from luminal receptors in the stomach or small intestine (Horowitz & Dent 1991) may all play a role.

Our observations support the concept that the blood glucose concentration has a major influence on gastric motility in diabetes (Fraser et al 1990, Horowitz et al 1991, Schwarcz et al 1993, Lartigue et al 1994). Significant hyperglycaemia (~15 mmol/L) has been shown to suppress antral pressure waves and stimulate pressure waves which are localised to the pylorus (Fraser et al 1991). Gastric emptying and gastric motility may be influenced by more modest elevation of plasma glucose within the physiological range (Barnett & Owyang 1988, Horowitz et al 1993). Clearly studies, of gastric emptying in diabetic patients, must take into account the blood glucose concentrations, which should ideally be stabilised in the euglycaemic range (Tack et al 1992).

In addition to these previously described effects of blood glucose on gastric motility and emptying in patients with diabetes, a reciprocal effect of gastric emptying on the blood glucose in both IDDM and NIDDM patients has been shown in this study. This study is the first to demonstrate in diabetes (predominately IDDM patients) a relationship between gastric emptying and the postprandial blood glucose response to oral carbohydrate. Although the liquid meal contained only a relatively small amount of carbohydrate (15 g dextrose), and all IDDM patients took their normal insulin dose before consumption of the test meal, there was a strong relationship between the rate of liquid gastric emptying and the rise in blood glucose in those subjects in whom the mean blood glucose during the gastric emptying measurement was $\leq$ 15 mmol/L. Because of deficient counter-regulatory responses, gastric emptying would be expected to have a greater effect on oral glucose tolerance in diabetics, particularly IDDM patients, than in normal subjects (Horowitz et al 1993) and such a relationship is likely to be more evident when preprandial blood glucose concentrations are low and meal carbohydrate content is high. The observations of this study are consistent with the hypotheses (Horowitz & Fraser 1994) that the rate of gastric emptying plays a significant role in determining the glycaemic response to

meals in patients with diabetes mellitus, and that disordered gastric emptying may contribute to, as well as result from, poor glycaemic control.

CHAPTER 14

GASTRIC EMPTYING IN "EARLY" NON-INSULIN DEPENDENT DIABETES MELLITUS

14.1 SUMMARY

The aims of this study were to determine in "early" non insulin-dependent diabetes mellitus (NIDDM): (i) the prevalence of disordered gastric emptying of glucose, (ii) the relationship between the blood glucose response to an oral glucose load and gastric emptying and (iii) the relationship between appetite and gastric emptying.

Sixteen patients (age 39-79 yr) with recently diagnosed NIDDM consumed 350 ml water containing 75 g glucose and ^{99m}Tc sulphur colloid while sitting in front of a gamma camera. Blood glucose concentrations were monitored immediately before and after the drink. Hunger and fullness were evaluated using visual analogue scales. Results were compared to those obtained in 13 normal subjects of similar age and body mass index. All patients and control subjects were Caucasian and not Hispanic.

Gastric emptying was slightly slower in the NIDDM patients when compared to the control subjects (retention at 180 min 15.9 ± 2.3% vs 3.8 ± 1.0%, $p<0.001$), but there was no significant difference in the 50% emptying time between the two groups. In the NIDDM patients there was an inverse relationship between the magnitude of the increase in the blood glucose concentration and gastric emptying e.g. between the area under the curve for blood glucose between 0-60 min and the intragastric retention of the drink at 60 min ($r=-0.60$, $p<0.05$). In the NIDDM patients, fullness was greater ($p<0.005$) both before and after the drink and the

score for hunger at 30 min was inversely related to the rate of gastric emptying ($r=-0.52$, $p<0.05$).

In patients with "early" NIDDM gastric emptying of 75 g glucose is similar to normal subjects and is a significant determinant of the glycaemic response.

14.2 INTRODUCTION

Disordered gastric motility is a frequent complication of diabetes mellitus (Horowitz & Fraser 1994). Cross-sectional studies of patients with "long-standing" (> ~3 years duration) diabetes mellitus indicate that gastric emptying of solid or nutrient liquid meals is delayed in about 50% of cases and that the prevalence of delayed emptying in insulin-dependent (IDDM) (Horowitz et al 1986a, Keshavarzian et al 1987, Lartigue et al 1994) and non-insulin-dependent diabetes mellitus (NIDDM) (Horowitz et al 1989a, Wegener et al 1990) is similar. While it is well recognised that in a minority of patients with longstanding diabetes mellitus gastric emptying, particularly that of liquids, is accelerated (Campbell et al 1980, Oliveira et al 1984, Horowitz et al 1991), Phillips et al have recently suggested that gastric emptying of a drink containing 50 g glucose is characteristically more rapid than normal in patients with "early" NIDDM (Phillips et al 1992). This conclusion was based on a comparison of 9 NIDDM patients, of whom the majority were of Hispanic origin, with 9 control subjects, all of whom were not Hispanic. As Schwartz et al have recently reported that gastric emptying of glucose is faster in non-diabetic Hispanic Americans when compared to non-diabetic, non-Hispanic Caucasian Americans (Phillips et al 1992), racial differences between the NIDDM and control groups may have contributed to the rapid gastric emptying observed in "early" NIDDM (Phillips et al 1992). We therefore wished to establish the prevalence of disordered gastric emptying of a glucose-containing drink in non-Hispanic Caucasian patients with

"early" NIDDM. A 75g, rather than 50g, glucose load (Phillips et al 1992) was used as the former is recommended by the World Health Organisation for the diagnosis of diabetes mellitus (Horowitz et al 1993).

The blood glucose response to oral carbohydrate is potentially dependent on many factors, including the rate at which carbohydrate enters the small intestine, the rate of digestion and intestinal absorption and the rate of insulin driven metabolism (Horowitz & Fraser 1994). An understanding of the relationship between the glycaemic response to carbohydrate and gastric emptying is therefore of fundamental importance to the treatment of diabetes mellitus. We, and others, have suggested that in IDDM disordered gastric emptying may contribute to poor glycaemic control by causing a mismatch between the onset of insulin action and the absorption of nutrients from the small intestine (Drenth et al 1992, Horowitz & Fraser 1994). In contrast, patients with NIDDM may theoretically benefit from retardation of gastric emptying, provided that carbohydrate is absorbed more slowly in coordination with the delayed insulin release characteristic of this disorder (Horowitz & Fraser 1994). The suggestion by Phillips et al that faster gastric emptying in NIDDM may worsen glycaemic control is consistent with this concept (Phillips et al 1992). We (Horowitz et al 1993) and others (Schwartz et al 1995) have reported in normal subjects that gastric emptying is a significant determinant of the rise in blood glucose after an oral glucose load. In IDDM patients, postprandial blood glucose concentrations are greater when gastric emptying is more rapid (Chapter 15, Stacher et al 1994) and in IDDM patients with gastroparesis, insulin requirement during the 120 min period following a meal is reduced (Ishii et al 1994). Although it may be expected that the rate of gastric emptying would have a substantial impact on the glycaemic response to oral carbohydrate in NIDDM, it has been suggested that the latter is primarily dependent on hepatic glucose release and does not correlate with gastric emptying (Butler & Rizza 1991, Frank et al 1995).

In this latter study gastric emptying of a mixed soild/liquid meal, containing 50g of carbohydrate as "Jell-O", was quantified (Frank et al 1995). We therefore sought to establish whether there is a relationship between blood glucose concentrations and gastric emptying of a drink containing 75g glucose in NIDDM.

Although the factors which influence appetite in humans are complex and poorly understood, recent studies suggest that both gastric distension (Bergmann et al 1992) and the extent of exposure of the small intestine to nutrients (Welch et al 1988, Chapter 10, Chapter 11) influence satiety. While it is well recognised that upper gastrointestinal symptoms occur frequently in patients with diabetes and correlate poorly with the rate of gastric emptying (Horowitz & Fraser 1994), to our knowledge, the relationship between appetite and gastric emptying in NIDDM has not been evaluated.

14.3 SUBJECTS AND METHODS

Sixteen patients with recently diagnosed non-insulin dependent diabetes mellitus (NIDDM), 11 male, 5 female, median age 57 yr (range 39 - 79) and median body mass index (BMI), defined as ($^{wt}/_{ht^2}$), 29 (range 22 - 36) were studied. The patients were randomly selected from ambulant outpatients presenting to the Royal Adelaide Hospital for treatment of NIDDM. In all cases the diagnosis of NIDDM, based on World Health Organisation criteria, had been established between 3 and 12 months previously. No patient had prior evidence of fasting hyperglycaemia and all were treated by diet alone. Patients taking oral hypoglycaemic drugs, antihypertensive agents or any medication known to affect gastrointestinal motility were excluded. None of the patients had retinopathy and the plasma creatinine concentration was within the normal range (0.05 - 0.12 mmol/L). In all cases glycosylated haemoglobin was >7.0% at the time of diagnosis of diabetes

(Horowitz et al 1991) and at the time of the study glycosylated haemoglobin was 7.5 ± 0.6 mmol/L. Results in the NIDDM group were compared to those obtained in 13 normal volunteers (8M, 5F), median age 48 yr (range 40 - 68) and median BMI 25 (range 20 - 35). None of the control subjects was taking medication known to influence gastrointestinal motility, had gastrointestinal symptoms or a history of gastrointestinal disease. There was no significant difference in age or BMI between the patients and the control subjects. All the NIDDM and control subjects were Caucasian and none was Hispanic.

14.3.1 *Experimental protocol*

Each subject was evaluated for upper gastrointestinal symptoms (Horowitz et al 1991) and then underwent concurrent measurements of gastric emptying (Collins et al 1983), blood glucose concentrations and appetite (Chapter 10, Chapter 11). The gastric emptying measurement was commenced at about 1000 h after an overnight fast (14h for solids and 12h for liquids). Smoking was prohibited on the study day. A cannula was placed in an antecubital vein for blood sampling and the subject was seated with their back against a gamma camera. After completion of these measurements cardiovascular autonomic nerve function was evaluated (Ewing & Clarke 1982). Written informed consent was obtained from each participant and the study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

14.3.2 *Assessment of upper gastrointestinal symptoms*

Upper gastrointestinal symptoms were assessed on entry into the study by questionnaire (Horowitz et al 1991). The following symptoms: anorexia, nausea, early satiety, bloating, vomiting, abdominal pain, dysphagia, heart burn and acid

regurgitation were graded: 0=none, 1=mild, 2=moderate or 3=severe, for a maximum score of 27. The frequency and consistency of bowel actions, as well as the presence or absence of nocturnal diarrhoea and faecal incontinence were also evaluated. Constipation was defined as ≤ 2 spontaneous bowel actions each week (Horowitz et al 1991).

14.3.3 *Measurement of gastric emptying and intragastric distribution*

Each subject drank 350 ml of water containing 75 g glucose and 20 MBq ^{99m}Tc - sulphur colloid within one minute. Radioisotopic data were acquired in 30 sec frames for the first 30 min and subsequently in three min frames, for a further 150 min. Time zero was defined as the time of completion of the drink. Data were corrected for subject movement, radionuclide decay and gamma ray attenuation using previously described methods (Collins et al 1983). Regions-of-interest (ROI's) for the total, proximal and distal stomach were drawn, with the proximal stomach ROI corresponding to the fundus and proximal corpus and the distal stomach ROI to the antrum and distal corpus (Collins et al 1988). Gastric emptying curves (expressed as % of the maximum content of the total stomach) were derived for total, proximal and distal stomach ROI's. The content of the total, proximal and distal stomach at 0, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min was calculated. For the total stomach the duration of the lag phase and the 50% emptying time (T50) were also obtained. The lag phase was determined visually as the time before any of the drink had entered the proximal small intestine (Collins et al 1983).

14.3.4 *Measurement of blood glucose concentrations*

Venous blood samples were obtained immediately before (-2 min) ingestion of the drink and then at 10, 15, 30, 45, 60, 90, 120, 150 and 180 min. Blood glucose concentrations were immediately determined using a portable blood glucose meter (MediSense Companion 2 meter; MediSense Inc., Waltham, MA) and the accuracy of these measurements was confirmed with the hexokinase method. The incremental areas under the blood glucose concentration/time curve (AUC) between 0-30 min, 0-60 min, 0-90 min and 0-120 min were calculated using the trapezoidal rule.

14.3.5 *Assessment of appetite*

Hunger and fullness were evaluated using a validated visual analogue questionnaire. Subjects placed a vertical mark along a 100mm line to indicate strength of the sensation. Measurements were obtained immediately before ingestion of the drink and at 15, 30, 60, 90, 120 and 180 min. Full details of this questionnaire have been published (Sepple & Read 1989).

14.3.6 *Assessment of autonomic nerve function*

Autonomic nerve function was assessed using standardised cardiovascular reflex tests (Ewing & Clarke 1982, Horowitz et al 1991). Parasympathetic function was calculated by the variation (R - R interval) of the heart rate during deep breathing and the immediate heart rate response to standing ("30:15" ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test results was scored as 0=normal, 1=borderline or 2=abnormal. A total score of $\geq$ 3 was considered to indicate definite autonomic nerve damage (Horowitz et al 1991, Chapter 13).

14.3.7 *Statistical analysis*

Data were evaluated using repeated measures analysis of variance (ANOVA) and are shown as mean values ± SEM. Relationships between gastric emptying, intragastric distribution, appetite, blood glucose concentrations, gastrointestinal symptoms and autonomic nerve function were assessed using linear regression analysis. Comparison of the slopes of the regressions between the blood glucose concentration and gastric emptying in the control subjects and patients with diabetes mellitus was done using Student's t-test (Armitage & Berry 1987). A p value < 0.05 was taken to indicate significance.

14.4 RESULTS

All subjects tolerated the study well and there were no untoward events. None of the NIDDM patients or the control subjects experienced nausea after the glucose drink. The median score for upper gastrointestinal symptoms in the NIDDM patients was 2 (range 0 - 9), whereas none of the normal subjects experienced symptoms ($p<0.001$). None of the patients with NIDDM suffered from constipation, diarrhoea or faecal incontinence. Four patients had definite autonomic neuropathy and the median score for the entire group was 2 (range 0 - 4). None of the control subjects had evidence of autonomic neuropathy. Blood glucose concentrations, including peak blood glucose, were higher ($p<0.001$) in the NIDDM patients both before and after the glucose load (Figure 14.1). The magnitude of the rise in blood glucose from baseline was greater in the NIDDM patients than the control subjects at all time points (Figure 14.1). The timing of peak blood glucose was later (92.8 ± 7.7 min vs 45.6 ± 4.5 min, $p<0.0001$) in the NIDDM patients.

14.4.1 *Gastric emptying and intragastric distribution*

Gastric emptying approximated an overall linear pattern after a short lag phase in both the NIDDM patients and control subjects. There was no difference in the lag phase between the two groups (1.8 ± 0.3 min vs 2.7 ± 0.7 min). Although there was no difference in the T50 (95 ± 7.3 min vs 89 ± 7.9 min), at both 150 min ($p<0.01$) and 180 min ($p<0.001$) more of the drink remained in the stomach in the NIDDM patients (Figures 14.2 and 14.3). There was a trend ($p=0.06$) for greater retention of the drink in the proximal stomach in the NIDDM patients at 180 min (Figure 14.3). At 150 min ($p<0.01$) and 180 min ($p<0.01$) the retention of the drink in the distal stomach was greater in the NIDDM patients (Figure 14.3).

14.4.2 *Relationships between total stomach emptying and intragastric distribution*

There were inverse relationships between the content of the proximal and distal stomach in NIDDM patients at 15, 30, 45 and 60 min, ($r>-0.67$, $p<0.005$) and control subjects at 10, 15, 30 and 45 min ($r>-0.66$, $p<0.05$). There were direct relationships between emptying from the total and proximal stomach in both NIDDM and control subjects e.g. between the total stomach T50 and the retention in the proximal stomach at 120 min, $r= 0.86$, $p<0.0001$ and $r= 0.70$, $p<0.01$ respectively. In the NIDDM patients there were relationships between the retention in the total and distal stomach at 150 min ($r= 0.59$, $p<0.05$) and 180 min ($r=0.62, p<0.05$). In the control subjects there were relationships between the retention in the total and distal stomach at 90, 120, 150 and 180 min ($r>0.63$, $p<0.05$).

14.4.3 *Relationships between gastrointestinal symptoms, autonomic nerve function and gastric emptying*

There were no significant relationships between the score for upper gastrointestinal symptoms and either age, BMI, the score for autonomic nerve dysfunction, gastric emptying or intragastric distribution. There was a relationship between the score for autonomic nerve dysfunction and age ($r=0.59$, $p<0.05$).

14.4.4 *Relationships between blood glucose concentrations and gastric emptying*

In the normal subjects, there were direct relationships between the immediate postprandial rise in blood glucose and gastric emptying e.g. the blood glucose concentration at 10 min was related to the T50 ($r=-0.57$, $p<0.05$) (Horowitz et al 1993). In the NIDDM patients there were direct relationships between blood glucose concentrations after the drink and gastric emptying e.g. blood glucose concentrations at 10, 15, 30, 45, 60 and 90 min, peak blood glucose, AUC 0-60 min and AUC 0-120 min were related ($r>-0.51$, $p<0.05$) to the T50. Similarly, the blood glucose concentration at 60 min and the AUC 0-60 min were inversely related to the retention of glucose in the stomach at 60 min (Figure 14.4). The slope of the regression between the blood glucose and gastric emptying (e.g. blood glucose at 10 min and T50) was greater ($p<0.05$) in the patients with NIDDM than the control subjects (Figure 14.5). There was no significant relationship between HbA_{1c} and gastric emptying.

14.4.5 *Hunger and fullness*

Hunger decreased after the drink in the NIDDM patients ($p<0.05$), but not significantly ($p=0.06$) in the control subjects (Figure 14.6a). At 180 min hunger

was greater than baseline in both NIDDM patients ($p<0.05$) and control subjects ($p<0.0001$), but the score was lower ($p<0.05$) in NIDDM patients.

At baseline the score for fullness was greater ($p<0.01$) in the NIDDM patients than the control subjects (Figure 14.6b). There was an increase in fullness after the drink in the control subjects ($p<0.05$) but not the NIDDM patients. Although postprandial fullness was greater in the NIDDM patients at all times ($p<0.05$) there was no significant difference between the two groups in the magnitude of the change in fullness from baseline.

14.4.6 *Relationships between appetite, gastric emptying and blood glucose concentrations*

In NIDDM patients there was a relationship between hunger and the retention of the drink in the stomach, so that the scores for hunger at 30 min ($r=0.52$, $p<0.05$) and at 60 min ($r=0.56$, $p<0.05$) were related to the retention of the drink in the stomach at these times. There was no significant relationship between hunger and gastric emptying in the control subjects. There was no relationship between fullness and gastric emptying in either the NIDDM or control groups. There were also no relationships between either blood glucose concentrations or gastrointestinal symptoms and hunger or fullness.

