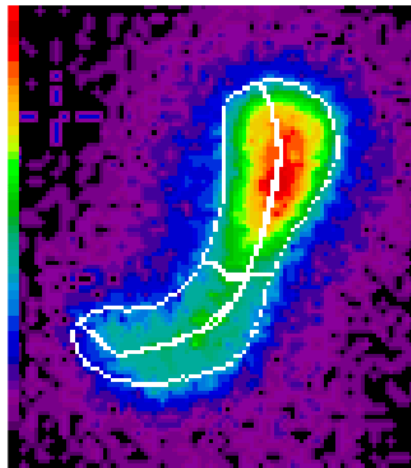




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PATHOPHYSIOLOGICAL ROLE OF FUNDIC TENSION RECEPTORS IN FUNCTIONAL DYSPEPSIA



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LIST OF PUBLICATIONS

Publications pertaining to this thesis

Articles

Piessevaux H, Tack J, Walrand S, Pauwels S, Geubel A. Intragastric distribution of a standardized meal in health and functional dyspepsia: correlation with specific symptoms. *Neurogastroenterol Motil* 2003; 15:447-55. (chapter 4)

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CHAPTER 1: INTRODUCTION

The motor functions of the stomach are to accommodate, store, triturate and empty the meal in a regulated fashion to the duodenum for digestion and absorption in the small intestine. These functions are not vital, since life is possible after total gastrectomy, providing vitamin B₁₂ is injected.

The action of the stomach is double: motor and secretory. The secretory aspect of the gastric physiology will not be discussed in this introduction, as it is not relevant to the object of this thesis.

1.1 Structural anatomy of the stomach

1.1.1 Tissue layers of the stomach

The gastric wall comprises four layers: the mucosa, the submucosa, the muscularis propria and the serosa (figure 1.1).

The mucosa is coated by a simple columnar epithelium that is punctuated generously by numerous pits (foveolae) which serve numerous, branched tubular glands. Differences in the gastric glands permit identification of three principal gastric regions. The cardiac glands are lined by mucous neck cells. The oxyntic glands contain mucous neck cells, parietal cells (secreting HCl), endocrine cells and chief cells (secreting pepsinogen). In the antrum, the pyloric glands are much deeper, coiled and branched. They contain mucous cells, (amine precursor uptake and decarboxylation) APUD-cells (secreting gastrin and other polypeptides and amines) and (enterochromaffin-like) ECL-cells in the antral region). The mucosa is separated from the submucosa by the muscularis mucosae. The submucosa contains a dense network of collagen fibres around vascular and nervous structures (submucosal plexus). The muscularis propria of the stomach contains not only circular internal and longitudinal external muscle layers but also oblique fibres predominantly on the anterior and posterior wall in continuity with the lower oesophageal sphincter and which are located in the innermost layer. The serosa forms a thin envelope covered by mesothelial cells.

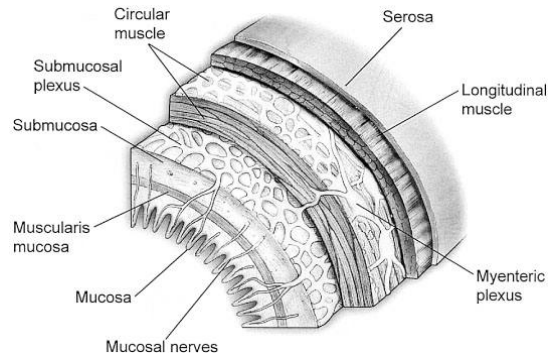


Figure 1.1: Organization of the enteric nervous system. The enteric nervous system is composed of two major plexi—one submucosal and one located between the circular and longitudinal smooth muscle layers. These neurons receive and coordinate neural transmission from the gut and central nervous system (adapted from Shetzline 2002).

1.1.2 Innervation of the stomach

The stomach is innervated both by sympathetic and parasympathetic components of the autonomic nervous system and contains a segment of the enteric nervous system (figures 1.2, 1.3 and 1.4).

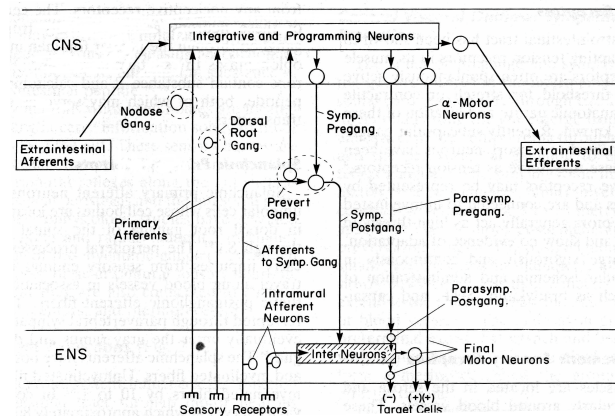


Figure 1.2: Diagrammatic representation of the innervation of the gut. The sensory fibres connected to sensory receptors in the gut can be classified into three groups: primary afferents to the CNS, afferents to the pre-vertebral sympathetic ganglia and intrinsic primary afferents. The efferent neurones can also be classified into 3 groups: α motor neurones located in the CNS, neurones located in the pre-vertebral sympathetic ganglia and intrinsic motor neurones (adapted from Goyal 1989)

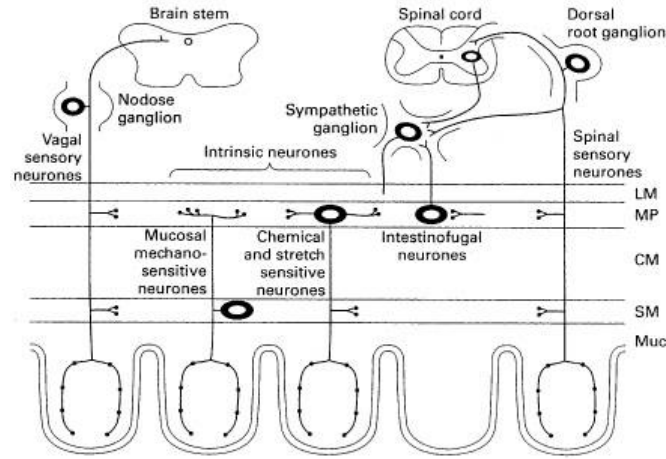


Figure 1.3: Types of sensory neurons in the gastrointestinal tract. Note: (1) Vagal and spinal sensory neurons, the location of their cell bodies, and their central connections are shown on the extreme left and right, respectively; (2) two types of intrinsic primary afferent neurons (IPANs) are represented in the centre. Their cell bodies lie either in the submucosal (SM) plexus or myenteric plexus (MP). (CM, circular muscle; LM, longitudinal muscle; MP, myenteric plexus; Muc, mucosa.) (adapted from Quigley 2002)

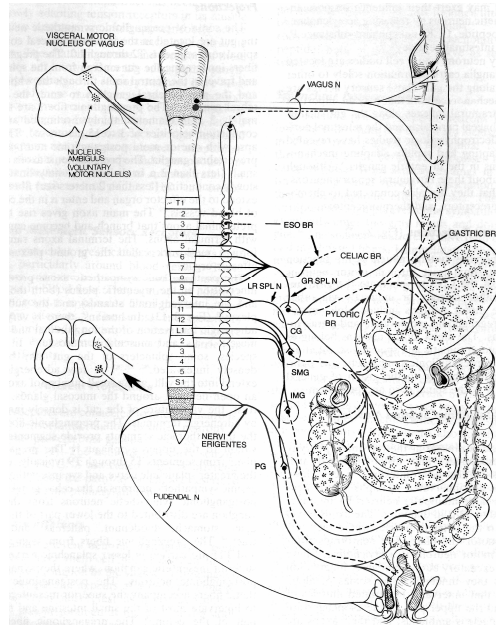


Figure 1.4: Innervation of the gastrointestinal tract (adapted from Goyal 1989).

The sympathetic innervation of the stomach is supplied by postganglionic fibres arising from the celiac plexus through nerve plexuses located adjacent to the gastric and gastro-epiploic arteries; the preganglionic sympathetic fibres arise from the sixth through the eighth thoracic segments of the spinal cord.

The parasympathetic nerve supply to the stomach is derived from the right and left vagus and their branches. The left vagus nerve, usually in the form of one or two vagal trunks, enters the abdomen on the anterior surface of the stomach. It then gives off several nerve filaments to the region of the cardia, an occasional celiac branch, and a longer major branch that runs anterior and to the right of the lesser curvature as the anterior nerve of Latarjet. This nerve supplies anterior gastric branches to the anterior surface of the stomach in a 'crow's foot' distribution in the region of the pylorus and distal antrum. The right vagus nerve, also usually as one or two trunks, enters the abdomen on the posterior surface of the gastro-oesophageal junction and supplies branches to both surfaces of the stomach and posterior nerve of Latarjet, which has a distribution to the posterior surface of the stomach similar to that of the anterior nerve.

The enteric nervous system comprises two major ganglionated plexuses and interconnecting fibres as well as several subsidiary groupings of fibres which arise from the plexuses and supply the muscle, blood vessels, endocrine cells and mucosa. The ganglionated plexuses within the enteric nervous system are the myenteric plexus, interpositioned between the circular and the longitudinal muscle layers, and the submucosal plexus in the submucosal connective tissue layer. It is generally accepted that the myenteric plexus is mainly involved in the control of gastrointestinal motility, while the submucosal plexus is mainly involved in control of secretion, absorption and blood flow (Furness and Costa 1987).

1.2 Motor physiology of the stomach

1.2.1 Electrical basis of gastric motility

Contractile activity at any level in the gastrointestinal tract is based on fundamental electrophysiological properties (Szurszewski 1987). A consistent feature of gastrointestinal myoelectric activity is an omnipresent, highly regular, and recurring electrical pattern called 'slow wave' in the smooth muscle cells. Contractions are however related to the occurrence of action potentials ('spikes'). Spikes may occur spontaneously in smooth muscle cells that have resting membrane potentials above the threshold value for generation of spike potential. Alternatively, spikes occur when membrane potential is depolarised above a certain threshold voltage by slow waves or stimulatory neurohumoral agents. Changes in electric potential determine calcium fluxes, which are the basis for muscle contraction. As spikes occur only on the crest of slow waves, the frequency of contractions are phase-locked to slow waves. Thus in the distal stomach, where slow waves occur at a frequency of three cycles per minute, the maximum frequency of phasic contractions is also three cycles per minute. In the duodenum the slow wave frequency is 12 cycles per minute. Along the length of the gut, patterns of motor activity during fasting and after food ingestion differ fundamentally.

1.2.2 Functional partition of the stomach

Although the stomach constitutes a single anatomic unit, it is functionally divisible into proximal and distal parts (Kelly 1980). While the distal stomach is involved in trituration of food particles to a small size before their delivery into the duodenum, the proximal stomach relaxes on meal ingestion to receive and store ingested food. Although the last two decades the knowledge of the motor function of the stomach has greatly progressed, there is still discussion about the respective role of the proximal and distal stomach on the emptying of the liquid and solid phases of a meal. Indeed, the correlation between manometric patterns, wall motion or deformation

and transpyloric flow is still difficult to establish in human studies (Horowitz 1994).

Motor activity of the proximal stomach and gastric accommodation

Some researchers have been convinced for many years that the proximal stomach is electrically silent (Kelly 1969; Hinder 1977). Some recent data however, obtained in humans undergoing various surgical interventions, have shown that oral propagation of slow wave activity at 3 cycles/min occurs originating from the gastric pacemaker region located on the greater curvature (Schirmer 1998). In spite of this finding, the phasic motor activity pattern is different from that of the antrum.

Whereas phasic pressure activity can be monitored manometrically, methodological difficulties have precluded the quantification of gastric tone in humans until the introduction of the electronic barostat in human research (Azpiroz 1987a). The barostat maintains a constant preselected pressure within a flaccid air-filled bag introduced into the stomach, changing the volume of air within the bag by an electronic feedback mechanism. Thus, the barostat measures gastric motor activity (contraction or relaxation) as changes in intragastric volume (reduction or enlargement, respectively) at a constant intragastric pressure (figure 1.4). Using this technique, cyclic variations in human gastric tone during fasting have been demonstrated. In addition, it has been demonstrated that these variations are co-ordinated and are phase locked shortly in advance of inter-digestive cyclic motor activity in the mid-duodenum. Each gastric motor cycle consists of a period of quiescence with stable gastric tone and minimal phasic activity, an intermediate period with increasing gastric tone and irregular phasic activity, and a period of activity with high level of gastric tone and regular phasic activity. During this period of activity, the phasic contractions of the proximal stomach occur at a frequency of 0.8 cycle/minute.