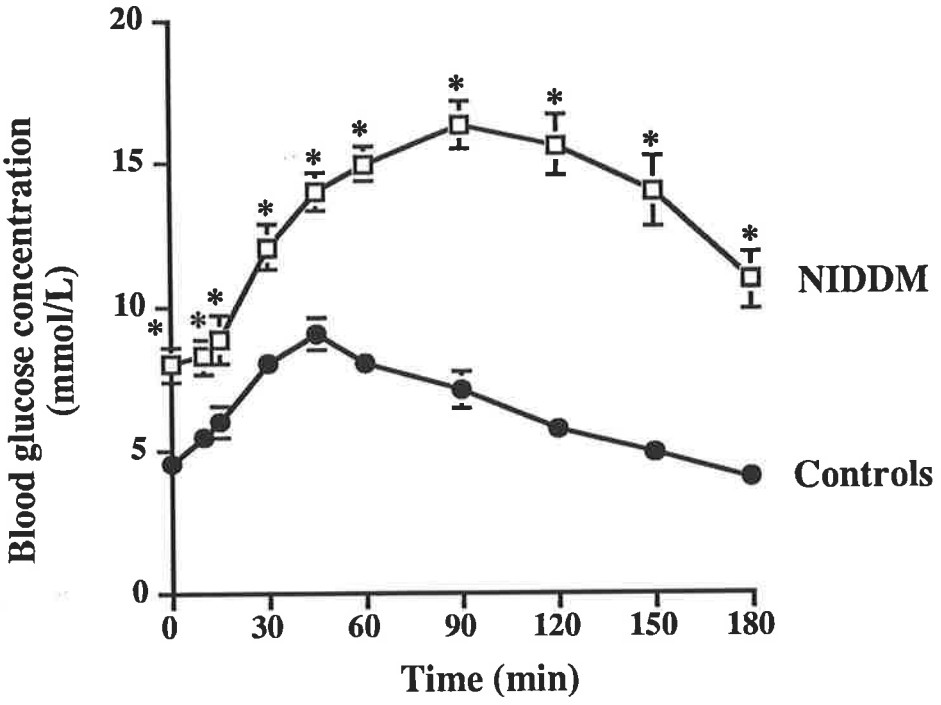

*Figure 14.1: Blood glucose concentrations in control subjects and NIDDM patients (mean values ± SEM). *p<0.001 between the two groups.*

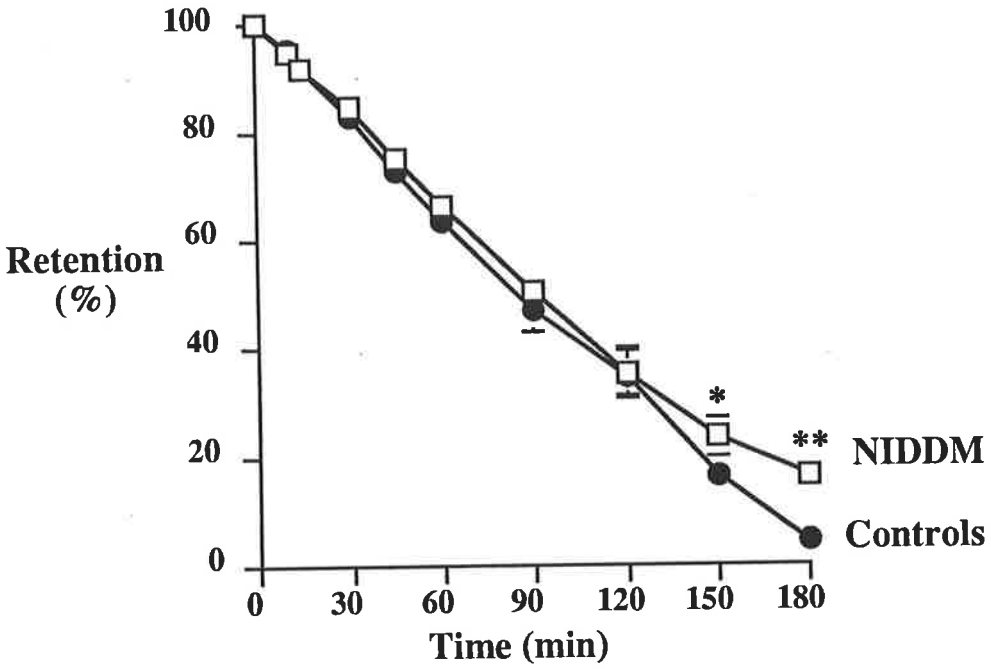

*Figure 14.2: Gastric emptying from the total stomach in control subjects and NIDDM patients (mean values ± SEM). *p<0.05, **p<0.01 between the two groups.*

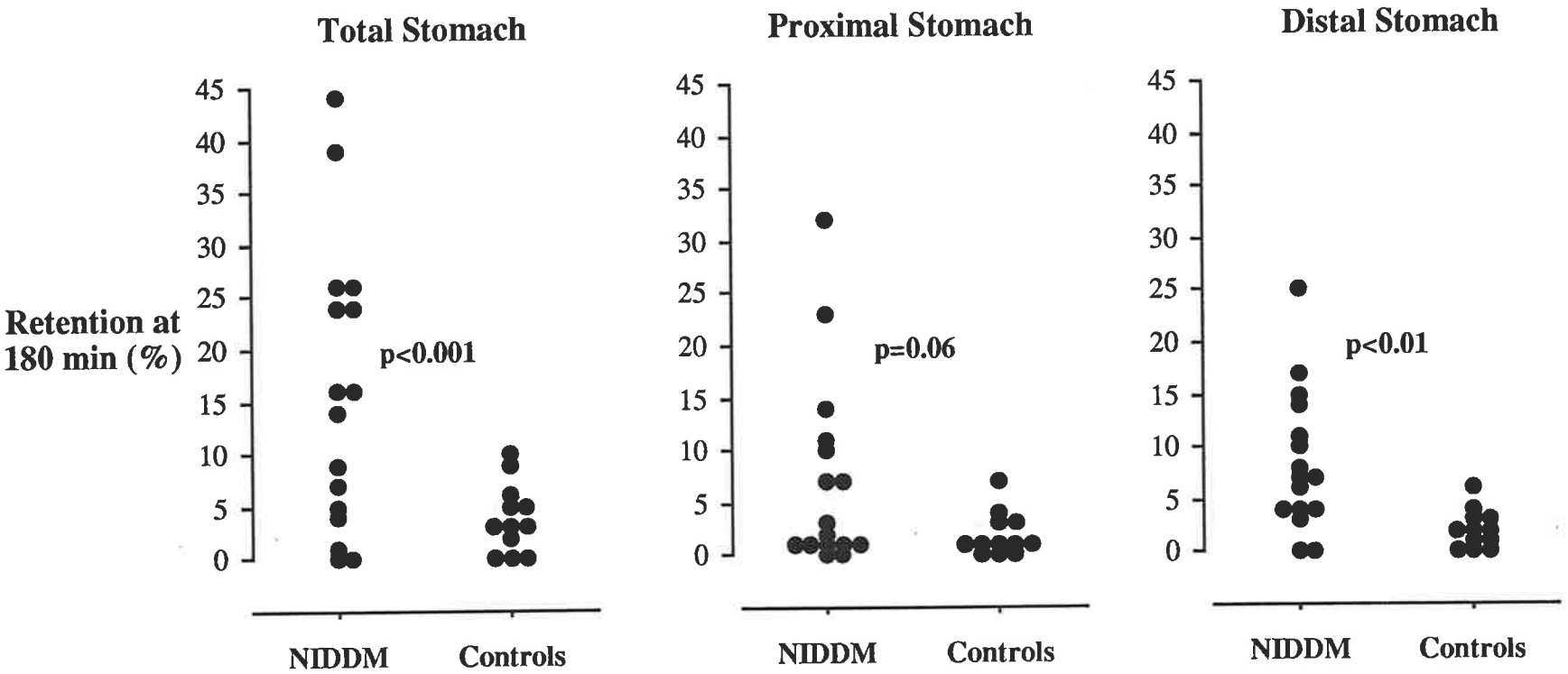

Figure 14.3: Total, proximal and distal stomach retention of glucose at 180 min in control subjects and NIDDM patients.

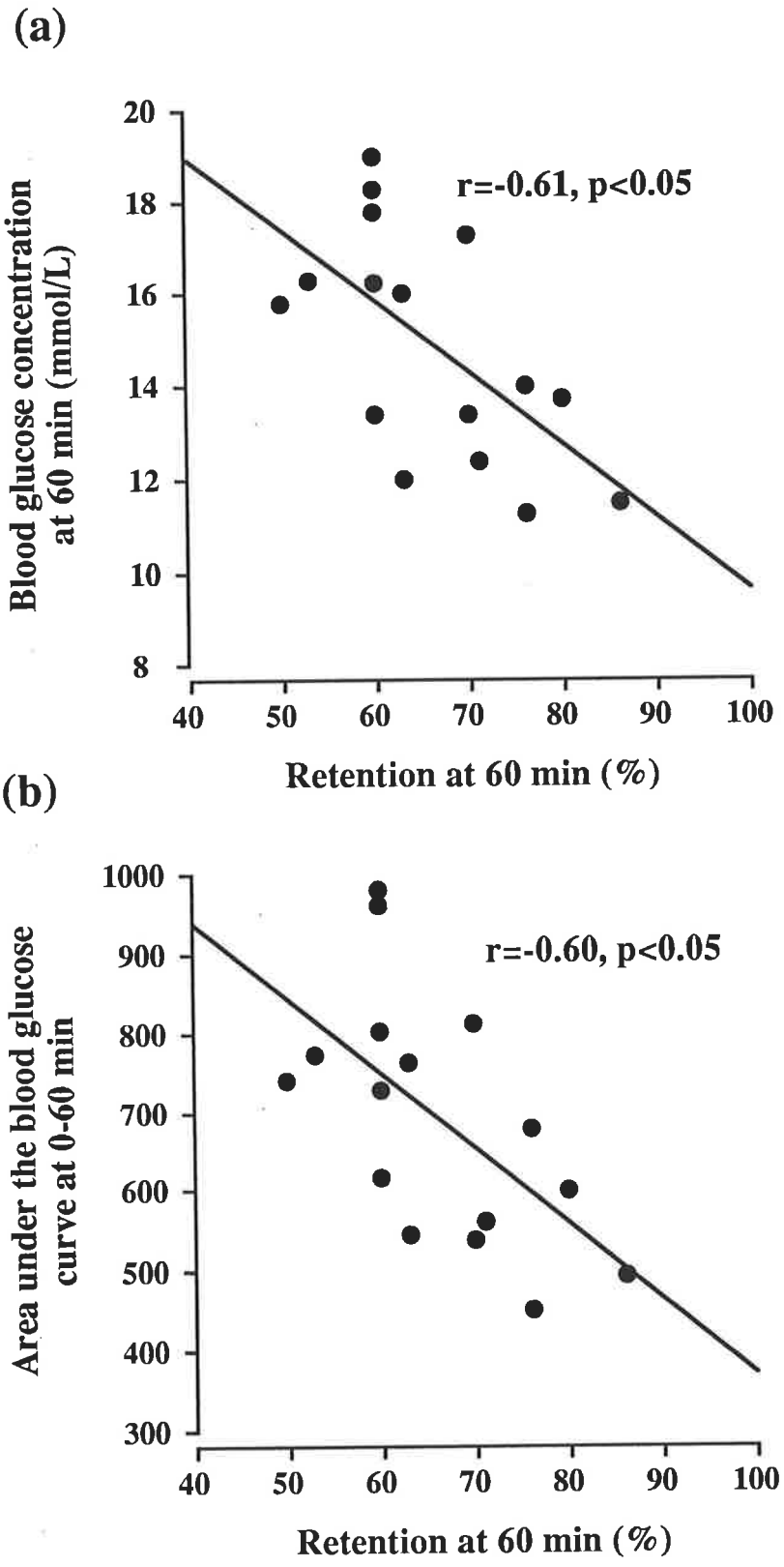

Figure 14.4: Relationship between: (a) the blood glucose concentration at 60 min (r=-0.61, p<0.05); (b) the area under the blood glucose concentration curve (AUC) between 0 and 60 min (r=-0.60, p<0.05) and the amount of the glucose drink remaining in the stomach at 60 min.

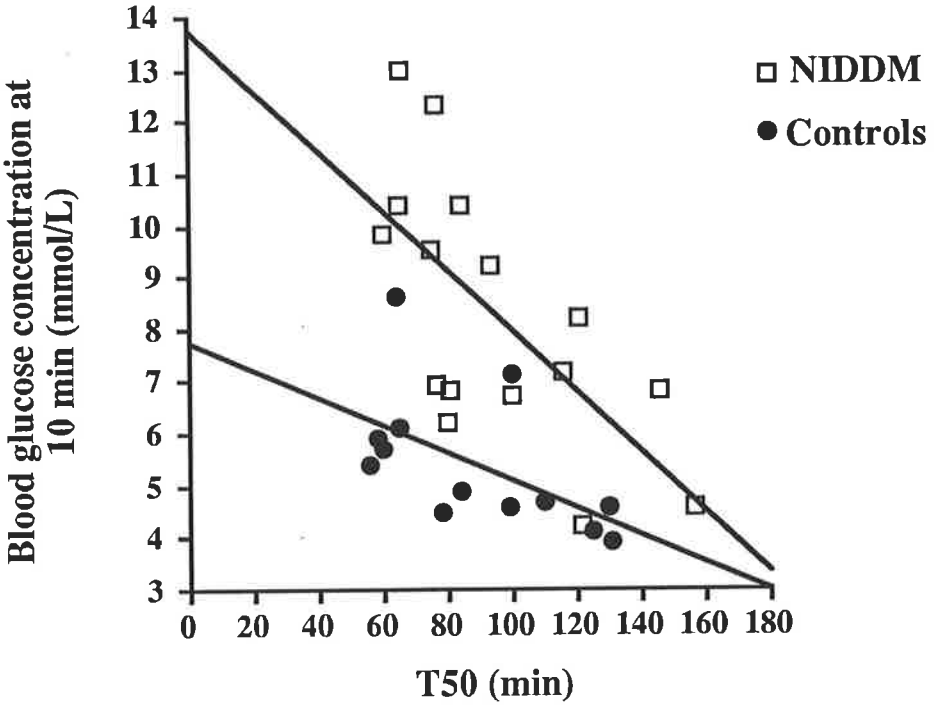

Figure 14.5: Relationship between the blood glucose concentration at 10 min and T50 for gastric emptying in NIDDM patients (r=-0.67, p<0.005; regression coefficient -0.058 ± 0.017) and control subjects (r=-0.058, p<0.05; regression coefficient -0.026 ± 0.011). These slopes are significantly different (p<0.05).

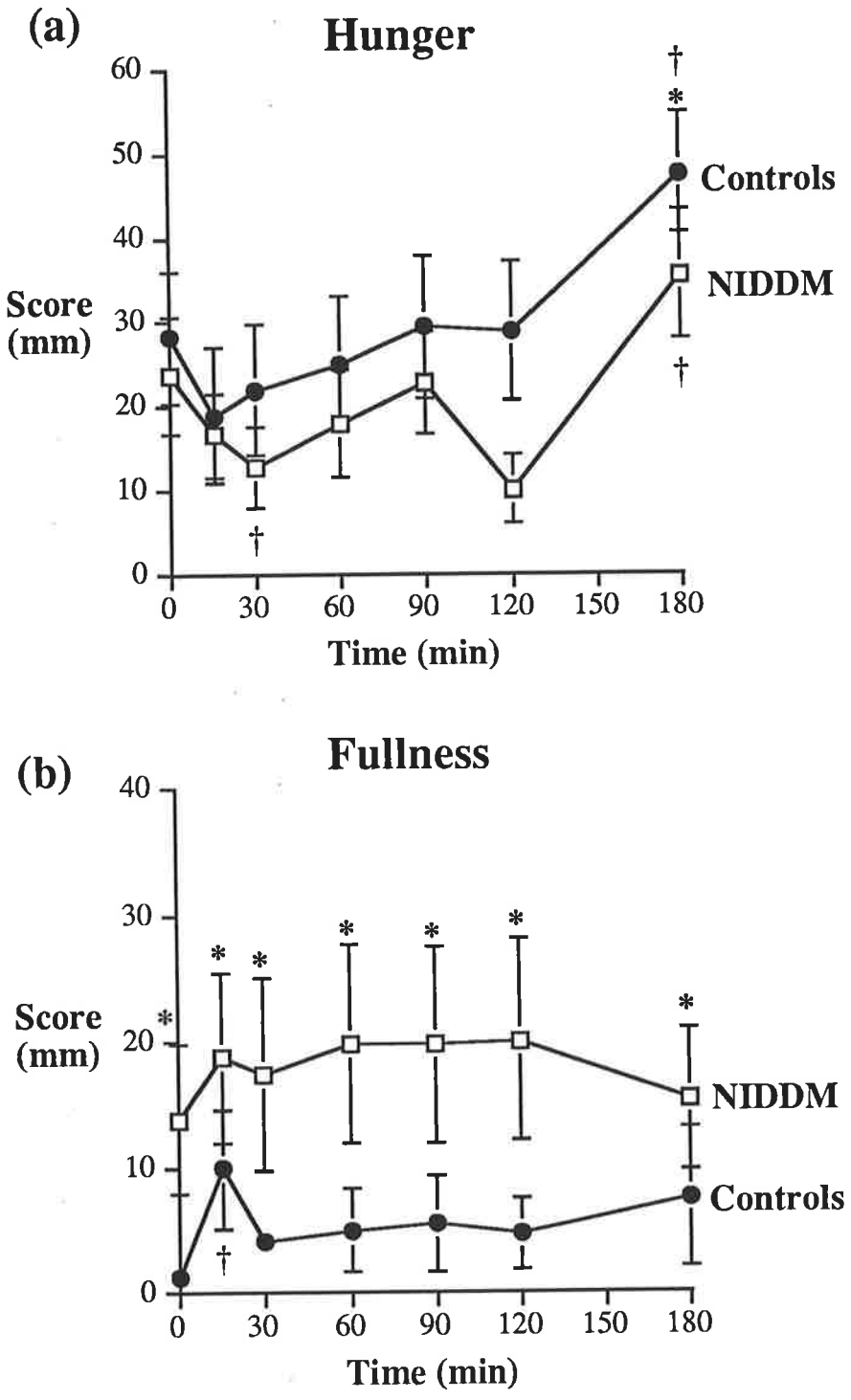

*Figure 14.6: Scores for (a) hunger and (b) fullness in control subjects and NIDDM patients (mean values ± SEM). †p<0.05 cf baseline. *p<0.05 between groups.*

14.5 DISCUSSION

The results of this study indicate that in patients with "early" NIDDM, gastric emptying of a 75g glucose load is similar to normal subjects and is a significant determinant of the glycaemic response.

We consider that the overall slower gastric emptying of glucose in patients with "early" NIDDM when compared to control subjects, while statistically significant, is unlikely to be of pathophysiological importance as the magnitude of the change was small e.g. there was no difference in the 50% emptying time between the two groups. This observation conflicts with Phillips et al who reported that gastric emptying of glucose was much more rapid than normal in such patients (Phillips et al 1992). This discrepancy may reflect the differences in racial distribution between the NIDDM and control subjects in the latter study (Phillips et al 1992), particularly as gastric emptying of glucose is more rapid in Hispanic Americans when compared to non-Hispanic American Caucasians (Schwartz et al 1995), although other factors should be considered. There are differences in both the glucose load (75g *vs* 50g) and its osmolality (Lin et al 1993) between our study and that of Phillips (Phillips et al 1992), but it seems unlikely that observations made with 75g glucose would differ fundamentally from 50g. In contrast to the patients in this study, the majority of the NIDDM patients in the study by Phillips et al were taking oral hypoglycaemic agents (Phillips et al 1992). It has not been established whether long term glycaemic control affects gastric emptying in diabetes mellitus but the NIDDM patients studied by Phillips et al may have had worse glycaemic control than our group (Phillips et al 1992). Certainly, mean blood glucose concentrations in their NIDDM patients were higher than those observed in this study, despite the lower oral glucose load. There was no significant difference in age or body weight between the two groups in this study although mean age and body weight were slightly greater in the NIDDM patients. The age range of the NIDDM patients was

similar to those studied by Phillips (Phillips et al 1992). These factors are therefore, unlikely to have influenced the results (Horowitz et al 1984a, Corvilain et al 1995). Although in many patients with NIDDM fasting hyperglycaemia is present for a number of years before diagnosis (Harris et al 1992), all of the NIDDM patients in this study had this diagnosis made no more than 12 months previously (compared to up to 3 years in the study by Phillips (Phillips et al 1992)) and none had retinopathy. Autonomic nerve function is frequently impaired soon after the onset of diabetes mellitus (Horowitz & Fraser 1994) and the observation that autonomic function was abnormal in some of the NIDDM patients was, therefore, not unexpected. Gastric emptying of glucose is influenced by prior patterns of dietary glucose intake (Corvilain et al 1995, Horowitz et al 1996a). For example, in normal subjects, dietary glucose supplementation accelerates (Horowitz et al 1996a), while caloric restriction delays, gastric emptying of glucose (Corvilain et al 1995). It is possible that potential differences in diet between the two groups, which were not evaluated, could have influenced our observations and those of Phillips (Phillips et al 1992). Gastric secretion cannot be quantified by radionuclide gastric emptying techniques, but the theoretical possibility that gastric acid secretion may be less in the NIDDM patients would result in a spurious increase in the rate of gastric emptying, rather than the observed slightly slower emptying. Frank et al have recently reported that gastric emptying of the liquid component of a mixed solid/liquid meal was more rapid in 10 patients with longstanding (mean duration 4.2 yr) NIDDM than the normal subjects (Frank et al 1995), the magnitude of the difference was relatively small and this observation conflicts with previous reports (Horowitz et al 1989a, Wegener et al 1990). Additional studies evaluating gastric emptying in NIDDM, with different test meals will be required to resolve these controversies.

Delayed gastric emptying in diabetes mellitus has been traditionally thought to reflect irreversible autonomic dysfunction (Camilleri & Malagelada 1984), but recent studies indicate that the blood glucose concentration has a substantial effect on gastric motility and gastric emptying (Barnett & Owyang 1988, Horowitz et al 1989a, Fraser et al 1990, Fraser et al 1991, Schwarcz et al 1993, Horowitz & Fraser 1994, Corvilain et al 1995, Horowitz et al 1996b). For example, in IDDM patients gastric emptying is slower during hyperglycaemia when compared to euglycaemia (Fraser et al 1990) and accelerated during hypoglycaemia (Schwarcz et al 1993). In this study the slightly slower emptying in NIDDM may therefore be attributable to the effects of hyperglycaemia. The threshold, or latency for slowing of gastric emptying by hyperglycaemia may be greater than normal in NIDDM patients (Dao et al 1990) and this perhaps accounts for the fact that slower emptying was only evident some time after ingestion of the drink (after 150 min). The prevalence of delayed gastric emptying during euglycaemia has not been evaluated in either NIDDM or IDDM, but is likely to be less than that reported for patients with diabetes mellitus in general and our study therefore does not exclude the possibility that gastric emptying may be accelerated or normal in "early" NIDDM during euglycaemia.

Dietary modification is the major approach to the management of NIDDM and the demonstration that postprandial hyperglycaemia in NIDDM, after a glucose load, is related to the rate of gastric emptying, has major implications for the management of these patients (Horowitz et al 1993). We have demonstrated that gastric emptying accounts for about 36% of the variance in blood glucose concentrations after a 75g glucose load in "early" NIDDM, similar to that reported in normal subjects (Horowitz et al 1993). The slope of the regression between blood glucose and gastric emptying was significantly greater in the NIDDM patients than the control subjects, indicative of a greater rise in blood glucose from the entry of glucose into

the small intestine. Frank et al have recently demonstrated that hepatic glucose release is a determinant of postprandial blood glucose concentrations in NIDDM (Frank et al 1995), perhaps because suppression of postprandial glucagon release is impaired. In contrast to this study, these authors were unable to demonstrate a relationship between the rate of systemic appearance of glucose and gastric emptying in NIDDM. There are several factors which may account for this discrepancy. Frank et al employed a solid/liquid meal, with 50g glucose included as "Jell-O" (Frank et al 1995). Although "Jell-O" is apparently a liquid at body temperature, its rate of emptying was slower than would be expected of a liquid (Phillips et al 1992, Horowitz et al 1993). The relationship between postprandial blood glucose concentrations and gastric emptying is likely to be the strongest with liquid meals of high glucose content which empty relatively rapidly from the stomach (Phillips et al 1992, Horowitz et al 1993, Corvilain et al 1995). Fasting blood glucose concentrations in the NIDDM patients were higher in the study by Frank et al (~11 mmol/L) compared to (~ 8mmol/L) and this may have influenced their results (Chapter 13). Most importantly, the relationship between the rate of systemic appearance of glucose and gastric emptying was evaluated by Frank et al at only one time point (60 min) and at this time the relationship was almost significant in the normal subjects ($r=0.50$, $p=0.1$) (Frank et al 1995). It is uncertain whether a relationship may have been evident at other times. It is not surprising that Frank et al found no difference in the systemic appearance of ingested glucose between the control and NIDDM groups as there was relatively little difference in gastric emptying of the liquid component of the meal, particularly in the first 50 min (65% *vs* 59%) (Frank et al 1995).

In contrast to the above, two recent studies demonstrating that slowing of gastric emptying improves glycaemic control in NIDDM (Phillips et al 1993, Schwartz et al 1994), strongly support the assertion that gastric emptying is a major determinant of

the blood glucose response to oral carbohydrate in NIDDM. In "early" NIDDM intravenous administration of cholecystokinin octapeptide (Phillips et al 1993) and oral administration of a proteinase inhibitor (Schwartz et al 1994) both retard gastric emptying of glucose and this is associated with lower postprandial blood concentrations of both glucose and insulin. Phillips et al (Phillips et al 1992, Phillips et al 1993) have accordingly suggested that pharmacological retardation of gastric emptying may have a therapeutic role in the treatment of NIDDM. The beneficial effects of low glycaemic index foods and certain forms of fibre on glycaemic control in NIDDM may reflect retardation of gastric emptying, as well as slower intestinal carbohydrate absorption (Schwartz et al 1994). The recent observation that caloric restriction improves glycaemic control in obese patients with NIDDM, independent of changes in body weight (Wing et al 1994) may reflect slowing of gastric emptying (Corvilain et al 1995), as well as changes in hepatic glucose metabolism (Wing et al 1994). The beneficial effects of α galactosidase inhibitors, such as acarbose, on glycaemic control in NIDDM (Chiasson et al 1994) may also be mediated by changes in gastric emptying.

The observed differences in hunger and fullness between the NIDDM and control subjects are of some interest, but require confirmation. In particular, the higher score for fullness in the patients with NIDDM may reflect the greater prevalence of gastrointestinal symptoms in this group. However, the observed direct relationship between hunger and gastric emptying of glucose suggests that the stimulation of small intestinal receptors, rather than gastric distension, influences postprandial hunger in NIDDM.

CHAPTER 15

THE BLOOD GLUCOSE CONCENTRATION INFLUENCES POSTPRANDIAL FULLNESS IN INSULIN DEPENDENT DIABETES MELLITUS

15.1 SUMMARY

Upper gastrointestinal symptoms and delayed gastric emptying both occur frequently in patients with longstanding insulin dependent diabetes mellitus (IDDM), but the relationship between them is relatively poor. Symptoms have, however, been evaluated in the fasted state rather than postprandially. Recent studies in normal subjects indicate that the blood glucose concentration may increase the perception of sensations arising from the upper gastrointestinal tract. In this study the hypotheses that in IDDM postprandial fullness will be related to both the rate of gastric emptying and the blood glucose concentration has been evaluated.

Forty patients (16M, 24F) with IDDM, aged 19-63 yr, had measurements of gastric emptying (GE), blood glucose concentrations, cardiovascular autonomic nerve function, upper gastrointestinal symptoms and postprandial hunger and fullness. GE of solids and liquids were measured scintigraphically, upper gastrointestinal symptoms by questionnaire immediately before ingestion of the test meal, and fullness and hunger by visual analogue scales administered every 15 min. Blood glucose concentrations were measured at -5, 30, 60, 90 and 120 min.

Solid GE was delayed in 58% of the patients and both solid and liquid GE were slower ($p<0.05$) in females than males. The score for upper gastrointestinal

symptoms was not significantly related to either solid or liquid emptying. In contrast, postprandial fullness, but not hunger, was related to the amount of solid ($r=0.36$, $p<0.05$), but not liquid in the stomach. Both before ($r=0.39$, $p<0.05$) and after ($r=0.47$, $p<0.01$) the meal fullness was related to the blood glucose concentration. Postprandial fullness was also related to autonomic nerve dysfunction ($r=0.39$, $p<0.05$). Multiple regression analysis confirmed that blood glucose concentration, solid GE and autonomic nerve dysfunction were independent determinants of postprandial fullness, together accounting for 47% of the variance.

These observations demontrate in IDDM that postprandial fullness is influenced by the blood glucose concentration, the rate of solid GE and autonomic nerve function.

15.2 INTRODUCTION

Although upper gastrointestinal symptoms, such as nausea, vomiting, fullness and abdominal distension, occur frequently in patients with insulin-dependent diabetes mellitus (IDDM) and represent a substantial cause of morbidity, the aetiology of symptoms is poorly understood (Feldman & Schiller 1983, Schwarcz et al 1996). Gastric emptying of solids and nutrient-containing liquids is delayed in 30-50% of patients with longstanding diabetes mellitus but, there is only a weak relationship between the presence of gastrointestinal symptoms and delay in gastric emptying (Horowitz et al 1989a, Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991, Chapter 13). The poor relationship between gastrointestinal symptoms and gastric emptying suggests that other factors may to be responsible for upper gastrointestinal symptoms in IDDM. However, it should also be recognised that, in all previous studies gastrointestinal symptoms have been evaluated in the fasted state, rather than postprandially, which is arguably more appropriate (Horowitz et

al 1989a, Keshavarzian et al 1987, Wegener et al 1990, Horowitz et al 1991, Chapter 13).

Delayed gastric emptying in diabetes mellitus has been traditionally attributed to irreversible autonomic nerve dysfunction (Rundles 1945), but it is now recognised that acute changes in the blood glucose concentration, even within the physiological range, have a major, reversible, influence on gastric motor function and gastric emptying (Barnett & Owyang 1988, Fraser et al 1990, Fraser et al 1991, Schwarcz et al 1993, Hasler et al 1995, Hebbard et al 1996a), as well as motor function in other areas of the gastrointestinal tract (de Boer et al 1992a, de Boer et al 1993, Chey et al 1995, Russo et al 1996, Russo et al 1997). In patients with IDDM gastric emptying is slower during hyperglycaemia (Fraser et al 1990) and accelerated by insulin-induced hypoglycaemia (Schwarcz et al 1993). Recent studies (Chey et al 1995, Hebbard et al 1996a, Hebbard et al 1996b, Lingenfelser et al 1996, Hebbard et al 1997, Boeckxstaens et al (in press)) have demonstrated that the blood glucose concentration may also modulate the perception of sensations arising from the gastrointestinal tract. For example, nausea and fullness produced by distension of the proximal stomach are more intense during hyperglycaemia (~15 mmol/L) than euglycaemia (Hebbard et al 1996a, Hebbard et al 1996b). The effects of the blood glucose concentration on gastrointestinal symptoms in patients with diabetes have not been evaluated. However, it is of interest that Schvarcz et al recently reported that the prevalence of upper gastrointestinal symptoms in IDDM is greater in those patients with poor glycaemic control (Schwarcz et al 1996), as assessed by measurement of glycosylated haemoglobin.

The hypotheses that in patients with IDDM postprandial fullness will be related to both the rate of gastric emptying and the blood glucose concentration has now been evaluated.

15.3 MATERIALS AND METHODS

Forty patients with (insulin dependent diabetes mellitus) IDDM, 16 male, 24 female, mean age 43.6 ± 1.9 yr, median body mass index (BMI) 25.9 kg/m^2 (range 19 - 34) and median body weight 77.2 kg (range 50 - 111) were studied. All were ambulatory outpatients, who were selected at random from those patients attending the Endocrine Unit of the Royal Adelaide Hospital, who had IDDM for at least 1 year (Horowitz et al 1989a, Horowitz et al 1991, Chapter 13). The median duration of known IDDM was 15 yr (range 2.5 - 44). No patient had a history of gastrointestinal disease or upper gastrointestinal surgery, or was taking any medication known to influence gastrointestinal motility. As assessed by a recent opthalmological examination, often including fluoroscein angiography, 15 patients had no retinopathy, 13 had proliferative retinopathy and 12 had background retinopathy. At the time of the study the median glycosylated haemoglobin (HbA_{1c}) was 8.8% (range 5.8 - 11.9); the range in normal subjects being 3.5 - 6.0% (Horowitz et al 1989a, Horowitz et al 1991). Plasma creatinine was normal ($\leq$ 0.12 mmol/L) in all subjects. Written, informed consent was obtained from each patient and the study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

15.3.1 *Experimental protocol*

Each patient had measurements of gastrointestinal symptoms, gastric emptying, glycaemic control, autonomic nerve function and appetite (Horowitz et al 1989a, Sepple & Read 1989, Horowitz et al 1991, Horowitz et al 1993). Patients attended the laboratory at about 0900h after an overnight fast (14h solids, 12h liquids). An intravenous cannula was inserted in an antecubital vein, immediately before commencement of the measurement of gastric emptying at 1000h. Smoking was prohibited on the study day and the morning dose of insulin was usually

administered 20 minutes prior to consumption of the test meal. After the completion of the gastric emptying measurement (at approximately 1230h) cardiovascular reflex tests were performed to assess autonomic nerve function (Horowitz et al 1989a, Horowitz et al 1991).

15.3.2 *Assessment of upper gastrointestinal symptoms*

The following gastrointestinal symptoms were assessed via a written questionnaire administered approximately 30 min before ingestion of the test meal: dysphagia, heartburn and acid regurgitation ("oesophageal symptoms"), anorexia, nausea, early satiety, bloating, vomiting and abdominal pain ("gastric symptoms"). Each symptom was scored as: 0 = none, 1 = mild, 2 = moderate or 3 = severe, for a maximum total score of 27 (Horowitz et al 1989a, Horowitz et al 1991, Chapter 13).

Hunger and fullness were evaluated using a validated visual analogue questionnaire (Sepple & Read 1989, Horowitz et al 1993). A vertical mark was placed along a 100 mm line to indicate the intensity of the sensation, where 0 = no sensation and 100 is the maximum sensation. Each patient completed the questionnaire immediately prior to meal consumption, and then at 15, 30, 45, 60, 90 and 120 min.

15.3.3 *Measurement of gastric emptying*

The test meal comprised both solid and liquid components. The solid component was 100g of cooked ground beef containing 20 MBq chicken liver, labelled in vivo with ^{99m}Tc-sulphur colloid and the liquid was 150 ml of 10% dextrose in water labelled with 10 MBq ^{67}Ga - ethylenediaminetetraacetic acid (EDTA) (Collins et al

1983). The study was performed with the patient sitting with their back against the gamma camera. The patient ate the ground beef initially and then immediately drank the glucose solution. The meal was consumed within 5 min and time zero was defined as the time of meal completion (Horowitz et al 1991). Radionuclide data were acquired on computer for at least 120 min (1 min frames for the first hour and 3 min frames for the subsequent hour) and were corrected for subject movement, radionuclide decay and gamma ray attenuation using previous described methods (Collins et al 1983). A region-of-interest (ROI) was drawn for the total stomach and the percent intragastric activity plotted over time. Several parameters were derived from the gastric emptying curves. For the solid, these were the lag phase and the retention at 100 and 120 min. The lag phase was defined as the time before any activity was seen in the proximal small intestine (Horowitz et al 1989a, Horowitz et al 1991, Chapter 13). For the liquid, the retention at 30 min and the time for 50% of the liquid to empty (T50) were calculated (Horowitz et al 1991). Gastric emptying for solid and liquid was categorised as normal or abnormal (delayed or more rapid) when values were outside the mean ± 2 standard deviations of an established normal range for the intragastric retention of solid at 100 min and liquid T50. -Delayed emptying of solid was a retention at 100 min of >61/%, where as that for the liquid T50 was >31 min (Chapter 13).

15.3.4 *Measurement of blood glucose concentrations*

Venous blood samples were obtained immediately prior to meal ingestion and then at 30, 60, 90 and 120 min for measurement of blood glucose using a portable glucose meter (MediSense Companion 2; MediSence Inc, Waltham, MA). The accuracy of these measurements was confirmed using the hexokinase method (Horowitz et al 1993).

15.3.5 *Assessment of autonomic nerve function*

Autonomic nerve function was assessed using standardised cardiovascular reflex tests (Horowitz et al 1989a, Horowitz et al 1991). Parasympathetic function was evaluated by the variation (R-R interval) of the heart rate during deep breathing and the immediate heart rate response to standing ("30:15" ratio). Sympathetic function was measured by the fall in systolic blood pressure in response to standing. Each of the results was scored as 0 = normal, 1 = borderline and 2 = abnormal. A total score ≥ 3 was taken to indicate definite autonomic nerve damage (Horowitz et al 1989a, Horowitz et al 1991, Chapter 13).