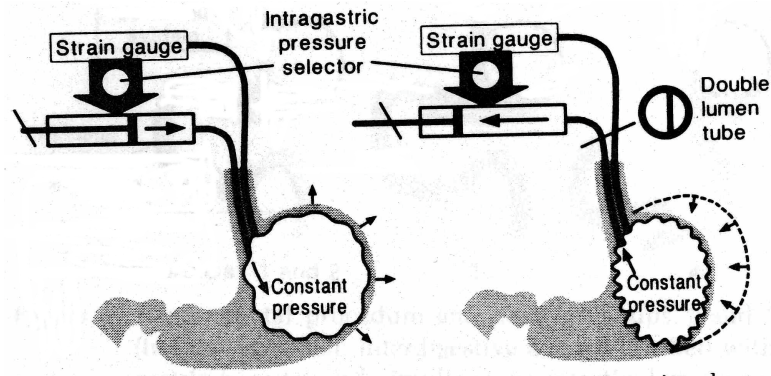


Figure 1.4: Schematic representation of a gastric barostat study: when gastric tone is decreasing, the air pump inflates air in the intragastric balloon in order to maintain a constant pressure; conversely during increases in gastric tone, air is withdrawn from the balloon. The variations in volume of the balloon therefore reflect the variations of gastric tone (adapted from Azpiroz 1987a).

In an other human study, investigators reproduced Azpiroz' findings on the phasic activity, but did not note any significant changes in tonic state during the different periods of this cycle (Parys 1993). It is known that physiological levels of motilin and its agonist erythromycin induce a tonic contraction of the proximal stomach associated with a phase III like phasic activity (Bruley des Varannes 1995, Coulie 1997c, Kamerling 2003). In response to ingestion of a meal, two phenomena have been described in the proximal stomach. On arrival of a swallow sequence at the oesophagogastric junction, the gastric fundus undergoes vagally mediated receptive relaxation. As the meal enters the stomach, tone and phasic contractions in the proximal stomach are inhibited leading to accommodation. The latter is important to provide the ingested bolus with a sufficient volume without corresponding increase in intragastric pressure. These phenomena enable the reservoir function of the proximal stomach for the ingested food bolus. They are followed by a progressive return to normal gastric tone, which has been hypothesised to be the driving force of liquid gastric emptying (Moragas 1993). This driving force is probably not the only determinant of (liquid) gastric emptying since patients with defective gastric accommodation in functional dyspepsia or

post-surgical gastroparesis do not have accelerated liquid gastric emptying, probably because outlet resistance of the antro-pyloric region is also important (Azpiroz 1994, Lindeboom 2003). The neural regulation of the motor activity of the proximal stomach has been thoroughly investigated, especially in the dog model. There is compelling evidence for an important role of vagal control. In dogs, for example, it has been demonstrated that the gastric tone is under vagal cholinergic control (Azpiroz 1987b). The canine gastric relaxation is mediated by vagal inhibitory fibres using NO as neurotransmitter (Meulemans 1995). There is evidence in animal studies that the fasting gastric fundus tone is not only dependent on excitatory cholinergic input but that it also depends on a continuous inhibitory nitrgenic drive (Coulie 1999). In humans vagotomy and cholinergic blockade decrease the tone of the proximal stomach (Azpiroz 1987a; Rashid 1990) and gastric accommodation also involves the activation of nitrgenic neurones (Tack 2000a). There are several triggers of the afferent limbs of the reflex gastric accommodation, such as lipid infusion in the duodenum (Azpiroz 1985), distension of the duodenum (De Ponti 1987) or the antrum (Caldarella 2003). In an initial study, sham feeding did not induce gastric accommodation (Parys 1993). Subsequently, however, in depth analysis of the site of triggering of the accommodation reflex has shown that pharyngeal, gastric or duodenal mechano- and/or chemoreceptors may trigger the reflex, but that the cephalic phase of the response to a meal was insufficient to trigger accommodation (Vanden Berghe 2000, Holzer 2003). α_2 -adrenergic pathways do not seem to be important in the control of the tone of the proximal stomach (Thumshirn 1999).

Antral motor activity

In the fasted state, motor activity is highly organised into a distinct and cyclically recurring sequence of events known as the migrating motor complex. The migrating motor complex consists of three distinct phases of motor activity that occur in sequence and migrate slowly along the length of the small intestine. Each sequence begins with a period of motor quiescence

(phase I), is followed by a period of apparently random and irregular contractions (phase II), and culminates in a burst of uninterrupted phasic contractions (phase III or the activity front). Individual cycles last between 1 and 2 hours, originate in the proximal gut, and migrate aborally. In the stomach, patterns of the migrating motor complex activity tend to begin and end simultaneously at all sites rather than propagate, as it occurs in the small bowel. As phase III develops in the proximal duodenum, several associated motor events occur in the stomach. The phasic activity of the proximal stomach occurring at that time has been described higher. The true rhythmic activity occurs only in the distal antrum, where contractions at three cycles per minute may be seen at the end of phase III. As phase III approaches and develops, antro-pyloro-duodenal co-ordination increases, and high-amplitude contractions propagate through the antrum across the pylorus into the proximal duodenum, where they are associated with brief clusters of phasic contractions. If food is ingested, the cyclic pattern is abolished and replaced by a band of random contractions called the fed pattern, which may last from 2.5 to 8 hours, at which time the fasted pattern resumes, assuming that no more food has been ingested. The gastric motor response to feeding is, in large part mediated through the vagus. The flow equivalents of the manometric patterns described in this paragraph are still matter of debate. There is still considerable uncertainty about the relative contribution of regional abnormalities of motor function.

1.3 Carrying sensory information from the gut lumen and wall to conscious perception: the gut-brain axis

Pain and sensation arising from the viscera has long posed problems for the clinician. Unlike pain associated with injury to cutaneous structures, visceral pain is not always associated with frank injury to a viscus. Visceral pain is poorly localised, diffuse in character and typically is referred to cutaneous sites, probably because their inputs converge in the dorsal horn of the spinal cord (Gebhart 1995). In contrast to the afferent neurones of the peristaltic and other intrinsic reflexes, which are contained in the enteric nervous

system, sensation arising from the gut is thought to be mediated primarily by the extrinsic nerves. Vagal and sacral parasympathetic nerves carry large numbers of sensory afferent fibres. Sensations more in the painful range are carried by spinal sympathetic afferents, whereas vagal pathways, primarily serve vegetative functions, and are thought to have little effect on pain or pressure perception under normal conditions (figure 1.5). There is however evidence that both pathways do interact, presumably at the level of the brainstem. These visceral afferents, through local and central reflexes, may modulate gastrointestinal motor and secretory activity to ensure that the digestive needs of the individual are met. Most of the information conveyed by these afferents is not consciously perceived. Accordingly, the principal conscious sensations that arise from the viscera are discomfort and pain.

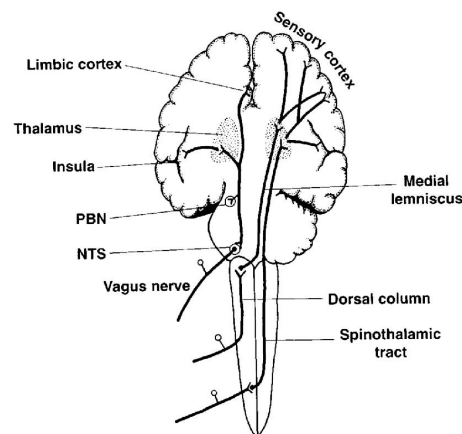


Figure 1.5: The bulbar and suprabulbar projections of vagal and spinal afferent pathways (adapted from Aziz 1998)

1.3.1 Receptors

The gut has mechano-, chemo-, osmo- and thermoreceptors (Wood 1999). These receptors of primary visceral afferents are located in the mucosa, the muscularis propria and in the serosa. Visceral receptors have no end organs or morphological specialisation (Gebhart 2001), except for the pacinian corpuscle located in the mesentery. They can however, be functionally

distinguished in terms of preferred sensed modality. Some mucosal receptors are more sensitive to chemical stimuli, whereas muscular or serosal receptors sense mechanical stimuli. It has been suggested that primary visceral afferents are polymodal. For example, mechanosensitive afferent fibre endings have also been found to be sensitive to chemical stimuli or to heat, and conversely, mucosal chemosensitive afferent fibres may sense mechanical stimuli.

Mechanosensitive visceral afferent fibre endings have been studied in animal studies at different levels of the gastrointestinal tract. They are located in the mucosa, the muscularis propria and at the serosal level. The predominant fibre pathways used by the muscular mechanoreceptors are in the vagus and splanchnic or pelvic afferents. They tend to respond to contraction and distension, in contrast to mucosal mechanoreceptors, which tend to respond to mucosal striking or pinching. Serosal mechanoreceptors are located in the mesentery and respond to movement or strong distension of the viscus.

It has been proposed that the gastric wall contains two types of mechanoreceptors. Mechanoreceptors arranged in a parallel fashion respond to stimuli that elongate the stomach wall. Mechanoreceptors arranged in series respond to stimuli that increase the tension of the stomach wall (Blackshaw 1987; Wood 1987). In series and in parallel mechanoreceptors in the gastric wall have been functionally identified, *in vitro*, in animal studies (Grundy 1988). In a model of in series tension receptors smooth-muscle tone determines the activation of these receptors (Iggo 1955, 1957). Therefore, many neurones in the brainstem that fire in response to noxious stimuli also fire in response to spontaneous contractions (Janig 1986). Glucagon for example reduces gastric smooth muscle tone in the gut and increases the distension volume required to produce pain (Notivol 1995). Similar observations were noted using the 5HT₁ agonist sumatriptan which decreases gastric tone through activation of intrinsic inhibitory nitroergic neurons (Tack 2000b).

Chemosensitivity most often occurs in two steps. The afferent neurone does not respond directly to a stimulus but responds after the release of a mediator from a primary sense cell (most often EC cells). These mucosal chemosensitive cells release chemical mediators that act in paracrine fashion on sensory nerve endings within their close proximity. 5-HT is the best characterised sensory mediator. It binds to 5HT₃ receptors on vagal primary afferent nerve endings evoking discharge in these fibres. It is unlikely that this normally gives rise to conscious sensation other than perhaps hunger or satiation.

Two types of fibres have been identified: about 25% of the fibres have high, supraphysiological thresholds and are told to be visceral nociceptors and are mostly spinal afferents. The remaining 75 % of afferent splanchnic fibres sense distending stimuli in the physiological range (Sengupta 1994). In addition to these classical mechanosensitive fibres, silent nociceptors have been described, which only sense mechanosensitivity after tissue insult. The role of these fibres in physiological or pathological conditions has not well been elucidated.

Mechanosensitive visceral afferent fibres, both those with low and those with high threshold, have the ability to sensitise. This means an increase in response magnitude, sometimes accompanied by an increase in spontaneous activity and/or a decrease in response threshold, after inflammation. Sensitisation occurring in low-threshold fibres might generate noxious perception. A similar mechanism might occur as a long-term consequence after visceral insult. Sensitisation may occur at the level of the primary afferents or at the dorsal horn level. The mechanisms of this process are under intense study (for review, see Bueno 1997 and Kirkup 2001) since this mechanism might explain the visceral hyperalgesia frequently found in patients with functional gastrointestinal disorders.

1.3.2 The peripheral sensory pathways originating from the stomach

The enteric nervous system

The enteric nervous system is an integrative system of neurones with structural complexity and functional heterogeneity similar to those of the brain and the spinal cord. The principal role of the enteric nervous system is to control and co-ordinate gastrointestinal functions such as motility, secretion, mucosal transport, and blood flow that are necessary for normal digestive processes. Although the enteric nervous system receives input from the central nervous system via parasympathetic and sympathetic pathways, it functions mainly independently, gathering information from primary intrinsic afferents and modulating it via interneurones.

Parasympathetic innervation

There are two parasympathetic systems innervating the gastrointestinal tract: the vagus nerve, which innervates the upper- and mid gastrointestinal tract and the right colon and in a less distinct structure emerging from the sacral spinal cord, which innervates the descending colon and the rectosigmoid (see 1.1.2). Approximately 90% of the vagal fibres are afferent. The cell bodies of the primary vagal afferents are located in the nodose ganglia. These vagal afferents terminate in the brain stem in the nucleus of the solitary tract. The remaining 10% are efferent fibres, originating from the dorsal motor nucleus, synapsing to ganglionic neurones located in the myenteric and submucosal plexuses. The postganglionic parasympathetic neurones are elements of the enteric nervous system and they provide the final common pathway to the muscle and to the mucosa for both long reflexes via the vagus nerve and for short reflexes within the plexuses. One of those long vago-vagal reflexes is the gastric accommodation to a meal, leading to activation of nitrergic inhibitory neurones of the myenteric plexus (see 1.2.2).