15.3.6 *Statistical analysis*

Data are shown as mean values ± SEM, and were evaluated using repeated measures ANOVA and Student's t-test. Relationships between gastric emptying, appetite, blood glucose concentrations, gastrointestinal symptoms and autonomic nerve function were assessed using simple and multiple linear regression analysis. A p value < 0.05 was used to indicate statistical significance.

15.4 RESULTS

All subjects tolerated the study well and there were no untoward events.

The score for upper gastrointestinal symptoms was 5.1 ± 0.7. 24 patients had definite autonomic neuropathy and the mean score in the whole group was 2.7 ± 0.3. The mean blood glucose concentration during the gastric emptying measurement was 14.8 ± 0.6 mmol/L. In 23 patients the mean blood glucose concentration was $\leq$15 mmol/L, while it was > 15 mmol/L in 17 patients. Blood

glucose concentrations at all time intervals were related ($r>0.88$, $p<0.001$). There was no significant relationship between HbA_{1c} and blood glucose concentrations.

15.4.1 *Gastric emptying*

In most cases gastric emptying of the solid meal followed a linear pattern after an initial lag phase (52.4 ± 4.3 min). In contrast, emptying of liquid approximated a monoexponential pattern (T50 41.3 ±3.1 min) (Horowitz et al 1989a, Horowitz et al 1991). Gastric emptying of the solid meal was delayed in 23 (58%) of the patients. None of the patients had accelerated emptying of solid or liquid. There was a significant relationship between the lag phase for solid and the liquid T50 ($r=0.45$, $p<0.01$).

15.4.2 *Relationships between gastric emptying and other variables*

Gastric emptying of both solid and liquid was slower in females when compared to males (retention of solid at 100 min 71.5 ± 4.4% *vs* 55.8 ± 5.6%; $p<0.05$; liquid T50 46.4 ± 3.1 min *vs* 33.6 ± 3.8 min; $p<0.05$)). There was no significant relationship between gastric emptying and either age, body weight or the score for autonomic nerve dysfunction. The score for upper gastrointestinal symptoms measured before ingestion of the test meal was not related significantly to either solid (% retention at 100 min, $r=-0.06$) or liquid (T50, $r=-0.25$) emptying. The score for "gastric" symptoms was also not significantly related to the rate of gastric emptying. There was no significant relationship between upper gastrointestinal symptoms and the blood glucose concentration before meal ingestion ($r=0.23$, NS).

The score for hunger was not related to gastric emptying. In contrast, fullness was significantly related to solid GE (eg the score for fullness at 45 min was related to

the lag phase; r = 0.35, p<0.05 (Figure 15.1), and fullness at 120 min was related to the amount of solid remaining in the stomach; r=0.36, p<0.05), but not to gastric emptying of liquid. The correlation between postprandial fullness and gastric emptying was not improved when the total intragastric content (ie. solid and liquid) was calculated (data not shown).

The lag phase for the solid meal (r=0.49, p<0.01), but not liquid gastric emptying, was related significantly to the mean blood glucose concentration. When patients were divided into two groups according to their mean blood glucose (≤15 mmol/L and >15 mmol/L), the lag phase was longer (64.3 ± 7.0 min *vs* 43.7 ± 4.7 min; p<0.05) in the group with the higher blood glucose concentration. Conversely, the postprandial rise in blood glucose was related to gastric emptying of liquid eg at 30 min, r=0.34, p<0.05, but not solid (Chapter 13). There were no significant relationships between HbA_{1c} and gastric emptying.

15.4.3 *Hunger and fullness*

Hunger decreased (p< 0.001) after the meal. There was a non significant postprandial increase in fullness. The score for fullness at baseline was related to the blood glucose concentration (r=0.33, p<0.05). There was also a significant relationship between postprandial fullness and the mean blood glucose concentration eg at 30 min, r=0.47, p<0.01, but not hunger (Figure 15.2). When patients were divided into two groups according to their mean blood glucose (≤15 mmol/L and >15 mmol/L), hunger was not significantly different between the two groups, but both fasting and postprandial fullness were greater (p<0.005) in the group with the higher mean blood glucose (Figure 15.3). Postprandial fullness at 60 min, 90 min, 120 min (but not hunger) was also related (r> 0.36, p<0.05) to the score for autonomic nerve dysfunction. An example of multiple regression analysis

to evaluate the determinants of postprandial fullness is shown in the table. Solid gastric emptying ($p<0.01$), the mean blood glucose concentration ($p<0.05$) and autonomic nerve function ($p<0.01$) were independent determinants of the score for fullness at 60 min, accounting for 47% of the variance. In this model fullness was not related significantly to sex (data not shown).

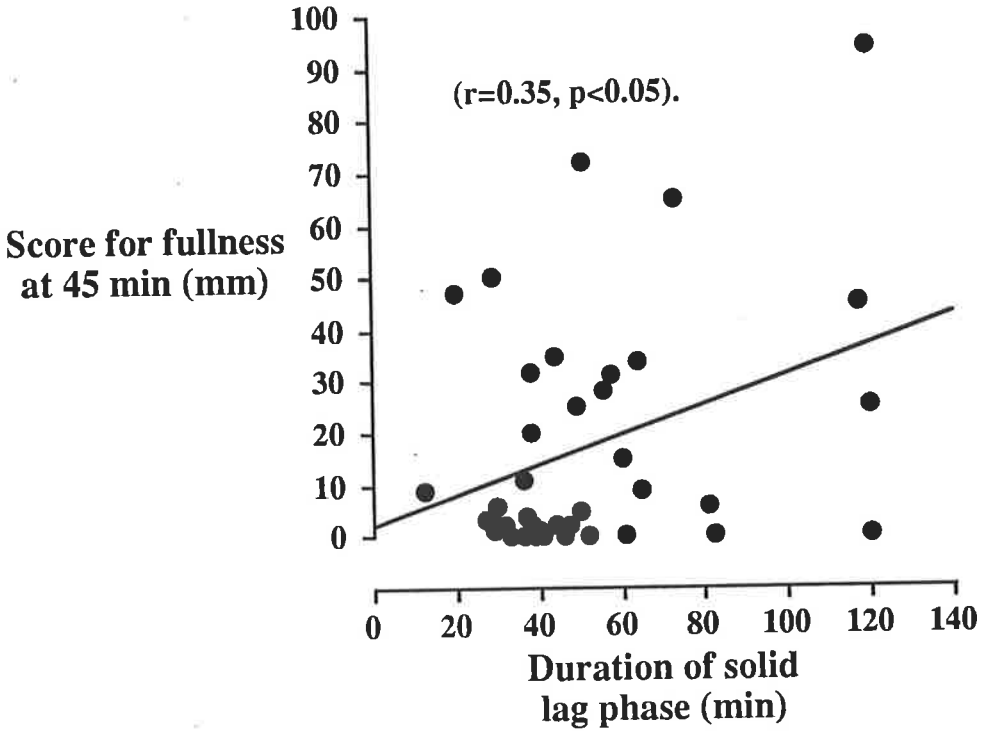

Figure 15.1: Relationship between the score for fullness at 45 min and duration of the lag phase for the solid meal.

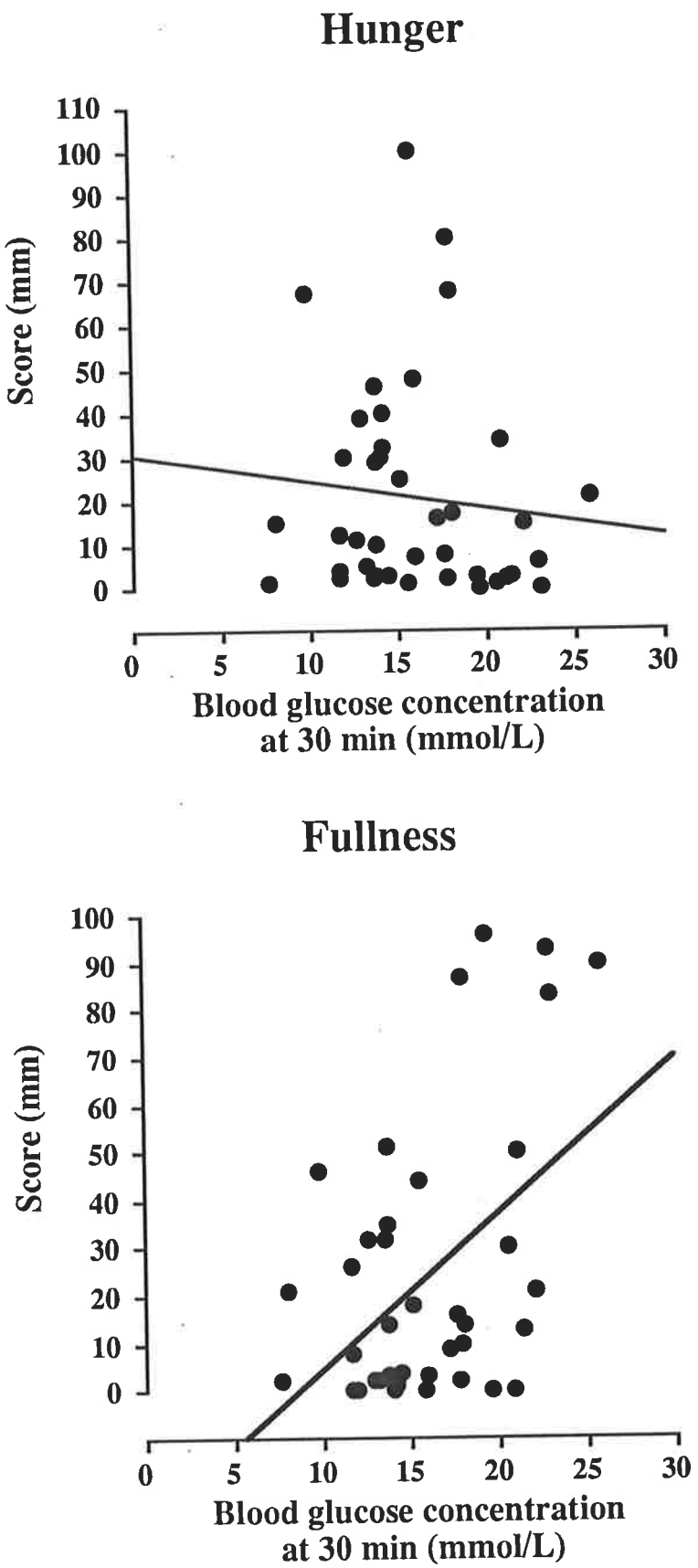

Figure 15.2: Relationship between the scores for hunger (r=-0.11, NS) and fullness (r=0.47, p<0.01) and the blood glucose concentration, at 30 min.

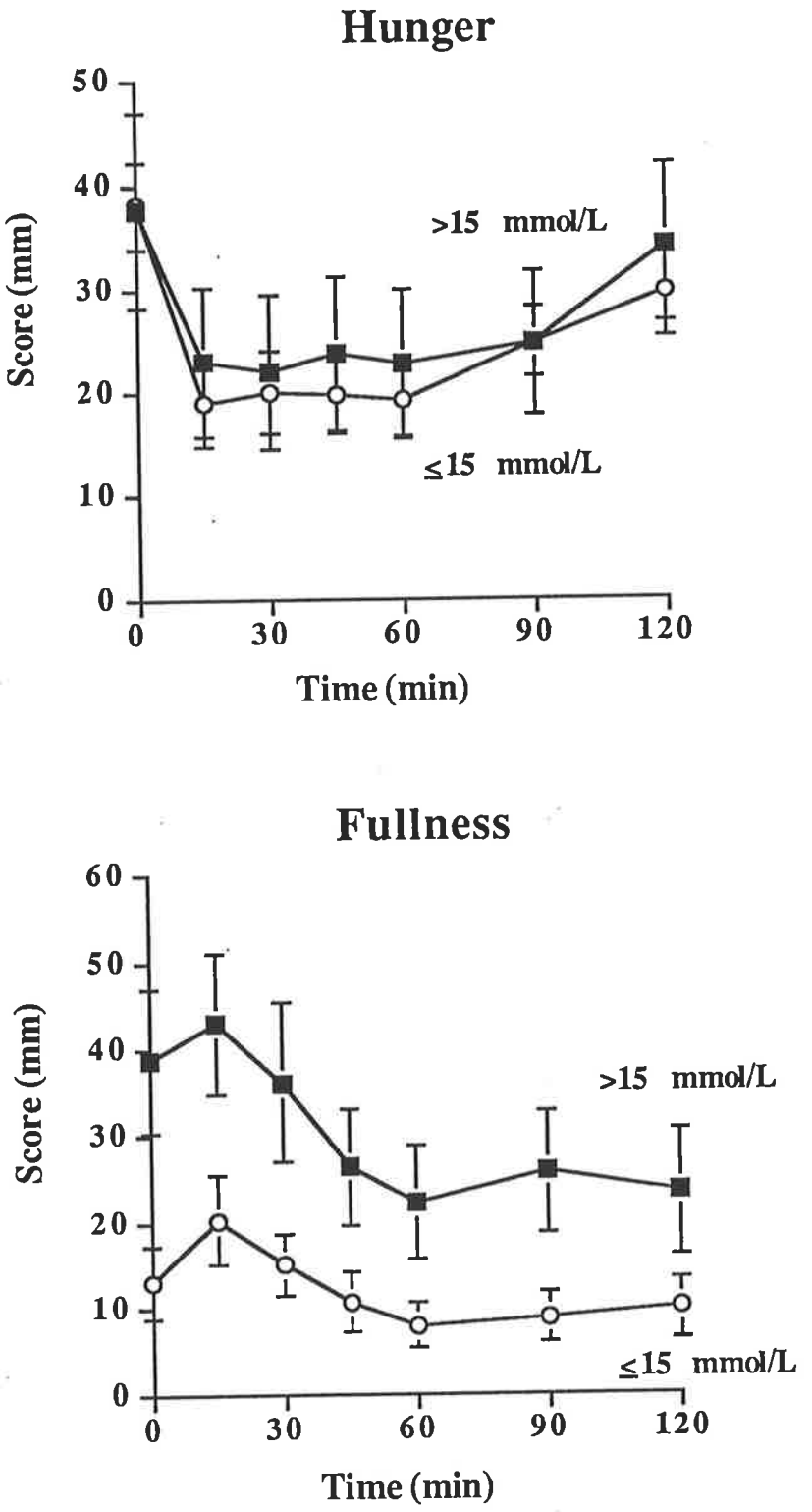

Figure 15.3: Scores for hunger (NS) and fullness ($p<0.005$) before and after meal ingestion, in patients with IDDM divided according to mean blood glucose concentration as ≤15 mmol/L (23 patients) and >15 mmol/L (17 patients).

Table 15.1 *Determinants of postprandial fullness at 60 min in 40 patients with insulin-dependent diabetes mellitus*

	Coefficient	*t-value*	*p-value*
intercept	-38.24	-3.03	0.005
retention of solid at 120 min (%)	0.37	2.86	0.007
liquid T50 (min)	-0.19	-1.14	0.260
mean blood glucose (mmol/L)	1.77	2.45	0.019
autonomic nerve dysfunction (score)	4.85	2.98	0.005

Multiple r=0.68, p<0.005

15.5 DISCUSSION

We have demonstrated in patients with insulin dependent diabetes mellitus (IDDM) that postprandial fullness, but not hunger, is related to the blood glucose concentration, the rate of gastric emptying of the solid component of a mixed solid/liquid meal, and the severity of cardiovascular autonomic nerve dysfunction. These relationships were evident on both simple and multiple regression analysis and together accounted for about 47% of the variance in postprandial fullness.

Upper gastrointestinal symptoms are a clinically important problem in many patients with IDDM (Feldman & Schiller 1983, Schwarcz et al 1996). For example, Schvarcz et al recently evaluated the prevalence of gastrointestinal symptoms in an unselected, population-based cohort of 110 patients with longstanding IDDM compared with 210 age - and sex-matched control subjects, and reported in the patients with IDDM that there was an increased prevalence of a number of upper gastrointestinal symptoms, including anorexia (17.8% vs 3.6%, $p<0.01$), vomiting (12.2% vs 3.0%, $p<0.01$), abdominal distension (42.3% vs 24.4%, $p<0.01$) and fullness (26.8% vs 6.1%, $p<0.001$) (Schwarcz et al 1996). Eating disorders also occur frequently in patients with IDDM (Rosmark et al 1986). Despite the high prevalence of upper gastrointestinal symptoms in IDDM, their aetiology is poorly defined.

We have confirmed that gastric emptying is delayed in about 50% of patients with long standing IDDM (Keshavarzian et al 1987, Horowitz et al 1989a, Horowitz et al 1991) and that the rate of gastric emptying in IDDM is influenced by the blood glucose concentration (Fraser et al 1990). The observation that gastric emptying is slower in females than males with IDDM is novel, and has not been evident in previous studies by our group (Horowitz et al 1989a, Horowitz et al 1991, Chapter 13) or others (Keshavarzian et al 1987). This result should therefore be viewed

with some caution and requires confirmation. However, it has been reported that gastric emptying is slower in normal females when compared to males in some (Datz et al 1987, Hutson et al 1989), but not all (Horowitz et al 1984a) studies. Moreover, in patients with functional dyspepsia delay in gastric emptying appears to occur more frequently in females (Stanghellini et al 1996). The observation that the postprandial rise in blood glucose was related to the rate of liquid emptying (which contained glucose) is also consistent with previous reports which have demonstrated that gastric emptying is a major determinant of postprandial blood glucose concentrations in IDDM (Chapter 13, Ishii et al 1994, Willms et al 1996). These studies support the concept that in IDDM disordered gastric emptying may contribute to poor glycaemic control by causing a mismatch between the onset of exogenous insulin action and the availability of nutrients (Horowitz & Fraser 1994). In NIDDM, postprandial blood glucose concentrations are also related to the rate of gastric emptying (Chapter 13, Schwartz et al 1995), as well as hepatic glucose metabolism (Frank et al 1995).

The absence of a significant relationship between the severity of upper gastrointestinal symptoms and gastric emptying is not surprising (Horowitz & Fraser 1994). Our study is the first to evaluate the diagnostic value of postprandial assessment in patients with diabetes and indicates that this may be greater, although the correlation is still weak. This observation is consistent with Stanghellini et al (Stanghellini et al 1996) who demonstrated in patients with functional dyspepsia that the symptom of postprandial fullness is predictive of delayed gastric emptying of solids. It should be recognised that the liquid component of our test meal emptied from the stomach much more rapidly than the solid, and the absence of a relationship between postprandial fullness and liquid emptying may therefore be partly spurious.