Vagal afferents have a low threshold of response to mechanical stimulation and are saturated at levels of stimulation well within the physiological range. They are therefore believed to mediate non-noxious physiological sensations such as satiety and nausea. Recently, however, a role for vagal afferents in the modulation of nociception has been established. Experimental studies suggest that vagal afferents acting via the brain stem exert both inhibitory and excitatory influences on spinal nociceptive transmission. Loss of such influences may be responsible for the altered sensation experienced by patients after vagotomy.

Spinal visceral innervation

Spinal visceral afferent nerves

Spinal visceral afferents constitute 5%–10% of all afferent fibres in the thoracic and lumbar dorsal nerve roots. Sensation from the soma and the viscera uses a three-neurone chain between the peripheral receptor and conscious perception (Camilleri 1996). The first order neurone has its cell body in the dorsal root ganglion, and it has two axons, one of which projects distally to the tissue and one centrally in the dorsal horn. The dorsal horn neurone, or second-order neurone crosses the spinal cord and ascends to the thalamus, reticular formation and midbrain. The third-order neurone projects from the thalamus to the cortex. Spinal afferents, originating from the muscularis propria and the serosa or mesentery, to the thoraco-lumbar spinal cord are important in pain sensation. The spinal afferents enter the cord and synapse on dorsal horn neurones.

The dorsal horn neurones

The dorsal horn neurones are the site of convergence of visceral and somatic signals. This convergence on the same neurones is responsible for convergence-projection or referred pain of a visceral stimulus (Camilleri 1996). The spinal afferents synapse on dorsal horn neurones at several levels contributing to the vague and diffuse nature of visceral abdominal pain. Another consequence of the convergence of visceral and somatic afferent signals is that impulses arriving in the spinal cord via somatic or

visceral afferents inhibit the response of a viscerosomatic dorsal horn to a second volley of stimuli arising in its peripheral field. Finally, increased excitability of these dorsal horn or viscerosomatic neurones occurs when they are stimulated. At this level, descending pathways, sometimes originating from vagal afferents, may modulate the firing rate of these neurones, thereby reducing or increasing the perception of pain and modifying their referral pattern.

1.3.3 Cerebral projections of painful or non painful sensations originating from the stomach

The nucleus of the solitary tract acts as a relay for the vast amount of information arriving to it from abdominal viscera via the vagus and, in turn, sends out a large ramifying fibre network to higher centres while also receiving information from these centres. The output from the nucleus of the solitary tract may either be directed to brainstem motor nuclei for short autonomic reflex loops or to the motor components of ingestion found in the trigeminal, facial, hypoglossal nuclei or directed to the thalamus or higher brain centres. Spinal visceral afferents project centrally via two ascending pathways, the spinothalamic and spinoreticular tracts. The visceral sensory cortex for painful and non painful stimuli is the insular cortex. The anterior cingulate cortex may play a role in the emotional interpretation of pain and the prefrontal cortex may be the centre of conscious awareness of pain.

1.4 Functional dyspepsia

1.4.1 Definition:

Functional dyspepsia is a clinical syndrome defined by chronic or recurrent upper abdominal symptoms whose cause cannot be identified by conventional diagnostic means (Talley 1999). The symptom complex is often related to feeding and includes epigastric pain, fullness, bloating, early satiety, belching, nausea, and vomiting.

1.4.2 Epidemiology

Dyspepsia accounts for 10% to 20% of general practitioners' consultations, and functional dyspepsia accounts for about 20% to 30% of gastroenterology consultations. These data indicate that functional dyspepsia is a clinical problem of considerable magnitude with obvious implications for the consumption of medical care.

1.4.3 Pathophysiology

The pathophysiology of functional dyspepsia is unknown, but many mechanisms have been suggested. These include delayed gastric emptying, hypersensitivity to gastric distension, impaired accommodation to meal, *Helicobacter pylori* infection, abnormal duodenojejunal motility, hypersensitivity to lipids or acid in the duodenum, or central nervous system dysfunction (Maes, 1997; Troncon 1994; Gilja 1996; Tack 1998; Camilleri 2001; Mearin 1991; Mertz 1998; Tack 2001; Danesh 2000; Wilmer 1998; Samsom 1999). Recent studies suggest that functional dyspepsia is in fact a heterogeneous disorder, with different pathophysiological disturbances underlying different symptom profiles. Several studies have investigated the relationship between delayed gastric emptying of solids and dyspeptic symptom pattern and severity. In the largest studies, around 30% of dyspeptic patients had delayed gastric emptying of solids (Stanghellini 1996; Maes 1997). Most small studies failed to find a convincing relationship between dyspeptic symptoms and delayed solid gastric emptying. In a large study, Stanghellini et al. reported that dyspeptic patients with delayed gastric emptying were more likely to have postprandial fullness and vomiting. Accommodation of the stomach to a meal consists of relaxation of the proximal stomach, providing the meal with a reservoir and enabling a volume increase without a rise in pressure. Scintigraphic and ultrasonographic studies have demonstrated an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach. This finding suggests defective postprandial accommodation of the proximal stomach (Troncon 1994; Gilja 1996; Salet 1998). During the

past decade, it has been suggested that visceral hypersensitivity might be a major pathophysiological mechanism in functional gastrointestinal diseases (Camilleri 2001; Mearin 1991; Mertz 1998). Gastric barostat studies have confirmed that, as a group, patients with functional dyspepsia have lower thresholds for discomfort or pain during balloon distension of the proximal stomach (Mearin 1991). Hypersensitivity to gastric distension, defined as perception or discomfort thresholds outside the normal range, is found in a subset of patients with functional dyspepsia but not in patients with organic causes of dyspepsia (Mertz 1998). The presence of *H. pylori* infection or the presence of abnormal small-intestinal motility in dyspeptic patients is not associated with a specific symptom profile (Danesh 2000). Balloon distension primarily assesses mechanosensitivity of the proximal gastrointestinal tract, but chemosensitivity may also play a role in the pathophysiology of functional dyspepsia. Recent studies reported that, as a group, patients with functional dyspepsia have increased sensitivity to duodenal perfusion with acid (Samsom 1999) or with lipids (Feinle 2001). The prevalence of these abnormalities and their association with the symptom pattern must be determined in large groups of patients. Cutaneous electrogastrography can demonstrate abnormalities of gastric myoelectrical activity in up to two thirds of patients with functional dyspepsia (Camilleri 1998). However, it is unclear whether these patients are primarily those that have delayed gastric emptying or whether this is associated with a specific symptom pattern.

The pathogenesis of functional dyspepsia has remained obscure, but a postinfectious origin has been suggested for some other functional bowel disorders. Both retrospective and prospective studies have shown that irritable bowel syndrome may follow an acute intestinal infection (Chaudhary 1962; Gwee 1996); another study reported the occurrence of the gastroparesis syndrome after viral infection (Bityutskiy 1997). Several studies have reported an association between dyspepsia and psychopathology (Wilhelmsen 1995; Nyrèn 1986; Langeluddecke 1990) but again the relevance to symptom pattern is unknown. It is unclear whether

the associated psychopathologic abnormalities have a pathogenic role or whether they are influencing symptom perception or health care-seeking behaviour in dyspeptic patients.

1.4.4 *Diagnosis*

In patients with dyspeptic symptoms, organic disease is usually excluded by careful history taking and clinical examination, upper gastrointestinal endoscopy with mucosal biopsies, routine biochemistry, and upper abdominal ultrasonography. *Giardia* infection or celiac disease should be considered in the differential diagnosis, and in selected patients, more extensive investigations, such as small-bowel radiography or computed tomography of the pancreas may be required. It is well known that dyspeptic symptoms may be the manifestation of gastro-oesophageal reflux disease. Erosive oesophagitis is readily recognized during endoscopy. In patients with non-erosive reflux disease, 24-hour pH monitoring may help to rule out acid-reflux disease, but a course of empirical proton-pump inhibitor therapy is often more practical.

1.4.5 *Treatment*

Lifestyle and dietary measures are usually prescribed for functional dyspepsia. Thus far, dietary therapy has not been systematically studied. It seems logical to have patients eat more frequent, smaller meals. Because the presence of lipids in the duodenum enhances mechanosensitivity of the stomach, avoiding meals with a high fat content may be advisable (Feinle 1997). For many patients, pharmacotherapy will be considered. *Acid-suppressive drugs* have been reported to relieve symptoms in some patients (Soo 2001). This seems to occur primarily in patients who also have some reflux symptoms, suggesting that the effect of acid suppression is really limited to patients with gastro-oesophageal reflux disease that has a dyspepsia-like symptom pattern (Talley 1998). Targeting potential therapeutic approaches toward the relevant, specific underlying pathophysiological disturbance seems logical. In patients with delayed

emptying, gastroprokinetic drugs should improve symptoms of postprandial fullness, nausea, and vomiting. Studies available so far fail to prove this hypothesis convincingly. *Prokinetic agents*, including metoclopramide, domperidone, and cisapride, have traditionally been used to enhance gastric emptying rate and to improve symptoms in these patients. However, their prokinetic effect was moderate and the symptomatic response was often poor (Soo 2001). In view of the limited options for treating these patients, the report of the strong gastroprokinetic effect of erythromycin (Janssens 1987), related to its ability to act as a motilin receptor agonist, was met with great enthusiasm. As a consequence, several motilin agonists lacking antibiotic activity were developed. In a large double-blind, placebo-controlled study, the motilin agonist ABT-229 did not improve symptoms. Even when only the subgroup of patients with delayed gastric emptying was analyzed, no symptomatic benefit was obtained and, on the contrary, higher doses of the drug apparently prevented the beneficial placebo effect (Talley 2000). Several factors connected with the drug and with the study design may have contributed to the negative outcome (Tack 2001b). The extent to which tachyphylaxis played a role in the therapeutic failure in patients with delayed gastric emptying is unclear. Moreover, erythromycin and related compounds reduce the meal-induced relaxation of the proximal stomach (Bruley des Varannes 1995), thereby mimicking impaired accommodation to a meal and enhancing sensitivity to gastric distension, which may worsen dyspeptic symptoms. Selective serotonin reuptake inhibitors (*SSRIs*) increase the availability of synaptically released 5HT, not only in the central nervous system but also at the level of the enteric nervous system. Clinical studies assessing their role in functional dyspepsia seem warranted. The 5HT₄ receptor agonist *cisapride* is often used to treat functional dyspepsia. The treatment approach to patients with hypersensitivity to gastric distension has not been established. Earlier studies suggested a beneficial effect of the peripheral opioid agonist *fedotozine* (Coffin 1996), but development of this drug has not been continued. *Antidepressants* were reported to improve symptoms of functional

dyspepsia (Tanum 1996; Mertz 1998b). A recent study showed that symptomatic benefit occurred in the absence of an effect on gastric sensitivity to distension (Mertz 1998b). Studies evaluating *H. pylori eradication* in functional dyspepsia yielded conflicting results. Meta-analyses show no or limited benefit from eradication. It is unclear whether eradication might be cost-effective or the marginal benefit truly represents an effect on functional dyspepsia, or if this is more related to prevention of peptic ulcer disease (Laine 2000; Moayyedi 2001). A recent study demonstrated reduction in dyspepsia symptoms in patients treated with the 5HT₃ receptor antagonist *alosetron* (Talley 2001). The mechanism underlying this effect remains to be elucidated, but 5HT₃ antagonists seem to have no effect on the gastric emptying rate or on sensitivity to gastric distension (Zerbib 1994). Access to alosetron prescription has been restricted because of side effects; thus, additional studies with this drug are unlikely. It is unclear whether 5HT₃ antagonists can improve impaired accommodation, but they were reported to decrease duodenal lipid sensitivity (Moayyedi 2001). Similarly, *cholecystokinin receptor antagonists* also decrease duodenal lipid sensitivity (Feinle 2001). In view of the association of functional bowel disorders with psychological factors and with psychopathology, *psychotherapy* has been used to treat these patients. In a randomized, controlled trial of psychotherapy versus supportive therapy in functional dyspepsia, no difference in symptoms after 1 year was recorded (Hamilton 2000). However, in a post hoc analysis that eliminated dyspeptic patients with severe heartburn, a significant difference in favour of psychotherapy was found. It is unclear whether patients with more severe symptoms responded less favourably or if patients with true reflux disease responded less favourably. Hence, it has not been established which patients are most likely to benefit from psychotherapy.

1.5 Aims of this thesis

Based on the rationale described in the introduction, we formulated the following hypothesis: activation of in series tension receptors located in the gastric wall leads to perceived symptoms in functional dyspepsia.