The demonstration that in IDDM postprandial fullness is related to acute, but not chronic blood glucose control does not establish causation, but is compatible with recent observations made in normal subjects. In particular, Hebbard et al reported that the perception of nausea and abdominal fullness during proximal gastric distension (Hebbard et al 1996a) and intraduodenal triglyceride infusion (Hebbard et al 1996b) are greater during hyperglycaemia (~14 mmol/L) than euglycaemia. Furthermore, the perception of duodenal distension is also greater during hyperglycaemia (Lingenfelser et al 1996). While the relationship between the degree of hyperglycaemia and perception has not been formally evaluated in either normal subjects or patients with diabetes, there is evidence that the blood glucose may act as a physiological modulator of gastrointestinal sensation. For example, in normal subjects the threshold for perception of oesophageal balloon distension is lower at a blood glucose concentration of 8 mmol/L when compared to 4 mmol/L (Boeckxstaens et al (in press)). In view of our observations, studies to evaluate the effect of the blood glucose concentration on visceral perception in IDDM are indicated. It has been reported that the perception of gastric distension is increased in IDDM patients with gastrointestinal symptoms and autonomic neuropathy during euglycaemia (Samsom et al 1995). Both fasting and postprandial antral area are greater in IDDM patients than normal subjects, and changes in antral tone may also contribute to disordered perception (Undeland et al 1996). There is little information about the mechanisms which may mediate the effects of the blood glucose concentration on visceral sensation, although it is known that hyperglycaemia may affect somatic sensation (Morley et al 1984). While insulin affects sympathetic nerve activity, which modulates gut sensitivity (Iovino et al 1995), changes in plasma insulin concentrations are most unlikely to be responsible for our observations (Chey et al 1995). Hyperglycaemia is known to effect the function of the gastric pacemaker, with an increased prevalence of tachygastria, and this may contribute to symptoms (Hasler et al 1995, Hebbard et al 1997).

A relationship between postprandial fullness and the severity of autonomic nerve dysfunction was also observed. It should be recognised that there is no good method of assessing gastrointestinal autonomic nerve function and evaluation of cardiovascular reflexes is likely to lack sensitivity (Frank et al 1995). Nevertheless, the observation suggests that autonomic nerve dysfunction may contribute to disordered visceral perception (Chapter 13) and this issue warrants exploration in future studies.

The observations from this study are likely to have substantial clinical relevance for an optimal approach to the treatment of upper gastrointestinal symptoms in patients with diabetes. Current treatment for symptomatic diabetic gastroparesis has not focussed on the optimisation of glycaemic control, and is based primarily on the use of prokinetic drugs including cisapride, metoclopramide, domperidone and erythromycin (Horowitz et al 1996b). These drugs all result in improvement in the rate of gastric emptying, but treatment is by no means uniformly satisfactory and the correlation between the magnitude of effects on gastric emptying and symptoms is known to be poor (Horowitz et al 1985a, Horowitz et al 1987, Janssens et al 1990). The possibility that the symptomatic response to prokinetic drugs is modified by the blood glucose concentration has also not been evaluated.

CHAPTER 16

THE RATE OF GASTRIC EMPTYING IS A SIGNIFICANT DETERMINANT OF POSTPRANDIAL HYPOTENSION IN NON-INSULIN DEPENDENT DIABETES MELLITUS

16.1 SUMMARY

Postprandial hypotension is now recognised as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction. The mechanisms responsible are poorly understood, however, impaired regulation of splanchnic blood flow and the release of gastrointestinal hormones appear important. The effect of gastric emptying on the magnitude of the postprandial fall in blood pressure has not been evaluated. The aim of this study was to determine whether there is a relationship between changes in blood pressure and gastric emptying after ingestion of 75g glucose in patients with non-insulin dependent diabetes mellitus (NIDDM) and both young and older normal subjects.

Sixteen patients with recently diagnosed NIDDM, median age 57 yr (39-79) 10 "young" subjects median age 23 yr (19-26) and in the 9 "older" group subjects, median age 48 yr (40-68) had simultaneous measurement of gastric emptying of 75g glucose in 350ml water, blood pressure and blood glucose concentrations, commencing at approximately 10.00h, after an overnight fast. Measurements were made in the sitting position immediately prior to glucose ingestion and at 15 min intervals up to 180 min. Autonomic nerve function tests were assessed using standardised cardiovascular reflex tests after the study.

Gastric emptying of glucose was not significantly different between the three groups (50% emptying time (T50) NIDDM: 95 ± 7.3 min vs young: 120 ± 13.2 min vs older: 97 ± 8.1 min). Blood glucose concentrations were greater both before ($p<0.005$) and after the glucose drink ($p<0.0001$) in the NIDDM group when compared to both the "young" and "older" normal subjects. There was a significant fall in mean blood pressure after the glucose load in the NIDDM patients ($p<0.0001$) and the "older" normal subjects ($p<0.05$) but not the "young" normal subjects. Postprandial hypotension (fall in systolic blood pressure ≥20 mmHg) was evident in 7 (44%) NIDDM patients and 3 (33%) "older" normals. The area under the change in mean blood pressure curve was significantly related to the gastric emptying T50 ($r=0.67$, $p<0.005$) in the NIDDM patients, but not in either control group.

In conclusion, in patients with recently diagnosed NIDDM the fall in blood pressure after to an oral glucose load is (i) greater than in both young and old normals and (ii) related to the rate of gastric emptying.

16.2 INTRODUCTION

Postprandial hypotension, leading to syncope and falls, is now recognised as an important clinical problem, particularly in the elderly and in patients with autonomic dysfunction (Mathias et al 1989, Jansen & Hoefnagels 1991, Mathias 1991, Mathias & Bannister 1993, Jansen & Lipsitz 1995). The mechanisms responsible for postprandial hypotension are poorly understood but impaired regulation of splanchnic blood flow and the release of gastrointestinal hormones appear important (Mathias et al 1989, Jansen & Hofenagels 1991, Mathias 1991, Mathias & Bannister 1993, Jansen & Lipsitz 1995). The magnitude of the postprandial fall in blood pressure is dependent on meal composition. Ingestion of carbohydrates,

particularly glucose, has the largest effect on blood pressure (Jansen et al 1987, Jansen & Hoefnagels 1987, Jansen et al 1990) with only minor falls occurring after ingestion of fat, protein or water (Jansen et al 1987, Potter et al 1989). While oral ingestion of glucose leads to a fall in blood pressure, intravenous infusion of glucose has no significant effect (Jansen & Hoefnagels 1987), indicating that the response is mediated from the gastrointestinal tract.

The onset of the fall in blood pressure after a meal is almost immediately evident, with a maximum response at 30 - 60 minutes (Mathias & Bannister 1993, Jansen & Lipsitz 1995) suggesting a relationship to the rate of delivery of carbohydrate to the small intestine. It is therefore surprising that no studies have formally evaluated the relationship between postprandial hypotension and gastric emptying. To our knowledge the only information relating to this issue was based on a small number of patients with autonomic failure and employed suboptimal methodology to quantify gastric emptying (Mathias & Bannister 1993). It is now recognised that disordered (delayed or more rapid) gastric emptying occurs frequently in patients with diabetes mellitus (Horowitz & Fraser 1994) and autonomic failure (Horowitz & Dent 1991), as well as the elderly (Horowitz et al 1984a). In this group abnormal gastric emptying is not predictable on the basis of gastrointestinal symptoms, such as nausea and postprandial fullness, as the relationship between the rate of gastrointestinal symptoms and gastric emptying is poor (Horowitz & Dent 1991).

The purpose of this study was to determine whether there is a relationship between the magnitude of the fall in blood pressure and gastric emptying following ingestion of 75g glucose in patients with non-insulin dependent diabetes mellitus (NIDDM), as well as both young and elderly normal subjects.

16.3 MATERIALS AND METHODS

The study population comprised three groups: patients with non-insulin dependent diabetes (NIDDM), "young" normal subjects and "older" normal subjects: The NIDDM group comprised 16 patients with recently diagnosed NIDDM, 11 male, 5 female, median age 57 yr (39 - 79) and median body mass index (BMI 29 (22 - 36). The patients were randomly selected from ambulant outpatients presenting to the Royal Adelaide Hospital for treatment of NIDDM. In all cases the diagnosis of NIDDM, based on World Health Organisation criteria, had been established between 3 and 12 months previously. All patients were treated by diet alone and none was taking oral hypoglycaemic drugs, antihypertensive agents or any medication known to affect blood pressure or gastrointestinal motility. None of the patients had retinopathy and in all cases, the plasma creatinine concentration was within the normal range (0.05-0.12 mmol/L). At the time of the study mean glycosylated haemoglobin was 7.5 ± 0.6% (normal < 6.0%). The results of measurements of gastric emptying in this group have been reported previously (Chapter 14). The "young" normal group comprised 10 subjects (9 male, 1 female), median age 23 yr (19 - 26) and median BMI 23 (20 - 27). In the "older" group there were 9 subjects (6 male, 3 female), median age 48 yr (40 - 68) and median BMI 25 (20 - 35). None of the normal subjects was taking medication, had gastrointestinal symptoms or a history of significant illness. Normal subjects responded to advertisements placed at the local University and Employment centre. There was no significant difference in either age or BMI between the NIDDM patients and the "older" normal subjects but both age ($p<0.0001$) and BMI ($p<0.05$) were greater in the NIDDM group when compared to the "young" normals. All the NIDDM and control subjects were Caucasian.

16.3.1 *Experimental protocol*

Each subject underwent concurrent measurements of gastric emptying, blood glucose and blood pressure. The gastric emptying measurement was commenced at about 10.00h after an overnight fast (14h for solids and 12h for liquids). Smoking was prohibited on the study day. A cannula was placed in an antecubital vein for blood sampling and the subjects were seated with their back against a gamma camera, with a blood pressure cuff around their left arm. Gastric emptying, blood glucose and blood pressure were monitored for three hours after meal ingestion (Chapter 14). About an hour after completion of these measurements (ie. at approximately 1400h) cardiovascular autonomic nerve function was evaluated (Chapter 14). Written informed consent was obtained from each participant and the study protocol was approved by the Human Ethics Committee of the Royal Adelaide Hospital.

16.3.2 *Measurement of gastric emptying*

Gastric emptying was measured using a previously described technique (Chapter 14). Each subject drank 350 ml of water containing 75 g glucose and 20 MBq ^{99m}Tc - sulphur colloid within one minute. Radioisotopic data were acquired in 30 sec frames for the first 30 min and subsequently in three min frames, for a further 150 min. Time zero was defined as the time of completion of the drink. Data were corrected for subject movement, radionuclide decay and gamma ray attenuation (Collins et al 1983). Gastric emptying curves (expressed as % of the maximum content of the total stomach) were derived and the content of the total stomach at 0, 15, 30, 45, 60, 90, 120, 150 and 180 min calculated. The duration of the lag phase and the 50% emptying time (T50) were also obtained. The lag phase was determined visually as the time period before any of the drink had entered the proximal small intestine (Chapter 14).

16.3.3 *Measurement of blood glucose concentrations*

Venous blood samples were obtained immediately before (-2 min) ingestion of the drink and then at 10, 15, 30, 45, 60, 90, 120, 150 and 180 min. Blood glucose concentrations were immediately determined using a portable blood glucose meter (MediSense Companion 2 meter; MediSense Inc., Waltham, MA) and the accuracy of these measurements confirmed subsequently with a hexokinase technique.

16.3.4 *Measurement of blood pressure*

Blood pressure (systolic (SBP) and diastolic (DBP)) was measured using an automated oscillometric blood pressure monitor (DINAMAP, Johnson & Johnson Pty. Ltd.) immediately before (-2 min) ingestion of the drink, at 3 min intervals for the first 60 min and subsequently for 15 min intervals until 180 min. Postprandial hypotension was defined as a fall in systolic blood pressure $\leq$ 20 mmHg after the drink, that was sustained for at least 30 min (Jansen & Lipsitz 1995). The mean arterial pressure (MAP) was calculated using the formula:

$$MAP=DBP + [^{(SBP-DBP)}/_{3}].$$

The incremental areas under the change in mean blood pressure curve (AUC) between 0-15 min, 0-30 min, 0-45 min, 0-60 min, 0-90 min, 0-120 min, 0-150 min and 0-180 min were calculated using the trapezoidal rule.

16.3.5 *Assessment of autonomic nerve function*

Autonomic nerve function was assessed using standardised cardiovascular reflex tests (Ewings & Clark 1982). Parasympathetic function was calculated by the variation (R - R interval) of the heart rate during deep breathing and the immediate heart rate response to standing ("30:15" ratio). Sympathetic function was assessed by the fall in systolic blood pressure in response to standing. Each of the test

results was scored according to the defined criteria as 0=normal, 1=borderline or 2=abnormal. A total score of ≥ 3 was considered to indicate definite autonomic nerve damage (Chapter 14).

16.3.6 *Statistical analysis*

Data were evaluated using repeated measures analysis of variance (ANOVA) and are shown as mean values ± SEM, unless stated otherwise. The difference in mean arterial blood pressure between groups and the change in blood pressure from baseline over time, were calculated using repeated measures ANOVA for the first 60 min (as the maximum fall in blood pressure had occurred in all subjects within this time). Relationships between blood pressure, gastric emptying and autonomic nerve function were assessed using linear regression analysis. A p value < 0.05 was taken to indicate significance.

16.4 RESULTS

All subjects tolerated the study well and there were no untoward events. In particular, none of the NIDDM patients or the control subjects experienced nausea, faintness or dizziness after the glucose drink. Four of the NIDDM patients had definite autonomic neuropathy and the median score for autonomic nerve function in the entire NIDDM group was 2 (range 0-4). The systolic blood pressure response to standing was not abnormal in any of the NIDDM patients. None of the control subjects had evidence of autonomic neuropathy. Both before and after the drink blood glucose concentrations were greater in the NIDDM patients compared to both the young ($p<0.005$) and old normal subjects ($p<0.005$), whereas there was no difference between the two groups of normal subjects. For example, mean blood glucose concentrations during the gastric emptying test, were in the NIDDM

13.1 ± 0.78 mmol/L, "young" normals 6.4 ± 0.16 mmol/L and "older" normals 6.4 ± 0.36 mmol/L). Postprandial hypotension was evident in seven NIDDM patients, three "older" normals, but not in any of the "young" normal subjects. Of the seven NIDDM patients with postprandial hypotension two had autonomic neuropathy. Mean arterial pressure (MAP) was higher ($p<0.005$) in the NIDDM patients compared to the "young" subjects, but the "older" subjects, both before and after the glucose load. Baseline blood pressures were in the NIDDM 98.1 ± 3.1 mmHg, "young" normals 78.4 ± 2.3 mmHg and "older" normals 87.3 ± 6.1 mmHg. There was a significant fall in blood pressure after the glucose load in the NIDDM patients ($p<0.0001$) and the "older" normals ($p<0.05$), but not the "young" subjects, with the majority of the difference being evident at 15 min and a maximum decrease between 30-45 min (Figure 16.1). The overall fall in MAP was greater in the NIDDM group, when compared to both the "young" and "older" normals ($p<0.05$ for both) whereas there was no significant difference between the latter two groups.

16.4.1 *Gastric emptying*

Gastric emptying approximated an overall linear pattern after a short lag phase in both the NIDDM patients and control subjects (Figure 16.2). There was no difference in the lag phase between the three groups (NIDDM: 1.8 ± 0.3 min "young" normals: 3.2 ± 0.9 min, "older" normals: 3.2 ± 1.0 min) or the T50 (NIDDM: 95 ± 7.3 min vs young: 120 ± 13.2 min vs older: 97 ± 8.1 min).

16.4.2 *Relationships between mean arterial pressure, gastric emptying, autonomic nerve function and blood glucose*

In the NIDDM patients, but not in either of the control groups, there was a significant relationship between the area under the change in mean blood pressure

curve and gastric emptying eg. at 15 min the area under the mean arterial blood pressure curve was related to both the intragastric retention at 15 min ($r=0.56$, $p<0.05$) and the T50 ($r=0.67$, $p<0.005$) (Figure 16.3). There were no significant relationships between the area under the blood pressure curve and either age, the score for autonomic nerve function, or the blood glucose concentration in either of the three groups.

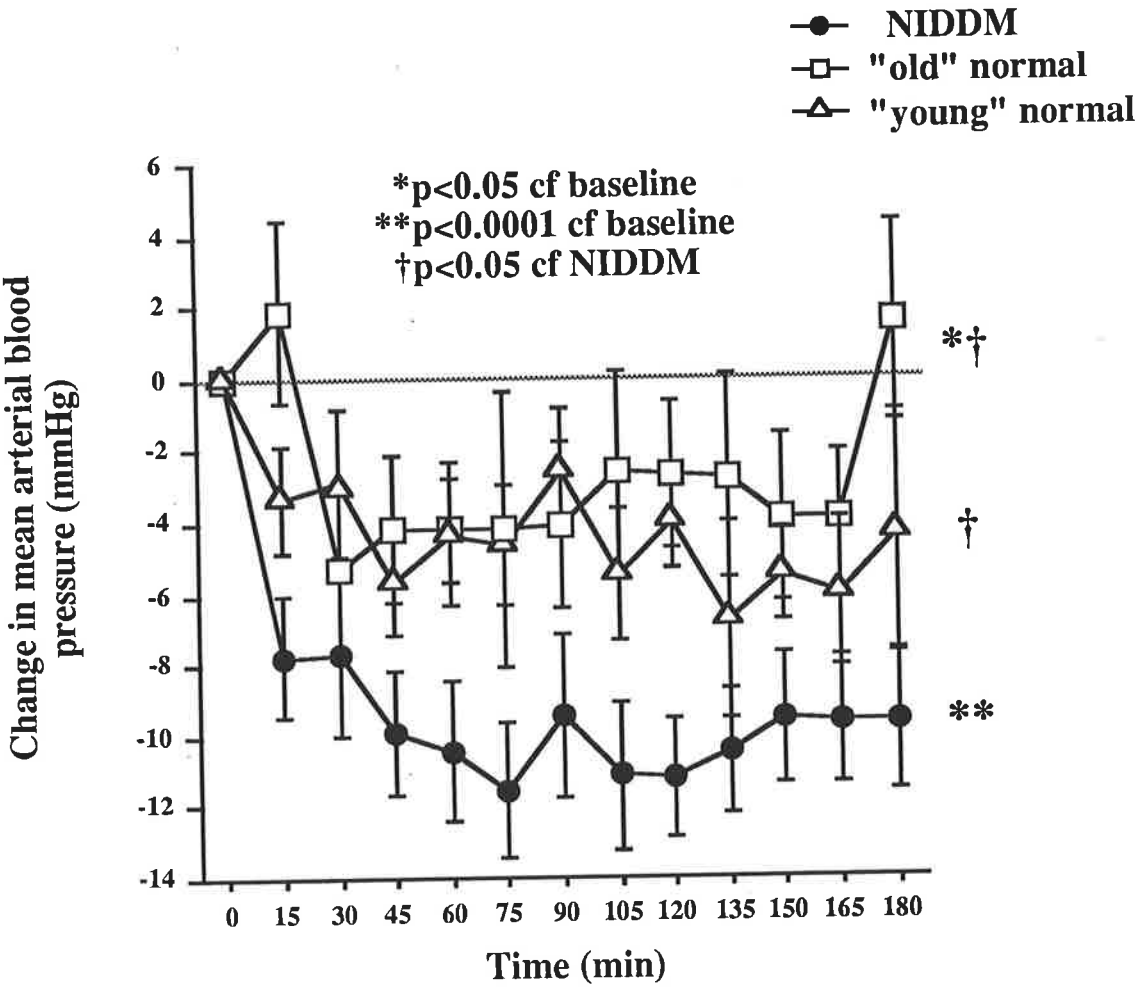

*Figure 16.1: Change in mean arterial blood pressure from baseline after a 75g oral glucose load in patients with non-insulin dependent diabetes mellitus (NIDDM), "young" normals and "older" normals. *p<0.05 cf baseline, **p<0.0001 cf baseline,†p<0.05 cf NIDDM vs "young" and "older".*

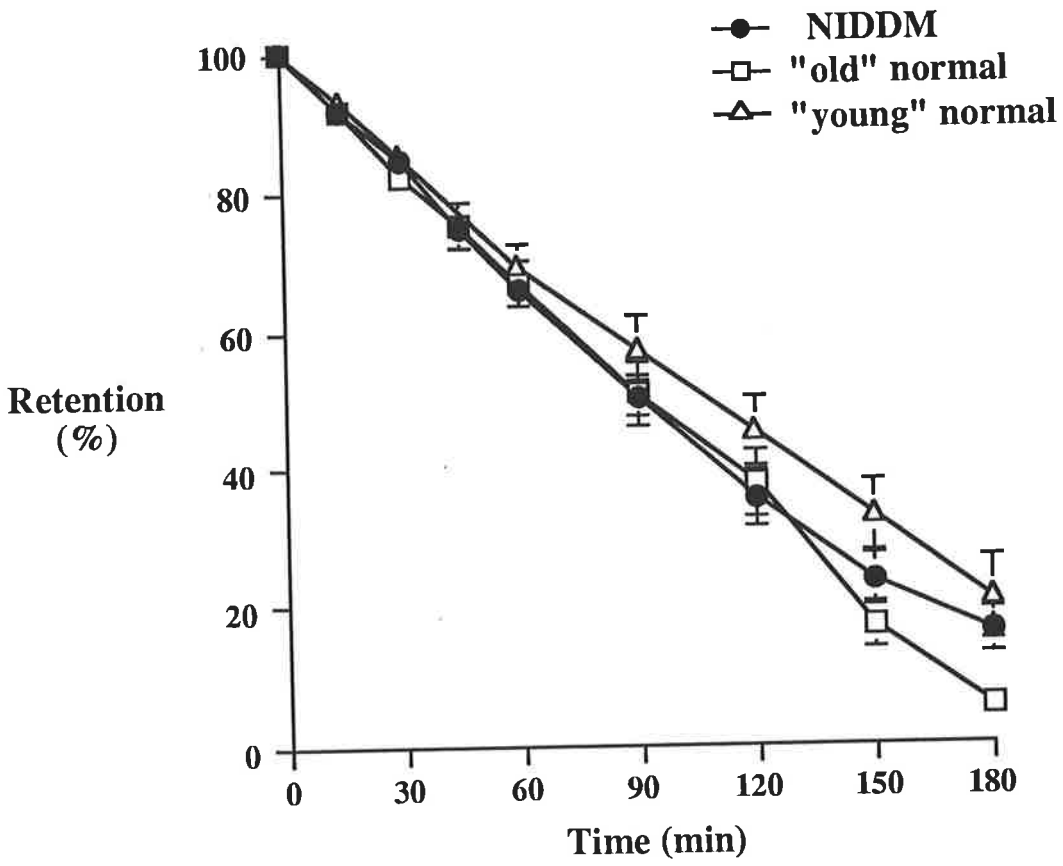

Figure 16.2: Gastric emptying of 75g glucose in 350ml water in patients with NIDDM, "young" normals and "older" normals.

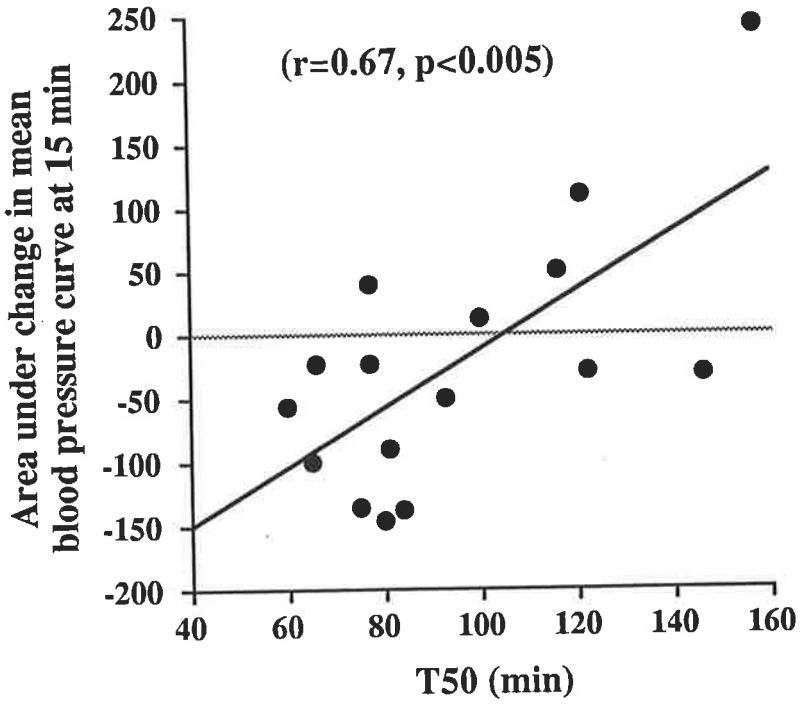

Figure 16.3: Relationship between the area under the change in mean arterial blood pressure curve between 0 and 15 min and the 50% emptying time (T50) for gastric emptying of 75g glucose in patients with NIDDM. (r=0.67, p<0.005).

16.5 DISCUSSION

The results of this study indicate that in patients with recently diagnosed NIDDM the magnitude of the reduction in blood pressure is related to the rate of gastric emptying and greater than normal, following a 75g oral glucose load. In contrast, in both "young" and "older" normal subjects, we were unable to demonstrate a significant relationship between the changes in blood pressure after oral glucose and the rate of gastric emptying of glucose.

In our study, postprandial hypotension was evident in 7 of 16 with NIDDM and 3 of the "older" controls, all of whom were symptom free. Sasaki et al reported that after ingestion of 75 g glucose a significant postprandial fall in blood pressure was evident in 7 (20%) of 35 patients with longstanding NIDDM, compatible with our observations (Sasaki et al 1992). However, in contrast to our observations, a relationship between postprandial hypotension and the presence of cardiovascular autonomic neuropathy was evident (Sasaki et al 1992). This discrepancy may reflect differences between the two studies in the duration of diabetes, as the mean duration of known NIDDM in the study by Sasaki et al was 11 yr (1-25 yr) and 23 of 35 patients had definite autonomic neuropathy, while in our study diabetes was less than one year in duration and autonomic neuropathy was evident in only 4 of 16 patients. It is not surprising that some of our patients had autonomic dysfunction, as in many cases fasting hyperglycaemia is present for several years prior to diagnosis of NIDDM (Harris et al 1992). However, our study also demonstrates that postprandial hypotension may occur in NIDDM patients who do not have evidence of cardiovascular autonomic dysfunction. The prevalence of postprandial hypotension in the "older" normal volunteers is compatible with that reported in previous studies in the elderly (Jansen & Lipsitz 1995). Studies in the elderly have shown that postprandial hypotension is more marked in hypertensive subjects, as a result of impaired baroreflex function (Jansen & Lipsitz 1995). In

our study, baseline blood pressure was greater in NIDDM patients compared to both the "young" and "older" normal subjects, although none of the NIDDM patients was hypertensive. This higher baseline blood pressure may potentially have contributed to the greater fall in blood pressure after the glucose load.

The demonstration of a significant relationship between the magnitude of the fall in blood pressure after a 75g oral glucose load and gastric emptying in patients with recently diagnosed NIDDM is novel and may be clinically important. In 30-50% of patients with both longstanding NIDDM and/or insulin dependent diabetes mellitus (IDDM) gastric emptying of either solid or nutrient liquid meals is delayed. While (Horowitz & Fraser 1994) it is recognised that gastric emptying is abnormally rapid in a small percentage of patients with longstanding diabetes mellitus, the prevalence of disordered gastric emptying in patients with recently diagnosed NIDDM is controversial. Phillips and co-workers have reported more rapid gastric emptying of both a 50g glucose load (Phillips et al 1992) and a solid meal (Schwartz et al 1996) in recently diagnosed NIDDM patients when compared to normal subjects, and have suggested that this increase in gastric emptying rate may predispose to the development of diabetes. In contrast, in Chapter 14, no difference in gastric emptying of a 75g glucose load was found between "early" NIDDM patients and age-matched control subjects. Further studies are therefore required to address this issue. It is not surprising that there was no relationship between changes in blood pressure and gastric emptying in either the "young" or "older" normals as the magnitude of the postprandial fall in blood pressure was substantially less than in the NIDDM patients; it should also be recognised that the number of subjects that we studied was relatively small. The demonstration of a relationship between the fall in blood pressure after an oral glucose load and the rate of gastric emptying has potential implications for the treatment of postprandial hypotension in NIDDM. For example, in such patients gastric emptying may be slowed significantly by either

dietary (Schwartz et al 1994) or pharmacological (Phillips et al 1993) means. In view of the observations, studies to evaluate the relationship between gastric emptying and postprandial hypotension in other groups, such as patients with autonomic failure, are appropriate. It should, however, be recognised that the rate of gastric emptying accounted for only 45% of the variance in the postprandial fall of blood pressure in NIDDM, indicating that other factors are important.

While the mechanisms responsible for postprandial hypotension are poorly understood, several factors are likely to play a role (Mathias et al 1989, Jansen & Hoefnagels 1991, Mathias 1991, Mathias & Bannister 1993, Jansen & Lipsitz 1995). The observation that oral glucose, rather than other food components such as fat or protein, causes postprandial hypotension, suggests a role for insulin (Jansen et al 1987, Jansen & Hoefnagels 1991, Jansen & Lipsitz 1995) which is known to reduce blood pressure in patients with autonomic failure and in the elderly (Jansen & Hoefnagels 1991, Jansen & Lipsitz 1995) and to increase sympathetic activity in healthy euglycaemic subjects (Anderson et al 1991, Kearney et al 1996). We have reported that there is a direct relationship between venous blood glucose concentrations and the rate of gastric emptying of an oral glucose load in normal subjects (Horowitz et al 1993, Horowitz et al 1996a) as well as patients with non insulin dependent diabetes mellitus (Chapter 14), despite the limitations of venous as opposed to arterial blood glucose measurements. While plasma insulin was not measured in our study, it can be anticipated that after the glucose load plasma glucose and insulin concentrations would have been closely related (Horowitz et al 1996a) and that the insulin response is likely to be dependent on the rate of gastric emptying (Horowitz et al 1996a). It should, however, be recognised that the previous observation that intravenous infusion of glucose has little effect on blood pressure (Jansen & Hoefnagels 1987), argues against a role for insulin. Other vasoactive gastrointestinal peptides have also been implicated in the hypotensive

response to a meal; in particular the hypotensive response to a meal is inhibited by somatostatin (Jansen & Hoefnagels 1991). Changes in sympathetic nervous system activity may also be important in postprandial hypotension. In normal subjects plasma noradrenaline rises after intake of carbohydrate, but not after other nutrients such as protein and fat (Haigh et al 1991). In both young and older subjects, oral glucose increases sympathetic activity, as measured directly by muscle sympathetic nerve activity (Haigh et al 1991); both this and the plasma noradrenaline response are attenuated in the elderly, particularly those with insulin resistance (Fagius et al 1996). In elderly patients with postprandial hypotension the rise in plasma noradrenaline after a meal is attenuated, indicative of a reduction in compensatory sympathetic nervous activity (Haigh et al 1991).

In conclusion, this study has demonstrated that while the rate of gastric emptying cannot be considered to be the direct mechanism responsible for postprandial hypotension, it is a significant determinant of the hypotensive response to an oral glucose load in patients with recently diagnosed NIDDM and is a factor that should be considered in the treatment of these patients.

CHAPTER 17

HYPERGLYCAEMIA ATTENUATES THE GASTROKINETIC EFFECT OF ERYTHROMYCIN AND AFFECTS THE PERCEPTION OF POSTPRANDIAL HUNGER IN NORMAL SUBJECTS

17.1 SUMMARY

Recent studies have demonstrated that acute changes in the blood glucose concentration may effect gastrointestinal motor function and the perception of sensations arising from the gastrointestinal tract. The major aims of this study were to determine in normal subjects whether the effects of erythromycin on gastric emptying, postprandial hunger and fullness are modified by the blood glucose concentration. Ten normal subjects (aged 20-39yr) underwent concurrent measurements of gastric emptying, blood glucose hunger and fullness on four separate occasions: twice during euglycaemia (~4mmol/L) and twice during hyperglycaemia (~15mmol/L). Either erythromycin (3mg/kg) or saline (0.9%) was administered intravenously immediately before ingestion of a radioisotopically labelled solid meal. Gastric emptying was slower ($p<0.0001$) during hyperglycaemia when compared to euglycaemia after both erythromycin and saline administration. Erythromycin accelerated the post-lag emptying rate during euglycaemia ($p<0.05$), but not hyperglycaemia. Hunger decreased ($p<0.001$) and fullness increased ($p<0.001$) after the meal. Postprandial hunger was less during hyperglycaemia after saline infusion ($p<0.05$), but not after erythromycin. Hunger was greater after erythromycin during both hyper- and euglycaemia ($p<0.05$). Postprandial fullness was greater during hyperglycaemia after saline ($p<0.05$), but not erythromycin. In conclusion, at a blood glucose concentration of ~15mmol/L

when compared to euglycaemia: (i) after administration of erythromycin (3mg/kg IV) gastric emptying of a solid meal is much slower, (ii) the effect of erythromycin on gastric emptying of a solid meal is attenuated, and (iii) the perception of postprandial hunger is reduced and that of fullness increased.

17.2 INTRODUCTION

Delayed gastric emptying occurs in 30-50% patients with long standing diabetes mellitus and may be associated with gastrointestinal symptoms such as nausea, vomiting and postprandial fullness, poor control of blood glucose concentrations and impaired oral drug absorption (Horowitz et al 1986a, Wegener et al 1990, Horowitz et al 1991, Horowitz & Fraser 1994). Although diabetic gastroparesis has been attributed to irreversible autonomic neuropathy (Feldman & Schiller 1983), it has now been established that acute changes in the blood glucose concentration have a major, reversible, effect on gastrointestinal motor function (Fraser et al 1990, Oster-Jorgensen et al 1990, Hebbard et al 1996a, de Boer et al 1992a, de Boer et al 1993, Chey et al 1995, Hasler et al 1995, Sims et al 1995, Masclee et al 1996, Russo et al 1996, Boeckxstaens et al (in press), Russo et al 1997, Schvarcz et al 1997). For example, in both normal subjects (MacGregor et al 1976, Oster-Jorgensen et al 1990) and patients with insulin dependent diabetes mellitus (Fraser et al 1990, Samsom et al 1997a) gastric emptying is slower during marked hyperglycaemia (~15mmol/L) when compared to euglycaemia, while hypoglycaemia accelerates gastric emptying (Schvarcz et al 1993, Schvarcz et al 1995). It has recently been demonstrated that physiological changes in blood glucose also affect gastric motility (Hasler et al 1995, Schvarcz et al 1997), as well as motor function in other regions of the gastrointestinal tract (Boeckxstaens et al (in press), Masclee et al 1996).

The most frequent indication for treatment of diabetic gastroparesis is the occurrence of gastrointestinal symptoms. There is a high prevalence of upper gastrointestinal symptoms in patients with insulin dependent diabetes mellitus (Schvarcz et al 1996). However, the relationship between gastrointestinal symptoms and gastric emptying in diabetes mellitus is relatively weak (Horowitz et al 1986a, Keshavarzian et al 1987, Wegener et al 1990), indicating that other factors are likely to be important in the aetiology of symptoms. Recent studies provide persuasive evidence that the blood glucose concentration may modulate the perception of sensations arising from the gastrointestinal tract (Boeckxstaens et al (in press), Chey et al 1995, Hebbard et al 1996a, Lingenfelser et al 1996, Hebbard et al 1997, Russo et al 1997, Chapter 15). For example, in normal subjects, the perceptions of nausea and fullness induced by proximal gastric distention (Hebbard et al 1996a, Hebbard et al 1996b), and small intestinal nutrient infusion (Hebbard et al 1997) are increased during hyperglycaemia, and in patients with insulin dependent diabetes mellitus, the sensation of postprandial fullness is related directly to the blood glucose concentration (Chapter 15). It has not been established whether changes in the blood glucose concentration affect postprandial sensations, such as hunger and fullness, in normal subjects.

Symptomatic diabetic gastroparesis is usually treated with prokinetic drugs (Drenth & Engels 1992), most frequently cisapride (Horowitz et al 1987, Camilleri et al 1989, McHugh et al 1992), metoclopramide (Albibi & McCallum 1983, Schade et al 1985, Snape et al 1992, McHugh et al 1992), domperidone (Brogden et al 1982, Horowitz et al 1985a) and erythromycin (Janssens et al 1990, Richards et al 1993 , Samsom et al 1997b). When given acutely in a dose of 200mg intravenously, erythromycin appears to be the most potent of these drugs and in patients with diabetic gastroparesis, may accelerate gastric emptying to a rate faster than normal (Janssens et al 1990). Erythromycin also increases the rate of gastric emptying in

normal subjects but, as with other prokinetic drugs, the magnitude of its effect is less than that observed in patients with gastroparesis (Urbain et al 1990b, Edelbroek et al 1993). In nearly all studies which have evaluated the effects of prokinetic drugs on gastrointestinal motor function in patients with diabetes, blood glucose concentrations have not been stabilised in the euglycaemic range and, at least in most cases, not monitored at all. It is also controversial whether the beneficial effect of these drugs on gastric emptying in diabetes, seen after short term administration, is sustained in the long term (Horowitz et al 1985a, Schade et al 1985, Richards et al 1993). The possibility that the blood glucose concentration may influence the motor response to prokinetic therapy has not been considered.