Several pathophysiological mechanisms in functional dyspepsia, such as defective gastric accommodation to a meal, may lead to excessive activation of the neuronal pathway leading to conscious perception and/or nociception of a distending stimulus in the gastric lumen. Since the initiating mechanical stimulus may be transduced by two types of mechanoreceptors located in the gastric wall: in series receptors sensing tension and in parallel receptors sensing elongation, we studied the respective role of both receptors in functional dyspepsia.

To test this hypothesis we performed the following research steps:

1.5.1 Evaluation of defective accommodation to a meal in functional dyspepsia

- to confirm that inadequate receptive relaxation of the gastric fundus is present in a subgroup of dyspeptic patients
- to describe the clinical characteristics of these patients
- to determine which other pathophysiological abnormalities, related to functional dyspepsia, can be found in this group of patients
- to reverse dyspeptic symptoms in these patients by acting pharmacologically on the mechanical properties of the stomach

1.5.2 Role of tension vs. elongation receptors in the genesis of dyspeptic symptoms.

- to evaluate mechanical response and perception during gastric distension studies under enhanced gastric tone and enhanced phasic activity
- to evaluate perception of phasic changes of gastric wall tension with unchanged elongation in healthy volunteers

- to evaluate perception of phasic changes of gastric wall tension with unchanged elongation patients with functional dyspepsia

1.5.3 Development of non-invasive methods for the assessment of gastric motor pathophysiology

- to develop a method to quantify satiety
- to evaluate intragastric distribution during conventional gastric emptying studies as a surrogate marker for gastric accommodation in healthy volunteers
- to evaluate intragastric distribution during conventional gastric emptying studies as a surrogate marker for gastric accommodation in patients with functional dyspepsia
- to evaluate intragastric distribution during satiety testing with liquid meals
- to evaluate gastric accommodation using SPECT technology and mucosal marking

1.5.4 Quantification of gastric wall tension during gastric barostat studies

- to evaluate regional changes of tension of the gastric wall during barostat studies

CHAPTER 2: ROLE OF IMPAIRED GASTRIC ACCOMMODATION TO A MEAL IN FUNCTIONAL DYSPEPSIA

2.1 Introduction

Accommodation of the stomach to a meal consists of a relaxation of the proximal stomach, providing the meal with a reservoir and enabling a volume increase without an increase in pressure. Recent studies have shown an abnormal intragastric distribution of food in patients with functional dyspepsia, with preferential accumulation in the distal stomach, suggesting defective accommodation of the proximal stomach to a meal (Troncon 1995; Gilja 1996; Hausken 1992; Ricci 1987). Barostat and ultrasonography studies of the proximal stomach confirmed impaired accommodation to a meal in patients with functional dyspepsia (Gilja 1996; Salet 1998). It is unclear whether impaired accommodation is causing symptoms in patients with functional dyspepsia. In view of the role of gastric accommodation in providing a reservoir during meal intake, absence of normal accommodation is likely to induce early satiety.

The aim of this part of the thesis was to demonstrate that impaired gastric accommodation to a meal is associated with symptoms of early satiety.

2.2 Materials and Methods

2.2.1 Study Subjects

Thirty-five healthy controls (24 men and 11 women; age, 19–34 years; mean age, 24.2 ± 0.6 years) and 40 patients with functional dyspepsia (12 men and 28 women; age, 17–69 years; mean age, 38.4 ± 2.1 years) participated in the study. None of the healthy subjects had symptoms of or a history of gastrointestinal disease or drug allergies, and none of the healthy subjects were taking any medication. The patients presented to the outpatient clinic

because of meal-related epigastric symptoms, and all underwent careful history taking and clinical examination, upper gastrointestinal endoscopy, routine biochemistry, and upper abdominal ultrasonography. Inclusion criteria were the presence of dyspeptic symptoms for at least 3 months in the absence of organic, systemic, or metabolic disease. Dyspeptic symptoms had to be present at least 3 days per week, with two or more symptoms scored as relevant or severe on the symptom questionnaire (see below). Exclusion criteria were the presence of oesophagitis, gastric atrophy, or erosive gastro-duodenal lesions at endoscopy; heartburn as a predominant symptom; a history of peptic ulcer, major abdominal surgery, or underlying psychiatric illness; and the use of non steroidal anti-inflammatory drugs, steroids, or drugs affecting gastric acid secretion. During upper gastrointestinal endoscopy, biopsy specimens were taken from the antrum and the corpus to search for the presence of *H. pylori*. In patients with relevant or severe epigastric burning on the symptom questionnaire ($n=9$), a 24-hour oesophageal pH monitoring was performed and found to be normal ($<4\%$ of time pH of <4). Patients with a weight loss of $>5\%$ of the initial body weight were assessed by a psychiatrist to rule out anorexia nervosa. All drugs potentially affecting gastrointestinal motility were discontinued at least 1 week before the barostat and gastric emptying studies. Informed consent was obtained from each participant. The protocol had been approved previously by the Ethics Committee of the University Hospital.

2.2.2 Symptom Questionnaire

Before the barostat studies, each patient completed a dyspepsia questionnaire. A previously described questionnaire was used (Stanghellini 1996) with the addition of three symptoms. The patient was asked to grade the intensity (0, absent; 1, mild; 2, relevant; and 3, severe and interfering with daily activities) of eight different symptoms (epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching, and epigastric burning). Also, the amount of weight lost since the onset of the symptoms was noted.

2.2.3 Gastric Emptying Studies

Gastric emptying for solids was measured in all patients, using the previously validated ^{14}C -octanoic acid breath test (Ghoos 1993). Briefly, all studies were performed in the morning after an overnight fast. The test meal consisted of 60 g white bread, one egg, the yolk of which was doped with 74 kBq of ^{14}C -octanoic acid sodium salt, and 300 ml water. Breath samples were taken before the meal and at 15-minute intervals for a period of 240 minutes postprandially. Gastric half-emptying time ($t_{1/2}$) was calculated as described previously (Maes 1998). Delayed emptying was defined as $t_{1/2}$ greater than the 95% confidence interval in healthy volunteers (Maes 1997).

2.2.4 Barostat Studies

After an overnight fast of at least 12 hours, a double-lumen polyvinyl tube (Salem sump tube 14 Ch.; Sherwood Medical, Petit Rechain, Belgium) with a finely folded adherent plastic bag (1200-ml capacity; maximal diameter, 17 cm) was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed-volume of 300 ml air for 2 minutes with the study subject in a recumbent position, and it was again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk upright in a specifically designed bed. After a 30-minute adaptation period, minimal distending pressure (MDP) was first determined by increasing intrabag pressure by 1 mm Hg every 3 minutes until a volume of ≥ 30 ml was reached (Notivol 1995). This pressure level equilibrates the intra-abdominal pressure. Subsequently, isobaric distensions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step using a graphic rating scale that combined verbal descriptors

on a scale graded 0–6 (Notivol 1995). The end point of each sequence of distensions was established at an intrabag volume of 1000 ml or when the subjects reported discomfort or pain (score of 5 or 6). After a 30-minute adaptation period with the bag completely deflated, the pressure level was set at MDP + 2mmHg for at least 90 minutes. After 30 minutes, a liquid meal (200 ml, 300 kcal, 13% proteins, 48% carbohydrates, and 39% lipids [Nutridrink; Nutricia, Bornem, Belgium]) was administered. In all patients and in 10 healthy subjects, gastric tone measurement was continued for 60 minutes after the meal. In the other 25 healthy subjects, the measurement continued until 120 minutes after the meal. In 6 patients with impaired gastric accommodation to the meal, the barostat study was repeated after 3–7 days with administration of 6 mg sumatriptan (Imitrex; Glaxo-Wellcome, Brussels, Belgium) subcutaneously immediately before the meal.

2.2.5 Data Analysis

The primary endpoint was the size of the meal-induced fundus relaxation. Secondary endpoints were the thresholds for perception and discomfort during gastric distension, the rate of gastric emptying, and the *H. pylori* status. For each 2-minute distending period, the intragastric volume was calculated by averaging the recording. Perception threshold was defined as the first level of pressure and the corresponding volume that evoked a perception score of ≥ 1 . Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of ≥ 5 . Gastric compliance was calculated as the slope of the pressure-volume curve obtained during the stepwise isobaric distensions. Hypersensitivity to gastric distension was defined as a discomfort threshold less than the mean -2SD in healthy volunteers. Gastric tone before and after administration of the meal was measured by calculation of the mean balloon volume for consecutive 5-minute intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 minutes before and 60 minutes after the administration of the meal. Also, the amplitude of the maximal relaxation was calculated as the difference between the average

preprandial volume and the highest postprandial 5-minute interval mean volume.

2.2.6 Statistical Analysis

Barostat results in healthy subjects and patients were compared by the Student's *t* test or after the Kolmogorov–Smirnov test for normal distribution. The normal range (mean $\pm$ 2SD) for the meal-induced gastric relaxation was calculated from the data for healthy volunteers. Subsequently, patients were divided into those with normal and those with insufficient meal-induced relaxation. Age, body weight, gastric compliance, thresholds to gastric distension, and $t_{1/2}$ for solid gastric emptying in both patient groups were compared using the Student's *t* test. The relationship between meal-induced relaxation and the amount of calories at maximum satiety was evaluated by linear regression analysis. Both meal-induced relaxation and the amount of calories at maximum satiety with or without administration of sumatriptan were compared by the Student *t* test. Furthermore, individual dyspeptic symptoms were analyzed using three possible cut-offs (≥ 1 vs. 0, ≥ 2 vs. ≤ 1 , and 3 vs. ≤ 2). The prevalence of dyspeptic symptoms, sex distribution, and presence of *H. pylori* infection in both patient groups were compared by χ^2 testing. Stepwise multiple logistic regression analysis was used to identify the association between the risk of impaired postprandial gastric relaxation, presence of dyspeptic symptoms, and patient variables. *P* values of 0.05 and 0.1 were chosen as cut-off points to enter and exit the stepwise procedure. Odds ratios (ORs) with 95% confidence interval (CI) were computed. Similar statistics were performed for the relation between symptoms, patient variables, *H. pylori* status, delayed gastric emptying, and hypersensitivity to gastric distension. Differences were considered to be significant at the 5% level. All data are given as means $\pm$ SEM. Statistical evaluations were performed using specialised software (SAS; SAS Institute, Cary, NC).

2.3 Results

2.3.1 Characteristics of patients with functional dyspepsia

Patients with functional dyspepsia were significantly older than healthy subjects, and a higher proportion of the patients were women ($p < 0.01$). Table 2.1 summarises the grading of dyspeptic symptoms in the patient group. Postprandial fullness and bloating were the most prevalent symptoms, both present in 82.5% of the patients. Epigastric pain (67.5%), early satiety (67.5%), nausea (65%), and belching (55%) were also reported frequently. Vomiting and burning sensation were present in 40% and 37.5% of the patients respectively. Weight loss of $>5\%$ was present in 22 patients (55%). In 11 patients (27.5%), *H. pylori* was demonstrated on gastric biopsy specimens. Fourteen patients (35%) had delayed gastric emptying of solids (t 1/2 of longer than 119 minutes).

	0 (Absent)	1 (Mild)	2 (Relevant)	3 (Severe)
Postprandial fullness	7 (17.5)	0 (0)	2 (5)	31 (77.5)
Bloating	7 (17.5)	2 (5)	4 (10)	27 (67.5)
Epigastric pain	13 (32.5)	3 (7.5)	2 (5)	22 (55)
Early satiety	13 (32.5)	3 (7.5)	5 (12.5)	19 (47.5)
Nausea	14 (35)	3 (7.5)	6 (15)	17 (42.5)
Vomiting	24 (60)	0 (0)	1 (2.5)	15 (37.5)
Belching	18 (45)	5 (12.5)	10 (25)	7 (17.5)
Epigastric burning	25 (62.5)	6 (15)	2 (5)	7 (17.5)

NOTE. Numbers in parentheses represent row percentages.

Table 2.1: Frequency of severity grading for each of six dyspepsia symptoms in 40 consecutive patients with functional dyspepsia.

2.3.2 Gastric accommodation in healthy subjects and patients

In healthy subjects, MDP was 7.4 ± 0.4 mm Hg. The preprandial intragastric balloon volume at MDP + 2 mm Hg was 178 ± 14 ml. In all volunteers, ingestion of the meal caused an immediate relaxation of the proximal stomach, reflected by an increase in the balloon volume (figure 2.1). Five

minutes after the meal, the intraballoon volume was significantly greater than the mean preprandial volume, and it remained significantly elevated until 115 minutes postprandially. During the first postprandial hour, the mean intraballoon volume was 401 ± 22 ml, which corresponds to an increase of 223 ± 13 ml. The lower range of normal (mean - 2SD) for the meal-induced increase in intraballoon volume was 64 ml (figure 2.2).