In patients with diabetic gastroparesis, the relationship between the magnitude of symptomatic improvement and change in gastric emptying resulting from prokinetic therapy is weak (Horowitz et al 1985a, de Caestecker et al 1989, Horowitz et al 1989a, Camilleri et al 1994). In patients with diabetes, some studies have been unable to establish a beneficial effect of prokinetic therapy on symptoms (Havelund et al 1987, Camilleri et al 1989, de Caestecker et al 1989, Camilleri et al 1994). While variations in the blood glucose concentration could potentially account for these apparent anomalies, there is also evidence that prokinetic drugs may modulate gastrointestinal symptoms by mechanisms unrelated to changes in gastric emptying per se (Chapter 12, Piessevaux et al 1997, Tack et al 1997).

The major aims of this study were to determine in normal subjects whether (i) the gastrokinetic effect of erythromycin is attenuated during hyperglycaemia and (ii) perceptions of postprandial hunger and fullness are affected by either the blood glucose concentration and/or erythromycin.

17.3 MATERIALS AND METHODS

Ten healthy, male subjects median age 25.5 yr, range (20-39) , median BMI 24.5 kg/m^2, range (20-28), participated in the study. None of the subjects had a history of gastrointestinal disease or surgery, or was taking medication. Smoking and strenuous exercise were prohibited in the 24 hour period before each experiment. Written, informed consent was obtained from each subject prior to enrolment in the study and the study protocol was approved by the Human Research Ethics Comimittee of the Royal Adelaide Hospital.

17.3.1 *Experimental protocol*

Each subject underwent concurrent measurements of gastric emptying, blood glucose concentrations and perceptions of hunger and fullness on either three or four occasions, each separated by 4-7 days. When four tests were performed, blood glucose concentrations were maintained in the euglycaemic range (4-6 mmol/L) on two days; on the other two days experiments were performed during hyperglycaemia (blood glucose 14-16 mmol/L). Either erythromycin (3mg/kg) or placebo (0.9% saline) was administered intravenously, in double-blind fashion, during both euglycaemia and hyperglycaemia. The four phases of the study (euglycaemia with saline infusion (Eug/Sal), euglycaemia with erythromycin (Eug/Ery), hyperglycaemia with saline (Hyper/Sal) and hyperglycaemia with erythromycin (Hyper/Ery)), were performed in single-blind fashion ie the investigator, but not the subject, was aware of the blood glucose concentration. In all cases the order of the experiments was randomised, however, it was initially believed that it may have been impractical for each volunteer to participate in four experiments and for this reason we elected not to perform the Hyper/Sal arm of the study in the first 4 subjects. The remaining 6 subjects underwent all four studies.

Each subject attended the Department of Nuclear Medicine at 9:00 am after an overnight fast (14 hours solids, 12 hours liquids). Two intravenous cannulae were inserted into antecubital veins (one in each arm); one cannula was used for infusion of either 0.9% saline (Eug) or 25% dextrose (Hyper) and the other for venous blood sampling and infusion of either placebo (0.9% saline) or erythromycin. After blood glucose concentrations had been stabilised at the desired concentration for 30 minutes, erythomycin (3mg/kg) as the lactobionate (David Bull Laboratories Pty. Ltd., Melbourne, Australia) mixed in saline, or saline was administered over 15 minutes (total volume 150ml). Immediately after completion of erythromycin or saline infusion, subjects started to eat the test meal. Gastric emptying was monitored for at least 180 minutes after completion of the meal while the desired blood glucose concentration was maintained.

17.3.2 *Stabilisation of blood glucose concentrations*

Hyperglycaemia was achieved using a modified glucose clamp technique (Fraser at al 1990, Hebbard et al 1996a). An intravenous bolus of 100ml 25% dextrose was given over 2 minutes, followed by an infusion of 25% dextrose (via an IMED volumetric infusion pump, San Diego, CA) starting at a rate of 400 ml/hr and adjusted to maintain the blood glucose concentration at approximately 15 mmol/L (Fraser at el 1990, Hebbard et al 1996a). During the experiments performed during euglycaemia, normal saline was infused and the rate adjusted so that the total volume was likely to be similar to that infused during the hyperglycaemic arms of the study. Starting immediately before the commencement of the intravenous infusions, venous blood samples for measurement of glucose were taken every 5 minutes. After consumption of the test meal blood samples were taken at least every 10 minutes. Blood glucose concentrations were measured using a portable blood glucose meter (MediSense Companion 2 meter; Medisense Inc, Waltham,

MA) (Jones et al 1996). The accuracy of these measurements has been confirmed using the hexokinase technique (Chapter 13).

17.3.3 *Measurement of gastric emptying*

The test meal comprised 300g lean minced beef labelled with 20MBq of ^{99m}Tc - sulphur colloid chicken liver and 150ml unlabelled water (Collins et al 1983). The solid meal was consumed over 5 minutes, followed by the water. The water was not radioisotopically labelled because of limitations in the radiation dose which could be administered to normal volunteers. Radioisotopic data were acquired with the subject seated with their back against a gamma camera (Siemens, Chicago, IL) in 1 minute frames for the first 60 minutes, and in three minute frames for the following 120 minutes. Time zero was defined as the time when the meal was completed (Collins et al 1983). Data were corrected for radionuclide decay, gamma ray attenuation and subject movement (Collins et al 1983).

A region-of-interest (ROI) was drawn around the total stomach, and this was divided into proximal and distal stomach regions (Collins et al 1988). Gastric emptying curves, expressed as percentage retention over time, were derived from total, proximal and distal stomach regions (Collins et al 1988). For the total, proximal and distal stomach the amount of the solid meal remaining at 15 minute intervals between 0 and 180 minutes, was derived. For the total stomach, the lag phase for the total stomach was determined visually as the time period before any of the solid meal had entered the small intestine (Collins et al 1983). The post-lag emptying rate (expressed as %/min) between the end of the lag phase and 150 min was also calculated (Chapter 14).

17.3.4 *Measurement of fullness and hunger*

Perceptions of fullness and hunger were quantified using a previously validated visual analog questionnaire (Sepple & Read 1989). Questionnaires were administered at -45, -30, -15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165 and 180 minutes, where time zero was the time of meal completion.

17.3.5 *Statistical Analysis*

Data were evaluated using repeated measures analysis of variance (ANOVA) with contrasts to test preplanned hypotheses of interest, enabling comparisons at specific time points, and the Wilcoxon signed rank test. Data are shown as mean values ± SEM. A p value < 0.05 was considered significant in all analyses.

17.4 RESULTS

All of the subjects tolerated the studies well and there were no untoward events. Mean blood glucose was 4.8 ± 0.4 mmol/L during euglycaemia and 14.4 ± 0.2 mmol/L during hyperglycaemia. There was no difference in the volume infused intravenously between the four study days.

17.4.1 *Gastric emptying*

Total Stomach (Figure 1a)

In all cases, gastric emptying approximated a linear pattern after an initial lag phase. The lag phase was longer during hyperglycaemia when compared to euglycaemia after administration of saline (Eug/Sal: 17.8 ± 3.6 vs Hyper/Sal: 77.8 ± 12.6 min; p=0.02), but not after erythromycin (Eug/Ery: 10.6 ± 1.4 min vs Hyper/Ery 20.2 ± 7.3 min). After administration of both saline and erythromycin, the post-lag

emptying rate was slower ($p<0.0001$) during hyperglycaemia. The lag phase was shorter after administration of erythromycin when compared to saline during both euglycaemia (Eug/Sal: 17.9 ± 11.5 min vs Eug/Ery: 10.6 ± 1.4 min; $p<0.05$) and hyperglycaemia (Hyper/Sal: 77.8 ± 12.6 min vs Hyper/Ery: 20.1 ± 7.3 min; $p<0.05$). Erythromycin accelerated the post-lag emptying rate during euglycaemia (Eug/Sal 0.56 ± 0.02 %/min vs Eug/Ery 0.63 ± 0.02 %/min; $p<0.05$), but not hyperglycaemia (Hyper/Sal 0.32 ± 0.07 %/min vs Hyper/Ery 0.24 ± 0.07 %/min).

Proximal stomach (Figure 1b)

The retention in the proximal stomach was greater during hyperglycaemia when compared to euglycaemia after both saline ($p<0.0005$) and erythromycin ($p<0.001$). Erythromycin did not affect the content of the proximal stomach during hyperglycaemia or euglycaemia.

Distal stomach (Figure 1c)

The content of the distal stomach was greater during hyperglycaemia when compared to euglycaemia after administration of both saline ($p<0.05$) and erythromycin ($p<0.05$). During both euglycaemia and hyperglycaemia, the retention in the distal stomach was less after erythromycin ($p<0.05$).

17.4.2 *Hunger and fullness*

Hunger (Figure 2a)

There were no significant differences between the groups in the score for hunger prior to meal ingestion. Hunger decreased ($p<0.0001$) after the meal on all study days. Hunger was less during hyperglycaemia than euglycaemia after administration of saline eg at 150 min; (Eug/Sal 34.3 ± 10.2mm vs Hyper/Sal 23.3

± 4.9 mm; $p<0.05$), but not erythromycin (Eug/Ery 42.7 ± 9.6mm vs Hyper/Ery 39.9 ± 10.4 mm). The score for hunger was greater after erythromycin on both study days when compared to saline ($p<0.05$). There was no significant difference in the score for hunger on the Hyper/Ery study day when compared to control (Eug/Sal).

Fullness (figure 2b)

Prior to ingestion of the meal, there were no differences in scores for fullness; fullness increased ($p<0.0001$) after the meal on all study days. The mean score for fullness between 0-180min was greater during hyperglycaemia after administration of saline, but not erythromycin (Eug/Sal 28.0 ± 8.4mm vs Hyper/Sal 32.4 ± 11.1mm; $p<0.05$ and Eug/Ery 26.4 ± 8.0mm vs Hyper/Ery 26.6 ± 7.4mm).

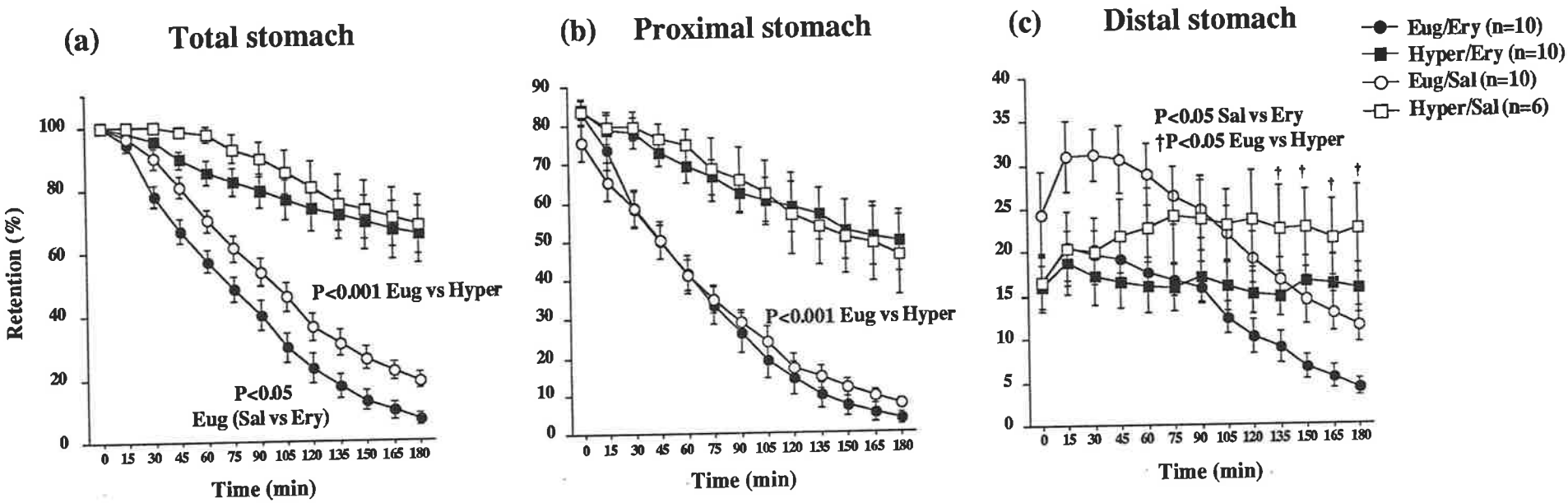

Figure 17.1: Retention of the meal in total, proximal and distal stomach regions of interest for the four study days; Eug/Ery, Hyper/Ery, Eug/Sal, Hyper/Sal. Data are mean values ± SEM.

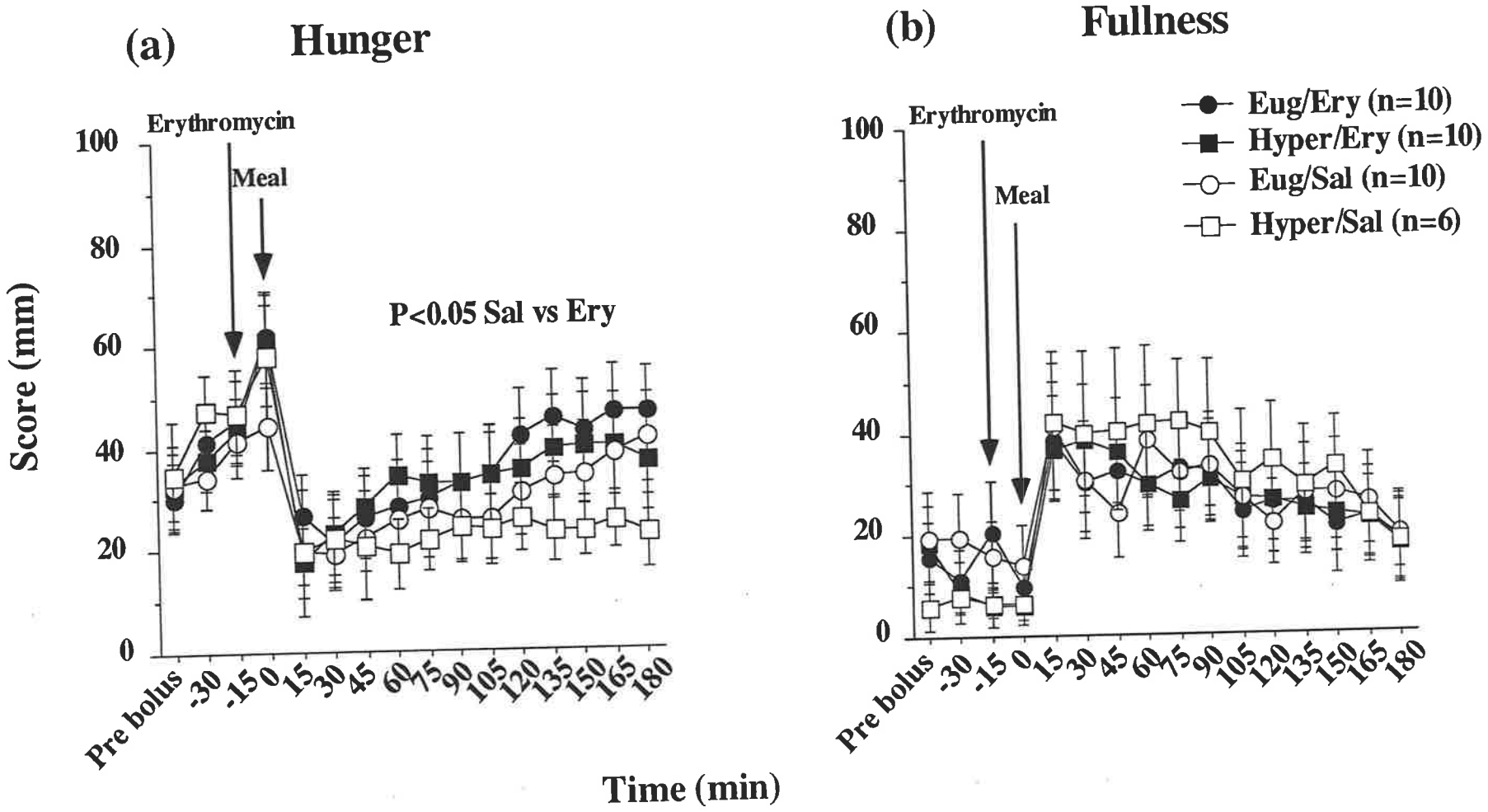

Figure 17.2: Scores for hunger and fullness before and after meal ingestion for the four study days; Eug/Ery, Hyper/Ery, Eug/Sal, Hyper/Sal. Data are mean values ± SEM.

17.5 DISCUSSION

This study has demonstrated in normal subjects that at a blood glucose concentration of ~15mmol/L when compared to euglycaemia: (i) after administration of erythromycin (3mg/kg IV) gastric emptying of a solid meal is much slower, (ii) the effect of erythromycin on gastric emptying of a solid meal is attenuated, and (iii) the perception of postprandial hunger is reduced and that of fullness increased. The study also suggests that erythromycin has the capacity to modulate the sensation of postprandial hunger. These observations have substantial implications for the treatment of gastroparesis and upper gastrointestinal symptoms in patients with diabetes mellitus.

The prokinetic effect of erythromycin on gastric emptying in both normal subjects and patients with diabetes mellitus (Janssens et al 1990, Urbain et al 1990b, Catnach & Fairclough 1992, Peeters et al 1992, Tack et al 1992, Edelbroek et al 1993, Samsom et al 1997b) is well established. These effects are dose-related (Peeters 1993). The magnitude of the observed reduction in the lag phase and acceleration of the post-lag emptying of a solid meal by erythromycin during euglycaemia is similar to that reported in previous studies in normal subjects (Urbain et al 1990b, Edelbroek et al 1993). This gastrokinetic effect is associated with the stimulation of highly expulsive antral contractions (Sarna et al 1991, Fraser et al 1992, Tack et al 1992), a reduction in the number of pressure waves localised to the pylorus (Fraser et al 1992) and an increase in proximal gastric tone (Bruley des Varannes et al 1995). The use of erythromycin is known to be associated with the delivery of larger solid particles into the small intestine (Lin et al 1994), as indicated by the reduction in the lag phase. In contrast to a previous study (Edelbroek et al 1993), the increased post-lag emptying rate observed in this study, was not associated more rapid emptying from the proximal stomach, but with a reduced content of the distal stomach. This apparent discrepancy may reflect

differences in the composition and volume of the test meal between studies, particularly the nutrient content of the liquid component of the meal (Horowitz et al 1989b).

It has been established that marked hyperglycaemia slows gastric emptying in both normal subjects (MacGregor et al 1976, Oster-Jorgensen et al 1990) and patients with diabetes (Fraser et al 1990, Samsom et al 1997a); the magnitude of the slowing of emptying during hyperglycaemia that we observed is consistent with these previous studies. Marked hyperglycaemia is known to be associated with the stimulation of pyloric motility (Fraser et al 1991), suppression of antral pressure waves (Hasler et al 1995), as well as a change in their organisation (Samsom et al 1996), and a reduction in fundic tone (Hebbard et al 1996a, Hebbard et al 1997). The observation that the slowing of gastric emptying by hyperglycaemia is associated with increased retention of the meal in the proximal stomach may be attributable to fundic relaxation (Hebbard et al 1996a, Hebbard et al 1997).

Erythromycin stimulates gastrointestinal motility by acting as an agonist of the gastrointestinal hormone motilin; this may reflect direct activation of motilin receptors located on smooth muscle cells (Peeters et al 1989) and/or the stimulation of acetylcholine release from motilin receptors on cholinergic nerves (Sarna et al 1991, Peeters 1993, Parkman et al 1995). The latter mechanism is likely to be more important in humans (Peeters 1993). This study has not addressed the mechanisms responsible for the effect of hyperglycaemia on the gastrokinetic effect of erythromycin, but modifications in cholinergic activity or sensitivity to motilin may potentially be important. In healthy subjects hyperglycaemia reduces plasma motilin (Barnett & Owyang 1988) and suppresses secretion of pancreatic polypeptide; the latter effect is indicative of a reduction in vagal cholinergic activity (de Boer et al 1992a). Exogenous administration of motilin has been shown to

accelerate gastric emptying in patients with diabetic gastroparesis, but blood glucose concentrations were apparently not monitored in these studies (Schmid et al 1991, Peeters et al 1992). In the study by Janssens et al which established the marked effect of intravenous erythromycin (200mg) on gastric emptying in diabetic gastroparesis (Janssens et al 1990), oral administration of erythromycin (250mg tds) for three weeks, had a lesser effect on gastric emptying. The effects of intravenous erythromycin were assessed when blood glucose concentrations were maintained in the euglycaemic range, however, it is unclear whether this was the case for oral erythromycin (Janssens et al 1990). In view of our observations, evaluation of the effects of hyperglycaemia on the motor effects of other prokinetic drugs, particularly those which are not motilin agonists, such as cisapride, domperidone and metoclopramide, would be of interest. While it is appropriate to determine whether the effects of erythromycin on gastric emptying in patients with diabetes mellitus are modified by the blood glucose concentration, it is likely that the effects would be similar to those observed in normal subjects, as the magnitude of the effects of hyperglycaemia on gastric emptying in patients with diabetes mellitus are comparable to those observed in normal subjects (MacGregor et al 1976, Fraser et al 1990, Oster-Jorgensen 1990, Samsom et al 1997a, Schvarcz et al 1997). The observations from this study suggest that in evaluating the effects of prokinetic drugs in patients with diabetes, blood glucose concentrations should ideally be maintained in the euglycaemic range; to date, this has been the case in only a few studies (Janssens et al 1990, Samsom et al 1997a).

The factors which influence postprandial upper gastrointestinal sensations and appetite are poorly defined. Acute changes in the blood glucose concentration affect sensations arising from the gastrointestinal tract (Chey et al 1995, Lingenfelser et al 1996, Hebbard et al 1996a, Russo et al 1997, Boeckxstaens et al (in press), Chapter 14, Chapter 15). In patients with insulin dependent diabetes,

gastrointestinal symptoms occur more frequently in those patients with poor, long term, glycaemic control as assessed by the glycosylated haemoglobin concentration (Schvarcz et al 1996). The mechanisms mediating the effects of the blood glucose concentration on gastrointestinal sensation are unknown. In this study we have demonstrated that marked hyperglycaemia reduced postprandial hunger and increased fullness in normal subjects. These observations are consistent with a previous study in patients with insulin dependent diabetes (Chapter 15) and may potentially relate to an increase in intragastric volume due to slowing of gastric emptying (MacGregor et al 1976, Fraser et al 1990, Oster-Jorgensen 1990, Samsom et al 1997, Schvarcz et al 1997). It is, however, of interest that both pre- and postprandial fullness have been reported to be increased in hyperglycaemic patients with non-insulin dependent diabetes when compared to age-matched normal volunteers, although in this study there was little difference in gastric emptying between the two groups (Chapter 14). It should be recognised that the symptomatic response to prokinetic therapy is also likely to be dependent on factors which are not related directly to the blood glucose concentration. For example, Camilleri et al have reported that patients with extrinsic vagal damage are less likely to respond (Camilleri et al 1994).

The sensation of postprandial hunger was greater after erythromycin during both euglycaemia and hyperglycaemia. Furthermore, an effect of hyperglycaemia on postprandial hunger and fullness was not evident after administration of erythromycin. These observations are unlikely to be attributable to differences in intragastric volume, as erythromycin had little effect on gastric emptying during hyperglycaemia. Previous studies of the effects of prokinetic therapy on gastrointestinal symptoms in patients with diabetes have not considered the potential impact of the blood glucose concentration. Recent studies also indicate that prokinetic agents such as cisapride (Chapter 12) and erythromycin (Piessevaux et al

1997) may alter gastrointestinal sensation by mechanisms unrelated to gastric emptying. For example, in normal subjects, cisapride increased preprandial hunger and reduced the satiating effect of a meal containing discrete oil and aqueous components (Chapter 12) and more recently, it has been reported in abstract form that intravenous erythromycin (200mg) increases the threshold perception of discomfort during proximal gastric distention (Piessevaux et al 1997).

CHAPTER 18

CONCLUSIONS

The studies presented in this thesis provide novel information relating to normal and disordered gastric motility and the role of the gastrointestinal tract in appetite regulation in humans.

In Chapter 6, two techniques to assess antral motility after a solid meal (manometry and scintigraphy), were compared. Manometry, accurately records lumen-occlusive pressure waves occurring as a result of gastric contractions. Such contractions are almost certainly mechanically significant ie. when the lumen is occluded, neither orad or aborad movement of ingesta is feasible. However, contractions which indent, but do not occlude the lumen may also be important. The scintigraphic method described in Chapter 6 is clearly more sensitive than manometry in detecting antral contractions but cannot identify those contractions which result in lumen-occlusion. Nevertheless, its non-invasiveness when compared to manometry as well as the capacity to simultaneously measure both total stomach gastric emptying and intragastric meal distribution make this technique very promising. Scintigraphic assessment of antral motility could possibly be developed further to provide information about the temporal and spatial organisation of antral contractions. While such measurements can also be performed using magnetic resonance imaging (MRI) (Schwizer et al 1994), this latter technique is both very expensive and has limited availability. It should also be recognised that it has not been established whether this scintigraphic technique can be used to assess antral motility after ingestion of liquid meals; such a study is indicated.

In Chapters 7 and 8 the use of ultrasound to measure gastric emptying of liquids in normal subjects was assessed. Ultrasound has many potential advantages over scintigraphy, in particular its widespread availability, lack of radiation and non-invasive nature. Measurements of gastric emptying of both a high and low nutrient liquid meal using ultrasound and scintigraphy correlated closely. Of interest was the fact that ultrasound measurements were more closely related to the content of the distal, rather than the proximal stomach, consistent with the concept that liquid emptying is dependent on the function of the antrum. While the results of this study indicated that ultrasound is a promising technique for measurement of gastric emptying in humans, it does have some disadvantages. In particular, it can be technically challenging and cannot discriminate between solid and liquid components of the meal. Ultrasound techniques do, however, have the capacity to measure contractile activity in the distal stomach (Hausken et al 1993) and transpyloric flow (Hausken et al 1992). While this study established that there is a close correlation between ultrasound and scintigraphic measurements of gastric emptying in normal subjects, further studies in patients with disordered gastric emptying are required to determine the clinical applicability of the technique.

The study reported in Chapter 8 demonstrated that in normal subjects the sensation of postprandial fullness; but not hunger, is related to both antral area and the content of the distal stomach; consistent with the concept that fullness is related to antral distension and that fullness and hunger are not simply reciprocals of each other. Previous studies in patients with functional dyspepsia (Hausken & Berstad 1992) and diabetes mellitus (Undeland et al 1996) have established a relationship between upper gastrointestinal symptoms and antral area; in symptomatic patients as a group, antral area is greater than normal. It has also been demonstrated that intragastric meal distribution is frequently abnormal in patients with non-ulcer dyspepsia (Mangnall et al 1994, Troncon et al 1994). These studies, therefore

suggest that antral tone is a major determinant of upper gastrointestinal symptoms in both health and disease. Unfortunately, at present there are no techniques available which have the capacity to evaluate antral tone effectively in humans; the barostat technique has only been used to assess the motor function of the proximal stomach (Azpiroz 1997). Nevertheless it would be of interest to determine whether other gastrointestinal stimuli which induce satiation, eg small intestinal nutrient infusion, also modify antral area.

The effects of meal volume and posture on gastric emptying of a solid meal and sensations of hunger and fullness in normal subjects were evaluated in the study reported in Chapter 9 and this established, for the first time, that gastric emptying of solids is load dependent. In contrast, body posture had no effect on gastric emptying. The mechanisms mediating the effects of meal volume are uncertain, but likely to involve changes in antral motility; accordingly it would be of interest to perform concurrent measurements of gastric emptying, antral area, antral wall motion, as well as patterns of lumen-occlusion. This study also evaluated the effect of meal volume and posture on appetite. Predictably, hunger was less after the larger meal in both postures. The difference was apparent soon after meal ingestion, when very little food had left the stomach and is therefore likely to be related to greater gastric distension induced by the larger meal, rather than differences in the exposure of the small intestine to nutrients. While postprandial hunger was less in the left lateral when compared to the sitting position, the differences were small. The observation that postprandial hunger was inversely related to the content of the distal stomach, is consistent with findings reported in Chapters 7 and 8, and indicate that antral tone/distension are important in regulating appetite.

In Chapters 10 and 11, the effects of posture on gastric emptying of oil and aqueous (low nutrient beef soup) meal components were evaluated. In normal subjects (Chapter 10) gastric emptying of oil was initially faster in the lateral decubitus when compared to the sitting position, which reflected the intragastric distribution of the oil; the oil "layered" on top of the aqueous phase and was closer to the pylorus in the lateral decubitus position. However, after the lag phase the overall rate emptying of oil was not different between postures, indicating the importance of small intestinal receptors in the regulation of gastric emptying of nutrients. As a result of small intestinal feedback, gastric emptying of the aqueous phase was markedly delayed in the lateral decubitus position, when compared to sitting. An understanding of the gastric emptying of fat is pivotal to the optimum use of pancreatic enzyme supplements in these patients with pancreatic insufficiency. In patients with cystic fibrosis and exocrine pancreatic insufficiency, gastric emptying of oil was faster than normal in both postures (Chapter 11), and faster in the lateral decubitus than in the sitting position. The more rapid emptying of oil in these patients is attributable to reduced feedback from small intestinal receptors as a result of impaired digestion. In normal subjects posture influenced postprandial hunger; the latter being less in the lateral decubitus position. It was believed that the decrease in hunger may have been attributed to the greater intragastric volume in this posture, however, this was not the case and hunger was inversely related to gastric emptying of the oil but not the aqueous, phase. Since the majority of the nutrients were contained in the oil phase, these observations suggest that in normal subjects after ingestion of a meal containing both oil and aqueous components, small intestinal mechanisms may be more important than gastric distension in regulating appetite. The observation in patients with cystic fibrosis that hunger did not change after the meal, suggests that the fat must be digested to cause satiety. These hypotheses could be addressed by an evaluation of the effect of administration of pancreatic enzymes (probably intraduodenally) on

gastric emptying of oil and appetite in patients with pancreatic insufficiency. It appears probable that pancreatic enzyme supplementation would slow gastric emptying and normalise sensations of hunger and fullness.

Cisapride is arguably the optimum drug for the treatment of gastrointestinal symptoms in patients with gastroparesis. The effects of cisapride on gastric emptying of a meal containing oil and aqueous meal components and appetite were evaluated in normal subjects and reported in Chapter 12. Cisapride accelerated gastric emptying of oil by shortening the lag phase, and increased the retention of oil in the distal stomach. These observations are consistent with the concept in normal subjects that cisapride, in a therapeutic dosage, does not overcome the small intestinal mechanisms which regulate gastric emptying of nutrient containing meals (Wiseman & Faulds 1994). It is unlikely that improvement in symptoms by prokinetic drugs in patients with gastroparesis is totally attributable to changes in gastric emptying, as the relationship between the magnitude of improvement in symptoms and gastric emptying is weak. Of interest was the observation that despite minimal changes in gastric emptying, preprandial hunger was greater, and postprandial fullness less on cisapride. Other, more recent studies also indicate that prokinetic agents have the capacity to modify sensations arising from the gastrointestinal tract in normal subjects (Chapter 17, Piessevaux et al 1997, Tack et al 1997). In view of the previous observations (Chapters 7 and 8), it would be of interest to determine the effects of cisapride on antral area. Although weight gain is not a recognised effect of cisapride, the possibility that this drug may alter food intake warrants exploration.

The studies reported in Chapters 13-17 focussed on gastric emptying in patients with diabetes mellitus and the effects of hyperglycaemia on the prokinetic action of

erythromycin, a drug commonly used to treat gastroparesis in patients with diabetes mellitus.

Gastric emptying has been reported to be delayed in approximately 30-50% of patients with longstanding diabetes mellitus (Horowitz et al 1996, Merio et al 1997). This was confirmed in Chapter 13 in which the prevalence of abnormal intragastric meal distribution was also assessed. While the intragastric distribution of both solids and liquids was frequently abnormal, evaluation of intragastric meal distribution had only a minor effect on the capacity of scintigraphy to detect abnormal gastric motility. The relationship between the presence of symptoms and intragastric meal distribution was relatively weak, indicating that abnormal intragastric meal distribution is not a direct cause of gastrointestinal symptoms but rather a marker of gastric motor abnormality.

The prevalence of disordered gastric emptying in patients with recently diagnosed NIDDM is controversial. In Chapter 14 it was established that gastric emptying of glucose was slightly slower in "early" NIDDM when compared to normal subjects. This observation conflicts with Phillips and co-workers who have reported that gastric emptying of both glucose (Phillips et al 1992) and a solid meal (Schwartz et al 1996) is much more rapid than normal in "early" NIDDM. While a number of factors may potentially contribute to this discrepancy, it should be recognised that the prevalence of disordered gastric emptying in this group during euglycaemia, has not been evaluated.

The determinants of gastrointestinal symptoms, in particular postprandial fullness, in IDDM and NIDDM patients were evaluated in studies reported in Chapters 14, 15 and 17. In IDDM, postprandial fullness was related to both the blood glucose concentration and the intragastric content (Chapter 15). The observation in patients

with "early" NIDDM that both pre- and postprandial fullness were greater in patients when compared to control subjects in whom blood glucose concentrations were much lower (Chapter 14) is also consistent with the concept that the blood glucose concentration modulates gut sensations. It should, however, be recognised that both studies were cross-sectional; the relationship between symptoms and glycaemic control in diabetes should be explored further, probably using a paired study design and a glucose clamp technique. The results of the study reported in Chapter 17 indicate that marked hyperglycaemia affects the sensations of postprandial hunger and fullness in normal subjects. The impact of chronic, as opposed to acute glycaemic control on symptoms also warrants additional evaluation.

The studies reported in Chapters 13 and 14 also support the concept that modulation of gastric emptying could be used to optimise glycaemic control in patients with diabetes. There was a direct relationship between the rise in blood glucose and the rate of liquid gastric emptying in patients with longstanding diabetes mellitus in whom the mean blood glucose during the gastric emptying measurement was $\leq$ 15mmol/L (Chapter 13). In patients with NIDDM, the rate of blood glucose after a 75g oral glucose load was also related to the rate of gastric emptying; accounting for $\approx$36% of the variance in peak blood glucose concentrations (Chapter 14). The observation of a relationship between the rise in blood glucose concentration and the rate of gastric emptying in patients with diabetes has important implications for the management of blood glucose levels in these patients, particularly in patients with NIDDM. In this group previous studies show that by slowing gastric emptying either by dietary (Schwartz et al 1994) or pharmacological (Phillips et al 1993) means, improves glycaemic control, at least in the short-term, probably because of the delay in insulin release which is characteristic of this disorder. It should be recognised that the blood glucose response to a carbohydrate load is

particularly dependent on several factors including digestion, absorption and hepatic glucose metabolism, as well as the rate of gastric emptying; the magnitude of the influence of gastric emptying on glucose absorption has not been assessed adequately. Further studies using either non-digestible glucose analogues, such as 3-O-methyl-D-glucose (3-OMG), or radiolabelled glucose, are required to explore this issue.

The observations reported in Chapter 16 indicate that disordered gastric emptying, particularly more rapid gastric emptying, may contribute to postprandial hypotension, which is now recognised as an important clinical problem in the elderly and in patients with autonomic dysfunction, leading to syncope and falls. While the observed relationships between the magnitude of the fall in blood pressure after oral glucose and gastric emptying in patients with NIDDM was not unexpected, the number of subjects was relatively small and further studies are required to explore this issue. In particular, it would be appropriate to study a large cohort of "young" and "elderly" normal subjects and to determine whether slowing of gastric emptying is associated with a reduction in the postprandial fall in blood pressure.

The symptoms associated with gastroparesis are often treated with prokinetic drugs such as cisapride, metoclopramide, domperidone and erythromycin. In the study reported in Chapter 17, the effects of marked hyperglycaemia on the prokinetic action of erythromycin were evaluated in normal subjects. Hyperglycaemia was shown to markedly slow gastric emptying of a solid meal when compared to euglycaemia, and reduce the prokinetic effect of erythromycin. The mechanisms responsible for these effects were not evaluated, although it is likely that modifications in cholinergic activity are important. Recent studies have demonstrated that physiological changes in the blood glucose concentration

influence gastrointestinal motility (Schvarcz et al 1997). Studies to examine the effects of physiological changes in blood glucose concentrations (eg 4mmol/L vs 8mmol/L) on the prokinetic action of erythromycin are warranted. The effects of hyperglycaemia on the response to other prokinetic agents such as cisapride, metoclopramide and domperidone, should also be evaluated (both on gastric motility and motility in other regions of the gastrointestinal tract). While it is likely that the effects of hyperglycaemia on the action of erythromycin would be similar in patients with diabetes mellitus to those observed in normal subjects, this issue should be formally assessed; both in patients who have normal and delayed gastric emptying during euglycaemia.

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