In patients with functional dyspepsia, MDP was 7.0 ± 0.4 mm Hg, and the average preprandial intragastric volume at MDP + 2 mm Hg was 184 ± 15 ml (not significant compared with healthy controls). The mean balloon volume averaged during the 60 minutes after the meal was 328 ± 26 ml, reflecting an average increase in intragastric volume of 144 ± 18 ml. The mean balloon volume during the first postprandial hour, the average increase in intragastric volume, and the maximum volume increase after the meal (190 ± 24 ml vs. 337 ± 18 ml) were all significantly less than in healthy volunteers ($P < 0.01$). Using the lower range of normal in healthy volunteers (64 ml) as a cut-off, 16 patients (40%) had an impaired gastric accommodation as measured by the barostat (figure 2.2).

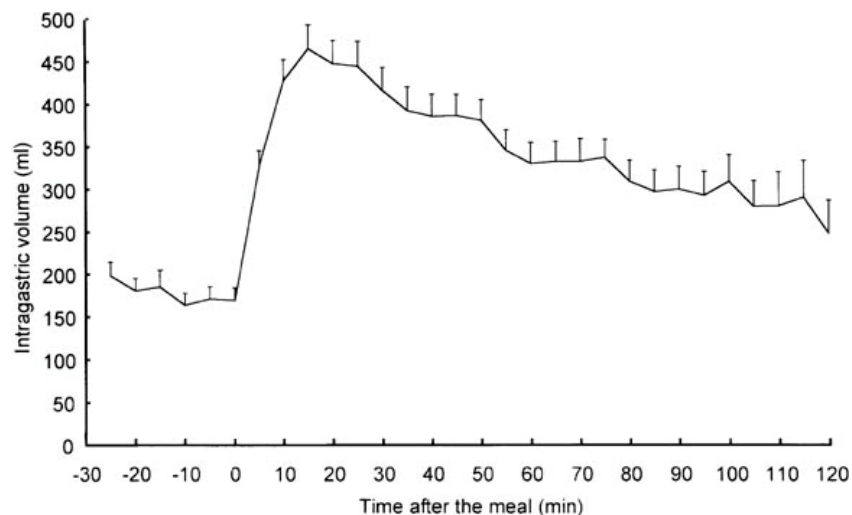


Figure 2.1: Mean intragastric volume at 5-minute intervals as measured by a gastric barostat in healthy volunteers (n=35) before and after administration of a mixed liquid meal.

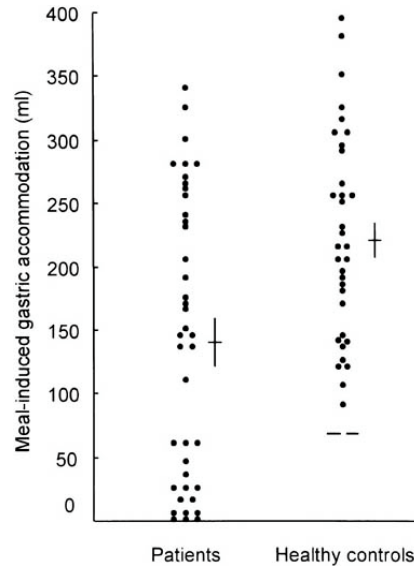


Figure 2.2: Gastric accommodation to a meal in 40 patients with functional dyspepsia and 35 healthy controls. Individual values are shown as dots; mean and SEM for each group are shown as bars. A subset of the patients has a meal-induced gastric relaxation below the normal range, indicated by the two horizontal bars.

2.3.3 Sensitivity to gastric distension in healthy subjects and patients

In healthy subjects, first perception and subsequently discomfort during gastric distension was reached at distending pressures of 4.1 ± 0.5 and 12.1 ± 0.4 mm Hg above MDP, respectively. The corresponding intragastric balloon volumes were 253 ± 22 and 660 ± 34 ml, respectively. Gastric compliance was 58 ± 6 ml/mm Hg. The lower range of normal (mean - 2SD) for the distending pressure inducing discomfort was 7.1 mm Hg above MDP. In patients with functional dyspepsia, first perception and discomfort during gastric distension were reached at pressures of 2.5 ± 0.2 and 9.1 ± 0.6 mm Hg above MDP, respectively ($P < 0.02$ compared with healthy controls). The corresponding intragastric volumes were 192 ± 19 and 496 ± 23 ml, respectively ($P < 0.05$ compared with healthy controls). Gastric compliance was 63.4 ± 7.2 ml/mm Hg (not significantly different compared with healthy

controls). Thirteen patients (32%) had hypersensitivity to gastric distension (distending pressure inducing discomfort <7.1 mm Hg above MDP).

2.3.4 Univariate analysis of pathophysiological and symptomatic correlates of impaired gastric accommodation

There was no significant difference in sex distribution, body weight, height, or age between patients with impaired and with normal gastric accommodation (5 males out of 16 patients vs. 7 males out of 24 patients, 56 ± 3 vs. 61 ± 2 kg, 168 ± 2 vs. 168 ± 2 cm, and 34 ± 4 vs. 41 ± 2 years, respectively). The prevalence of *Helicobacter* infection also did not differ (5 out of 16 vs. 6 out of 24 patients). There was no difference in $t_{1/2}$ for solids between both groups (116 ± 14 vs. 123 ± 17 minutes; not significant), and the prevalence of delayed emptying for solids did not differ (4 out of 16 and 9 out of 24 patients; not significant). The pressure and volume thresholds inducing first perception (2.3 ± 0.2 vs. 2.6 ± 0.2 mm Hg above MDP and 233 ± 43 vs. 165 ± 13 ml; not significant) or discomfort (8.0 ± 0.7 vs. 9.8 ± 0.9 mm Hg above MDP and 537 ± 43 vs. 469 ± 25 ml; not significant) and the prevalence of hypersensitivity to gastric distension did not differ between both groups (7 out of 16 and 6 out of 24; not significant). Gastric compliance was similar in both patient groups (68 ± 6 vs. 57 ± 5 ml/mm Hg; not significant).

Weight loss of $>5\%$ of the initial body weight was significantly more prevalent in patients with impaired gastric accommodation (12 out of 16 vs. 10 out of 24 patients; $P < 0.05$). The association between individual symptom grading and impaired gastric accommodation to a meal was investigated. The presence of relevant or severe early satiety (score of ≥ 2) was significantly more prevalent in patients with impaired accommodation to a meal (15 of 16 vs. 9 of 24 patients; $P < 0.0005$). Figure 2.3 shows the percentage of patients grading individual symptoms as relevant or severe and the presence of weight loss in the subgroups with normal or impaired gastric accommodation. Similarly, the presence of early satiety (score of ≥ 1) and of

severe early satiety (score of ≥ 3) was significantly more prevalent in patients with impaired accommodation (15 of 16 vs. 12 of 24 patients, $P < 0.005$; and 11 of 16 vs. 8 of 24 patients, $P < 0.05$, respectively). The prevalence of the other symptoms did not differ between both groups, regardless of the symptom score cut-off level.

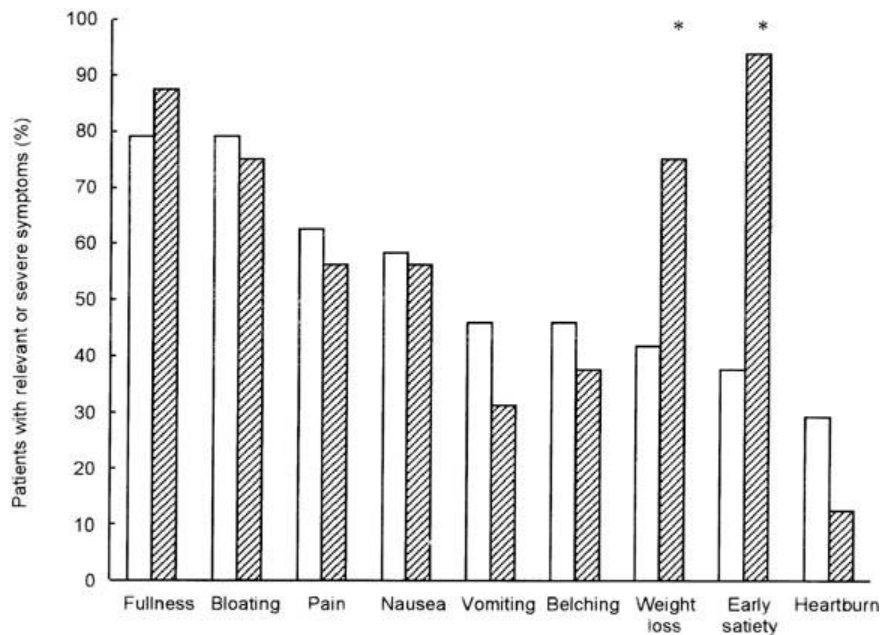


Figure 2.3: Dyspepsia symptoms in 40 consecutive patients with functional dyspepsia. The figure shows the number of patients grading individual symptoms as relevant or severe in the subgroups with normal (open bars) or impaired gastric accommodation (shaded bars). Early satiety and weight loss of .5% of the initial body weight were significantly more prevalent in patients with impaired accommodation to a meal.

2.3.4 Multivariate analysis of pathophysiological and symptomatic correlates of impaired gastric accommodation

Stepwise multiple logistic regression analysis was used to identify the association between the risk of impaired accommodation and different patient variables and symptoms. Age, sex, body weight, and height did not influence the risk of impaired postprandial gastric relaxation. When symptoms coded as relevant or severe symptoms (score of ≥ 2) were

considered, early satiety was the only symptom that was independently associated with impaired accommodation (OR, 25; 95% CI, 4.03–491.8; $P = 0.004$). Similarly, when the presence of symptoms (score of ≥ 1) or the presence of severe symptoms (score of ≥ 3) was considered, only early satiety was significantly associated with impaired accommodation (OR, 15; 95% CI, 2.43–293.2; $P = 0.01$; and OR, 4.4; 95% CI, 1.19–18.4; $P = 0.03$, respectively). Weight loss, which was associated with impaired accommodation in the univariate analysis, and all other symptoms, were not independent factors in the multiple logistic regression.

Similar statistics were performed using *H. pylori* status, delayed gastric emptying, or hypersensitivity to gastric distension as the response variable. The only significant association obtained was between the presence of severe nausea and delayed gastric emptying (OR, 9.52; 95% CI, 2.22–52.8; $P = 0.002$). A negative association was observed between the presence of relevant or severe nausea and hypersensitivity to gastric distension (OR, 0.187; 95% CI, 0.04–0.75; $P = 0.02$).

2.3.5 Effect of sumatriptan on impaired accommodation to a meal

In 6 patients with impaired gastric accommodation (6 women; age, 32.7 ± 4.3 years), the gastric barostat study was repeated with administration of 6 mg sumatriptan subcutaneously before the meal. Pre-treatment with sumatriptan significantly increased the meal-induced relaxation from 42 ± 22 to 116 ± 37 ml ($P = 0.005$) (figure 2.4).

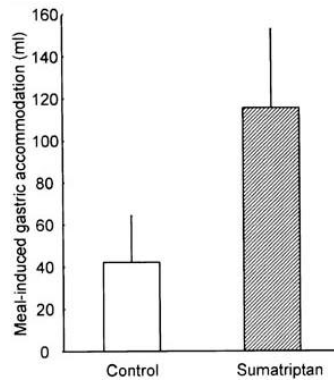


Figure 2.4: Influence of sumatriptan on postprandial gastric relaxation in patients with functional dyspepsia and impaired gastric accommodation to a meal.

2.4 Discussion

Recent studies have reported impaired gastric accommodation to a meal in patients with functional dyspepsia (Gilja 1996; Salet 1998). The prevalence of impaired accommodation and its relevance and relationship to symptoms are unknown. We studied postprandial relaxation of the proximal stomach in 40 consecutive dyspeptic patients. We showed that impaired gastric accommodation is present in 40% of these patients. No correlation was present between defective postprandial relaxation of the proximal stomach and other pathophysiological mechanisms, such as the presence of *H. pylori* infection, delayed gastric emptying, or hypersensitivity to gastric distension. In univariate and multivariate analyses, impaired gastric accommodation was significantly associated with symptoms of early satiety. Weight loss was significantly associated with impaired gastric accommodation in univariate analysis but was not an independent factor in multivariate analysis. Therefore, weight loss is occurring secondary to early satiety: when early satiety is severe enough to interfere with adequate intake of calories, it leads to weight loss. Insufficient adaptive relaxation of the proximal stomach during and after the ingestion of a meal may be accompanied by activation of mechanoreceptors in the gastric wall, thus inducing symptoms. This implies that restoring gastric accommodation should improve symptoms of

early satiety. We showed that sumatriptan, a 5-HT₁ receptor agonist, enhances the meal-induced relaxation in patients with impaired gastric accommodation. The mechanism underlying impaired postprandial relaxation of the gastric fundus is unknown. Several possible pathways can be involved. Relaxation of the proximal stomach can be activated by duodenal distension or nutrient infusion via a vagal reflex pathway (Azpiroz 1986; De Ponti 1987). It requires activation of intrinsic nitrergic neurones in the stomach (Desai 1991). Theoretically, impaired relaxation can result from a disorder at the level of the sensory apparatus, vagal reflex pathway, or intrinsic inhibitory innervation. The presence of a relaxing effect of sumatriptan, which activates intrinsic inhibitory neurons (Coulie 1999), suggests that gastric nitrergic neurones are functional in patients with an impaired gastric accommodation.

The current study has important implications for the treatment of patients with functional dyspepsia. So far, the pharmacological treatment of functional dyspepsia has relied on the use of prokinetic drugs. However, recent studies show that delayed gastric emptying is only present in a minority of dyspeptic patients (Stanghellini 1996) and the reported therapeutic effects of prokinetics on symptoms are variable (Hausken 1992; Champion 1997; de Groot 1997; Kellow 1995). Long-term studies with orally active fundus-relaxing drugs, such as buspirone or clonidine, seem warranted to confirm this therapeutic potential (Coulie 1997; Thumshirn 1999).

In conclusion, our study showed that impaired gastric accommodation to a meal is present in a large proportion of patients with functional dyspepsia. It is associated with symptoms of early satiety, which may lead to weight loss. The mechanism underlying impaired postprandial fundus relaxation is unclear, but it does not seem to involve *H. pylori* infection, visceral hypersensitivity, or delayed gastric emptying. These observations confirm the therapeutic potential of fundus-relaxing drugs in functional dyspepsia patients with early satiety.

CHAPTER 3: PERCEPTION OF CHANGES IN WALL TENSION OF THE PROXIMAL STOMACH

3.1 Introduction

In patients with functional dyspepsia, balloon distension of the proximal stomach can reproduce the symptoms they commonly complain about (Bradette 1991). In these patients, first perception and discomfort during distension of the proximal stomach with a balloon occur at lower thresholds than in healthy subjects (Mearin 1991; Lemann 1991; Troncon 1995; Salet 1996, Tack 2001a). Even though the causes of this hypersensitivity to distension of the proximal stomach are unclear, mechanoreceptors receptive to either changes in elongation or wall tension or both must be activated to transduce the distending stimulus. It has been proposed that the gastric wall contains two types of mechanoreceptors (Notivol 1995) (figure 3.1). In animals, serosal mechanoreceptors arranged in a parallel fashion respond to stimuli that elongate the stomach wall (Paintal 1954). Mechanoreceptors arranged in series respond to stimuli that increase or decrease the tension of the stomach wall (Blackshaw 1987; Wood 1987). Gastric distension in man increases both elongation and wall tension of the stomach. Hence distension studies do not allow distinguishing which of these mechanoreceptors induces perception (figure 3.1) (Notivol 1995). Recently, it was suggested that the simplified law of Laplace can be used to estimate wall tension during gastric barostat studies, and that this level of wall tension determined the level of perception during distension studies (Distrutti 1999). Others, however, found that most of the variance in sensation scores during a pharmacological study of gastric sensitivity was not accounted for by changes in wall tension, estimated by Laplace's law (Thumshirn 1999, Tack 2000b). All of these studies compared the sensitivity to gastric distension before and after administration of agents that relax the proximal stomach. A combination of gastric distension and relaxation is invariably associated with

elongation of the proximal stomach, but may have opposing effects on tension receptors. An alternative way to assess the role of volume (elongation) versus tension in gastric sensation might be to evaluate the influence of an agent that contracts the proximal stomach. An additional method to distinguish the role of elongation from tension might be to use volume-clamping by fixed-volume inflation of an intragastric balloon. When the proximal stomach contracts isometrically against the fixed volume balloon, elongation is unchanged while changes in intraballoon pressure directly reflect changes in wall tension.

Our aim was to distinguish changes in wall tension from changes in elongation in the genesis of perception of mechanical stimuli originating from the proximal stomach in healthy subjects. Perception of graded distensions or of a continuous distending stimulus in the presence or absence of erythromycin (Ery) was studied with two different protocols that included gastric barostat and antro-duodenal manometry methodology. In order to achieve an in vivo model of isometric contraction of the proximal stomach, we used Ery to increase circumferential fundic wall tension and to induce fundic phasic contractions in the presence of a fixed volume inflated balloon placed in the proximal stomach.

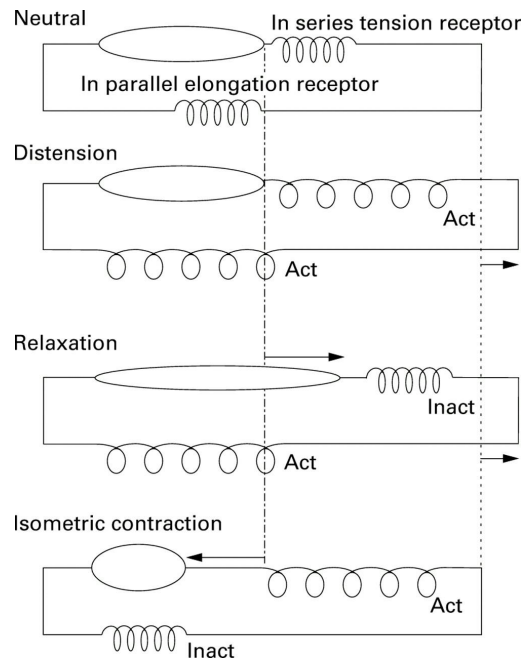


Figure 3.1: Schematic model of the proximal stomach wall with muscular component, in series tension receptor and in parallel elongation receptor. The four panels represent the behaviour of the model in various experimental conditions. Top panel: Neutral condition. Second panel: During distension both elongation and tension receptors are activated. Muscular contraction status is unchanged. Third panel: During relaxation elongation but not tension receptors are activated. The muscular component is lengthened. Bottom panel: During isometric contraction only tension receptors but not elongation receptors are activated. The muscular component is shortened.

3.2 Methods

3.2.1 Study subjects.

Twenty-six healthy volunteers (18 men and 8 women, mean age 24.0 ± 2.0 years) were included. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were taking any medication. Informed consent was obtained from each participant. The Ethics Committee of the University Hospital had previously approved the protocol.

3.2.2 Study technique

After an overnight fast of at least 12 hours, the volunteers were orally intubated with a stationary perfused antro-duodenal manometry catheter, with recording sites located 6, 4 and 2 cm above and 2 and 4 cm below a radio-opaque marker that was placed at the pylorus under fluoroscopic control. Afterwards, a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded, was introduced through the mouth. The positions of the bag in the gastric fundus and of the manometry catheter were checked fluoroscopically. Both probes were secured to the subject's chin with adhesive tape.

The antro-duodenal manometry catheter was connected to a low compliance hydraulic capillary infusion pump. The polyvinyl tube with the bag was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Synectics, Stockholm, Sweden). The barostat device can deliver volume ramps or pressure steps at different rates, while simultaneously monitoring pressure and volume. The intrabag pressure, the bag volume and the six antro-duodenal manometry channels were recorded and monitored on-line using a specially designed software program (Polygram for Windows®, Synectics, Stockholm, Sweden). Sampling rate for all variables was 8 sec⁻¹. To unfold the intragastric bag, a fixed volume of 500 ml air was inflated during two minutes with the study subject in a recumbent position. After a 10 minute equilibration period, the subjects were positioned in a comfortable sitting position with the knees slightly bent (80°) in a bed, specifically designed for that purpose. Finally an intravenous catheter was placed in an antecubital vein and flushed with saline.

3.2.3 Study protocol

Study 1: Perception of stepwise gastric distensions before and after Ery and effect of Ery on tone of the proximal stomach

The effect of Ery on the perception of stepwise distension of the proximal stomach was studied in 14 volunteers. After a 30-minute accommodation period, minimal intragastric distending pressure (MDP) was first determined as the lowest pressure level that provided an intrabag volume of 30 ml or more (Notivol 1995). This pressure level equilibrates the intra-abdominal pressure and was determined with the subjects in sitting position, by increasing intrabag pressure with 1 mm Hg every 3 minutes. After a 30 minute accommodation period, we performed one series of stepwise isobaric distensions and one series of isovolumetric distensions. The sequence of the type of distensions was randomized with sealed envelopes so that half the subjects underwent isobaric distensions first, followed by isovolumetric distensions, and the other half of the subjects underwent distensions in reverse order. During isobaric distensions the selected pressure was increased by 2 mm Hg every 2 minutes starting from MDP, whereas during isovolumetric distensions the balloon volume was increased by 100 ml and kept constant during the whole 2-minute distension step. During the distension protocols, at the end of each distending step, subjects were instructed to score their perception of upper abdominal sensations induced by either isobaric or isovolumetric distension. Perception was graded with a graphic rating scale that combined verbal descriptors on a scale graded from 0 to 6 (Notivol 1995). The end point of each sequence of distensions was established at an intrabag volume of 1000 ml, or when the subjects reported discomfort or pain (score 5 or 6). Previously, we have demonstrated the reproducibility of the responses and perception scores to gastric distensions performed according to this protocol (Coffin 1994). After performing both series of distensions, the pump was switched to barostat mode (isobaric conditions) and the pressure level was adjusted to obtain an intrabag volume

of approximately 400 ml. This corresponded most often to MDP + 4 mm Hg. After 30 minutes of baseline recording, an infusion of 10 mg/min of erythromycin lactobionate (Erythrocin, Abbott, Ottignies-L.L.N., Belgium) was started. Ten minutes after initiation of the infusion, graded distensions were repeated in the same order as before administration of Ery.

Data analysis and statistics

To evaluate the effect of Ery on gastric tone, the mean intrabag volumes during the 5-minute period before and during the initial two 5-minute periods while the drug was administered were compared using the paired Student's t-test. To evaluate the effect of Ery on the mechanical characteristics of the wall of the proximal stomach during gastric distension, for each two minute distending period, the average of the dependent variable (volume or pressure) was calculated. Pressure-volume curves of isobaric distensions and volume pressure curves of isovolumetric distensions before and after Ery were compared by two-way ANOVA.

Perception threshold was defined as the first level of pressure (during isobaric distensions) or volume (during isovolumetric distensions) that evoked a perception score of 1 or more. Discomfort or pain threshold was defined as the first level of pressure (during isobaric distensions) or volume (during isovolumetric distensions) that provoked a perception score of 5 or more. The perception and discomfort thresholds before and after Ery were compared using the paired Student's t-test. In addition, the areas under the curve of the pressure-perception and volume-perception relations before and after Ery were also compared using the paired Student's t-test. All data are expressed as mean $\pm$ SEM. Differences were considered to be significant at the 5% level.

Study 2: Perception of phasic pressure waves before and after Ery

The perception of phasic pressure waves of the proximal stomach was studied in all 26 volunteers. Fourteen of these 26 volunteers had undergone the first study on a separate day at least 72 hours before. After an

accommodation period of 30 minutes after the unfolding of the bag, the subjects underwent an isovolumetric distension with the same protocol as in study 1. Subsequently, the balloon was deflated during 20 minutes. After this resting period, the balloon was inflated at a fixed volume corresponding to the perception threshold determined during the initial distension procedure. The volunteers were asked to indicate the perception of upper abdominal symptoms using a keypad connected to the recording computer, using the same rating scale as in study 1. They were instructed to score every 30 seconds or earlier if they noticed any change in perception. The balloon was kept inflated during 10 minutes and the intraballoon pressure was constantly recorded. Twenty minutes after balloon deflation an intravenous infusion of 10 mg/min of Ery was started. Ten minutes after start of Ery, the balloon was inflated to the same volume as before for a new period of 10 minutes, while the subjects were asked to score their symptoms again.

Data analysis and statistics:

The intraballoon pressure baseline was calculated using dedicated software developed in our own laboratory (Andrioli, KULeuven). A phasic pressure wave of the proximal stomach was defined as a rise of intraballoon pressure of 5 mm Hg above baseline during at least 5 seconds. For each pressure wave, the amplitude and the area under the curve were calculated. If the onset of this pressure wave was followed by a rise in perception score within 10 seconds it was considered as recognized. Every antral and duodenal channel of the perfusion manometry tracings was analyzed in a similar fashion to the intraballoon pressure. The proportion of perceived fundic, antral and combined fundic and antral contractions before and during infusion of Ery was compared using the χ^2 -test. To rule out non-specific score increases, the proportion of score increases, effectively corresponding to pressure waves, was calculated and compared using the χ^2 -test. All results are expressed as mean $\pm$ SEM.

3.3 Results

3.3.1 Effect of erythromycin on tone of the proximal stomach

Minimal distending pressure was 8.1 ± 1.5 mm Hg. Before Ery, the mean volume of the intragastric barostat balloon was 425 ± 30 ml. The drug induced a profound and significant tone enhancement of the proximal stomach reflected by a decrease in balloon volume to 266 ± 30 and 126 ± 35 ml ($P < 0.001$, $P < 0.001$), respectively during the first and the second 5-minute period following the start of the infusion (figure 3.2). The Ery-induced fundic tone enhancement occurred significantly earlier than the antral phase III-like activity (85 ± 9 vs. 224 ± 30 seconds after the infusion was started, $P < 0.01$) (figure 3.3). Antral contractions were not accompanied by phasic changes in intraballoon volume, except during the maximal phase III-like activity.

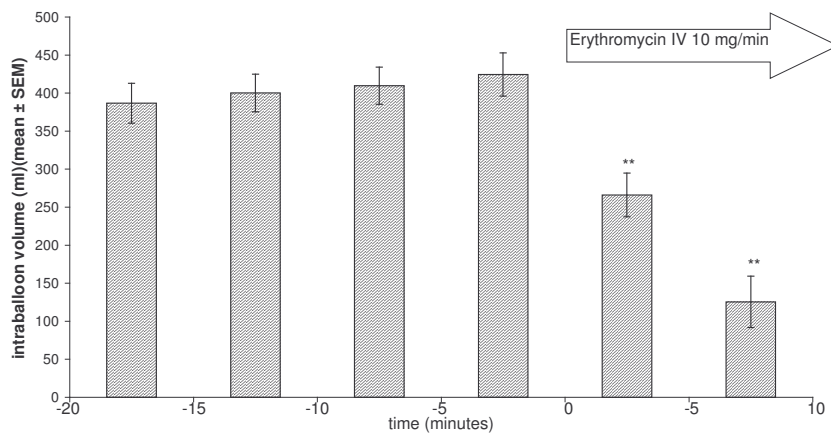


Figure 3.2: Influence of intravenous (IV) erythromycin on tone of the proximal stomach. Gastric tone is reflected by the volume of a barostat balloon in the proximal stomach. Intraballoon pressure is kept constant at a fixed pressure selected to obtain an initial volume of approximately 400 ml. Values are mean $\pm$ SEM. Student's t test: ** $p < 0.01$ ($n = 14$). Intraballoon volume (ml)

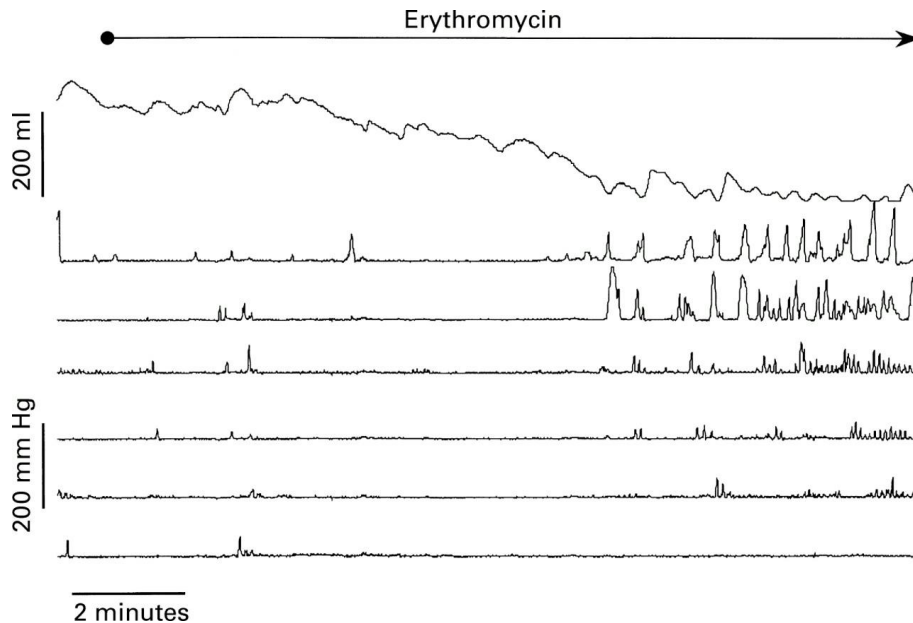


Figure 3.3: Influence of erythromycin 10 mg/min given intravenously on motor activity of the stomach and duodenum. Combined barostat of the proximal stomach and antro-duodenal manometry in a healthy volunteer. The highest trace represents intraballoon volume. The second and third channels show antral pressure and the four other channels duodenal pressure. Erythromycin induced enhancement of fundic tone (represented as a decrease in intraballoon volume) which preceded the appearance of antral phase III-like contractions.

3.3.2 Influence of erythromycin on distension of the proximal stomach

During isobaric distensions, at identical distending pressures, intragastric volumes during Ery were significantly lower than the corresponding volumes prior to drug administration ($P < 0.05$). Similarly, during isovolumetric distensions, higher intragastric pressure were recorded at every distension step during administration of the drug ($P < 0.05$).

Ery significantly decreased the pressure at threshold perception (2.3 ± 0.7 vs. 4.3 ± 0.8 mm Hg above MDP, $P = 0.05$) or discomfort (7.8 ± 0.8 vs. 9.2 ± 0.7 mm Hg above MDP, $P = 0.01$) during isobaric distensions. Similar results were obtained during isovolumetric distensions: mean perception threshold (157 ± 36 vs. 264 ± 41 ml, $P < 0.01$) and mean discomfort threshold (521 ± 59

vs. 700 ± 38 ml, $P < 0.01$) were both lowered during the administration of Ery. The areas under the curve of the pressure-perception and volume-perception relations were significantly higher during Ery (114.0 ± 3.4 vs. 103.8 ± 3.9 mm Hg above MDP X perception score unit, $P < 0.01$ and 3678 ± 203 vs. 2950 ± 150 ml X perception score unit, $P < 0.01$, respectively) (figure 3.4).

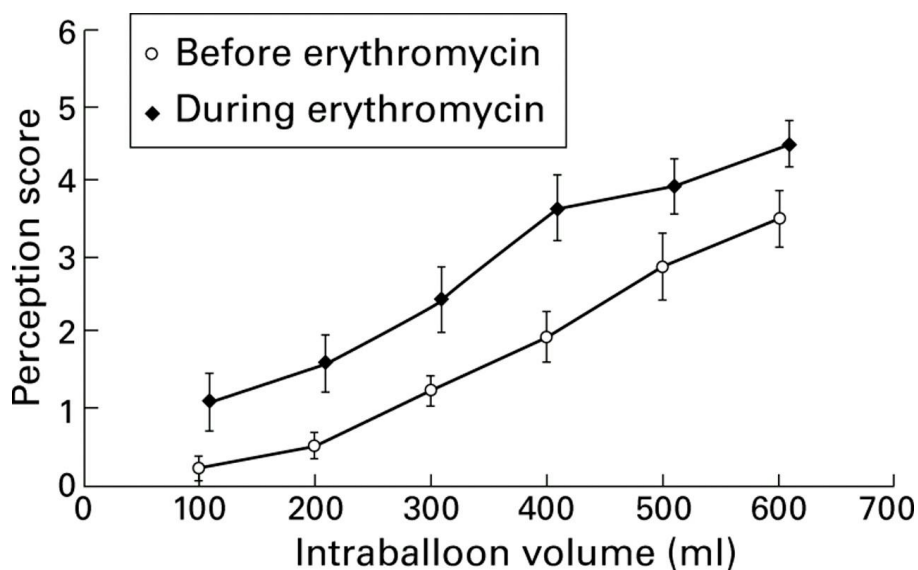


Figure 3.4: Distension-perception relation during isovolumetric distensions of the proximal stomach. Erythromycin (10 mg/min) significantly enhanced perception of gastric distension. Values are mean (SEM) perception scores (area under the curve; $P < 0.01$) ($n = 14$).

3.3.3 Perception of phasic activity of the proximal stomach

The balloon was inflated at a fixed volume of 265 ± 21 ml, which was the perception threshold determined during the initial stepwise distension protocol.

During the first perception period of ten minutes, a mean of 4.5 ± 0.7 phasic pressure waves of the fundus occurred. Thirty-two percent of these were followed by an antral pressure wave during phase III-like activity. Only 0.8 ± 0.4 isolated antral pressure waves occurred during the same period. There were no differences in amplitude between the isolated fundic and the fundic

pressure waves propagated to the antrum. Ery significantly increased both the amplitude (22.8 ± 0.3 vs. 20.6 ± 0.5 mm Hg, $P < 0.01$) and the number (12.4 ± 0.8 vs. 4.5 ± 0.7 , $P < 0.01$) of fundic pressure waves. During Ery induced phase III-like activity a 1 over 1 ratio of phasic contractile activity of the fundus over the antrum was observed for a short period of time.

When consciously perceived by the volunteers, phasic contractions of the proximal stomach were most frequently described as a sensation of increasing fullness. Using the fluctuations in this perception, the volunteers could correctly identify $51.1 \pm 7.4\%$ of the fundic pressure waves, in contrast to only $6.0 \pm 4.2\%$ of the isolated antral contractions. A characteristic tracing is depicted in figure 3.5.

During Ery, the proportion of perceived phasic contractions of the proximal stomach as compared to those identified on the intraballoon pressure tracing significantly rose to $64.0 \pm 4.7\%$ ($P < 0.01$). The accuracy, expressed as the proportion of score increases corresponding to fundic pressure waves, increased from $47.3 \pm 0.7\%$ to $81.5 \pm 0.5\%$ ($P < 0.01$).

The amplitude and the area under the curve of the correctly identified isolated fundic pressure waves were higher compared to non-perceived pressure waves (23.2 ± 0.5 vs. 21.9 ± 0.5 mm Hg ($P = 0.06$) and 109.5 ± 4.0 vs. 95.9 ± 4.1 mm Hg X sec ($P = 0.02$), respectively).

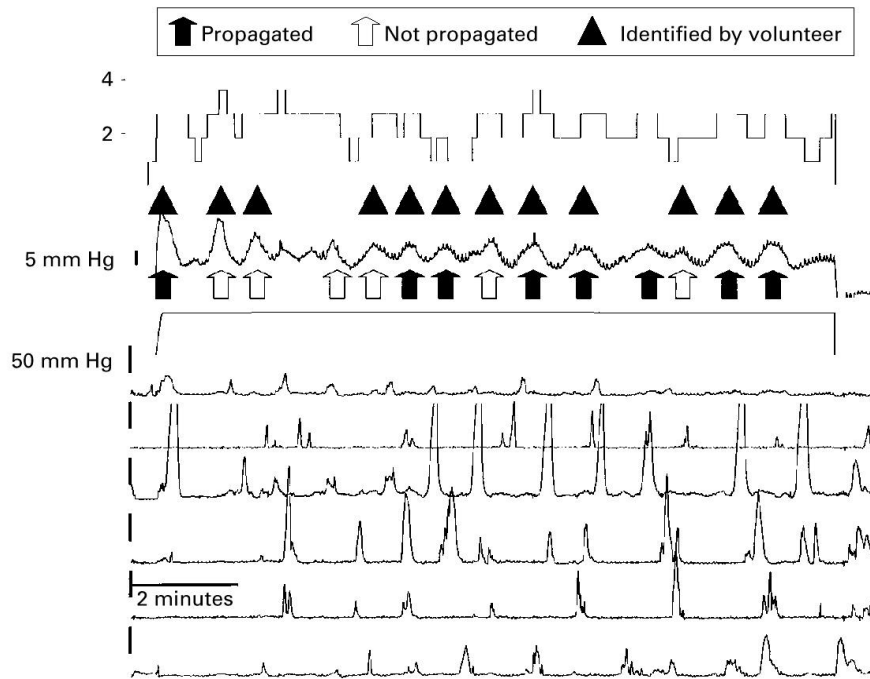


Figure 3.5: Perception of phasic activity of the proximal stomach. Combined barostat of the proximal stomach and antro-duodenal manometry in a healthy volunteer. The highest trace represents perception score. The second and third traces show intraballloon pressure and volume, respectively. The six other traces represent antro-duodenal manometry. This tracing illustrates fundic pressure waves propagated or not to the antrum. Some of the fundic pressure waves were identified by the volunteer.

3.4 Discussion

Hypersensitivity to distension of the proximal stomach is found in a large proportion of patients presenting with functional dyspepsia (Bradette 1991; Lemann 1991, Coffin 1994). The mechanism underlying this hypersensitivity is not fully understood (Gebhart 1995). In theory, the dysfunction leading to visceral hypersensitivity might be located at one or more of the levels involved in transduction of a stimulus such as distension of the proximal stomach. Defective processing might occur at the level of mechanoreceptors in the gastric wall, of afferent nerves or their targets in the central nervous system and result in the perception of discomfort or pain of an otherwise

normal sensorial stimulus. In this study, we focused on the distinction between changes in wall tension and changes in elongation as the initiating stimuli activating the brain-gut axis.

It has been previously shown that changes in gastric tone have a major influence on the perception of stepwise gastric distensions (Notivol 1995). In agreement with the results of Bruley des Varannes administration of Ery resulted in a significant increase of gastric tone (Bruley des Varannes 1995). When we repeated gastric distensions during Ery infusion, i.e. under conditions of increased tone of the proximal stomach, the subjects reported significantly higher perception scores at identical distending volumes or pressures. Gastric distension causes both elongation and increase in tension of the gastric wall. Isobaric and isovolumetric distensions have different effects on elongation and tension. Under isobaric conditions, at equal distension levels but different levels of gastric tone, both elongation and tension are influenced. While it is clear that increased tone of the proximal stomach during isobaric conditions will not be accompanied by increased elongation, it is very difficult to determine how this affects gastric wall tension (figure 3.1).

In contrast, under isovolumetric conditions, at equal distension levels but different levels of gastric tone, only tension varies in the segments in close apposition to the balloon. The fact that we measured significantly increased perception of gastric distension during Ery infusion also in isovolumetric mode, supports the concept that changes in gastric wall tension without simultaneous changes in elongation are sufficient to activate the brain-gut axis. This finding is also consistent with the observation that decreasing gastric tone with the 5-HT₁ agonist sumatriptan also decreases sensitivity to gastric isovolumetric distension (Tack 2001, 1998).

If gastric wall tension seems to be an important element in the transduction of mechanical stimuli, it would be tempting to calculate absolute values for this parameter. Indeed, several authors have chosen this approach (Bradette 1991; Mearin 1991; Notivol 1995; Distrutti 1999). We have preferred not to calculate absolute values for gastric wall tension, but to

measure relative changes over time of wall tension for the following reasons. In a static model of distension, circumferential wall tension can be approximated using the simplified law of Laplace $T = \Delta P(r/2)$, where T stands for wall tension, P stands for pressure (in-out) and r stands for the radius. Applying this formula to the gastric wall requires a number of assumptions which are not necessarily fulfilled: the stomach has a spherical shape, the gastric wall is infinitely thin and no active contractile activity occurs (Gregersen 1996). Alternatively, when the intraballoon volume is kept constant, isometric contractions (against an intragastric balloon with fixed volume) of the proximal stomach in close apposition to the balloon generate increases of intraballoon pressure. These changes in pressure reflect changes in gastric wall tension and the need for calculation of absolute values of wall tension is overcome. Using this technique, we observed that spontaneous phasic changes of wall tension of the proximal stomach can indeed be perceived. Moreover, increasing the intensity and the frequency of the stimulus with Ery resulted in a significant increase in the proportion of perceived contractions. Antral and duodenal contractions were most often not perceived. To date there is no evidence that Ery might influence afferent pathways at any level. Therefore, and in addition to the results obtained with the distension studies, the findings support the concept that changes in tension are sufficient to activate afferent sensorial pathways.

By logic, any change in tension or elongation must be sensed and relayed by mechanoreceptors in the gastric wall. It has been proposed that the gastric wall contains two types of mechanoreceptors (Notivol 1995). Mechanoreceptors arranged in a parallel fashion respond to stimuli that elongate the stomach wall. Mechanoreceptors arranged in series respond to stimuli that increase the tension of the stomach wall (Blackshaw 1987; Wood 1987). In series and in parallel mechanoreceptors in the gastric wall have been functionally identified, in vitro, in animal studies (Grundy 1988). Recently, Distrutti et al. reported that gastric wall tension, measured according to the simplified law of Laplace, is determining the perception of

gastric distension below the pain threshold (Distrutti 1999). Our observations are consistent with a model in which activation of in series mechanoreceptors is sufficient to transduce perception of changes in gastric wall tension.

The findings of this study may be relevant for a better understanding of the pathophysiology and for the treatment of functional dyspepsia. Hypersensitivity to mechanical distension is considered an important mechanism of symptom-production in functional dyspepsia. Even if the dysfunction leading to hypersensitivity is located at higher levels of the brain-gut axis, mechanoreceptors in the gastric wall must be involved in the process of perception of a mechanical stimulus. Furthermore, impaired accommodation of the proximal stomach to a meal, a frequent finding in patients with functional dyspepsia (chapter 2; Troncon 1994; Gilja 1996), might increase gastric wall tension and lead to the per- and early postprandial symptoms associated to the ingestion of meals. Fundus-relaxing agents can decrease wall tension of the proximal stomach and thus might decrease symptoms.

In summary, in the present chapter we have demonstrated that Ery increases tone and phasic contractile activity in the proximal stomach. Both the tonic and phasic contractions are accompanied by changes of the wall tension of the proximal stomach, leading to an increased sensitivity to distension and to an enhanced perception of phasic contractions. Changes in wall tension but not necessarily changes in elongation of the proximal stomach are required for perception of a distending stimulus. Our observations support the hypothesis that changes in gastric wall tension might be involved in the genesis of symptoms in functional dyspepsia.

CHAPTER 4: DEVELOPMENT OF NON-INVASIVE TOOLS TO ASSESS GASTRIC PHYSIOLOGY

4.1 Introduction

In the general introduction we have described the gastric accommodation to a meal in humans. In summary we can say that this vago-vagal reflex is very reproducible in healthy humans. It leads to a decrease of the tone of the proximal stomach after a meal, thereby providing the stomach with a reservoir function, without simultaneously increasing the intragastric pressure.

In functional dyspepsia, we have demonstrated that about 40% of patients have a defective accommodation as defined by a barostat test where, at $MDP + 2$ mmHg, the postprandial volume increase is lower than 64 ml (chapter 2). Interestingly, this defective mechanism is associated to one specific symptom in the array of complaints in functional dyspepsia: early satiety. Reversal of this defective mechanism leads to restored symptom profile both in acute studies (chapter 2) and in a chronic clinical trial (Tack 1999). This reversal can be achieved, using fundus relaxing drugs. These medications tend to slow down gastric emptying. It is therefore theoretically important to differentiate between functional dyspepsia patients with defective gastric accommodation or gastroparesis, since their treatments, if aimed at correcting a defective mechanism, would be opposite.

The reference method for evaluation of gastric accommodation is the use of a gastric barostat procedure. This exploration however is time consuming, invasive and poorly tolerated.

The aims of this part of the thesis were (1) to develop a test to quantify satiety, (2) to evaluate the intragastric distribution of a liquid meal during satiety testing, (3) to evaluate the intragastric distribution of a mixed meal during a standard scintigraphic gastric emptying study and (4) to improve the acceptability and the efficacy of gastric SPECT studies.

4.2 The satiety test

In functional dyspepsia, hypersensitivity to balloon distension and defective gastric accommodation have been clearly demonstrated (Bradette 1991, Mertz 1998, Tack 1998, Tack 2001a). There have been several attempts to avoid the use of a balloon and to apply a more physiological stimulus. Some authors have suggested the usefulness of a water load test (Koch 2000; Tosetti 1999; Boeckxstaens 1999). In this test the subjects are asked to drink water rapidly until full satiety. With this test however, some important aspects of the physiological response to a meal are not accounted for: water is rapidly absorbed even in the stomach and also rapidly emptied so that the net gastric filling is difficult to predict. In addition, the physiological brake on gastric emptying mediated by neural and hormonal (CCK) pathways, starting from chemoreceptors in the duodenum is overlooked. Finally, it is supposed that the gastric accommodation is triggered by the presence of caloric content in the stomach or the duodenum. Therefore, this water test might not accurately represent the real life situation where patients do complain about symptoms occurring especially after caloric meals.

We developed and validated a reproducible test to quantify satiety and compared the results obtained in healthy volunteers to those of functional dyspepsia patients (experiment 1). Then we studied the influence of pharmacological manipulations of gastric tone on the test (experiment 2). Finally we studied the site and modality of triggering of satiety in this setting (experiments 3 and 4).

4.2.1 Description of the test

In experiments 1, 2 and 3, a peristaltic pump (Minipuls 2; Gilson, Villiers-Le-Bel, France) filled one of two beakers at a fixed rate of 15 ml/min with a liquid meal (Nutridrink; Nutricia) (1.5 kcal/ml, proteins 13%, carbohydrates 48%, lipids 39%). The subjects were requested to maintain intake at the filling rate, thereby alternating the beakers as they were filled and emptied. There was no frequency of drinking the beakers that was imposed, as long as they kept up with the filling. In experiment 4 the subjects were provided

with new beakers containing 75 ml of the liquid meal every 5 minutes. In all experiments, at 5-minute intervals, they were asked to score their satiety using a graphic rating scale that combined verbal descriptors on a scale graded of 0–5 (1, threshold; 5, maximum satiety). Participants were instructed to stop meal intake when a score of 5 was reached.

4.2.2 Protocols:

Experiment 1: Satiety testing in functional dyspepsia

Ten healthy volunteers (7 males, ages 20-42 years) were studied while overnight fasted and compared to ten dyspeptic patients presenting with early satiety as their predominant symptom.

Experiment 2: Influence of enhancement of gastric tone on satiety testing

Eight volunteers were enrolled for the study. The study was performed twice either with placebo infusion or erythromycin 200 mg intravenously over 20 minutes, given at the initiation of the test.

Experiment 3: Influence of caloric content on satiety testing and CCK response

Fourteen healthy volunteers (7 males, ages 20-42 years) were studied on two separate occasions after an overnight fast. They underwent the test with two different types of liquid meal in random order: Nutridrink (1.5 kcal/ml) or Nutri 40 (2.0 kcal/ml, proteins 8%, carbohydrates 47%, lipids 45%). An intravenous catheter was placed in an antecubital vein. Blood samples were taken every 10 minutes and immediately centrifuged and frozen for further processing. Plasma CCK levels were determined using RIA methodology. Integrated CCK plasma response over one hour was calculated and compared for both tests using a paired student's t test.

Experiment 4: Intragastric distribution pattern of a liquid meal during satiety testing

Ten healthy volunteers (7 males, ages 23-35 years) participated in the study. They were asked to drink a liquid meal (Nutridrink) radiolabelled with 1mCurie of ^{99m}Tc -sulphur colloid/l at an imposed rate of 75ml/5 min. Anteroposterior (AP) and posteroanterior (PA) images were acquired during 1 minute in upright position using a gamma camera Diacam (Siemens Gammasonics Inc, 1990 IL, USA) equipped with a medium energy all purpose collimator. Scintigraphic planar images were obtained every 5 minutes during filling and every 20 minutes for the next 2 hours. The scans were transferred to a computer for further analysis. The image analysis was done using dedicated in house programs. The obtained images were aligned on external anterior and posterior references. The anteroposterior and posteroanterior scans were geometrically averaged. This means that the resulting pixel has the activity corresponding to $\sqrt{AP \times PA}$. Consequently all aligned images of one study were summated. A region of interest was automatically drawn around the stomach using an activity threshold. Then, the longitudinal axis of the stomach was indicated manually and the computer automatically divided the region of interest of the stomach in two parts: the proximal stomach and the distal stomach. The separation was computed based on the mid-length of the stomach axis and an angle of 30°. The number of counts in each region of interest was computed. These curves were correlated with the satiety scores at the corresponding time periods. The activity which would correspond to the presence of the total ingested volume in the stomach was calculated by extrapolating the filling of the first 10 minutes to the end of the drinking period. The residual fraction was calculated by dividing the activity at the end of the drinking period by the extrapolated total ingested activity.

4.2.3 Results

Experiment 1: Satiety testing in functional dyspepsia

In healthy subjects, a highly significant correlation existed between satiety scores and the amount of kilocalories ingested ($r=0.98$; $p<0.0001$). The amount of calories ingested until the occurrence of maximum satiety was 1028 ± 325 kcal. In patients, a significant correlation existed between satiety scores and the amount of calories ingested ($r = 0.61$; $p<0.0001$). The amount of calories ingested at maximum satiety was only 450 ± 156 kcal ($p<0.0001$ compared with healthy volunteers).

Experiment 2: Influence of enhancement of gastric tone on satiety testing

Erythromycin significantly decreased the amount of meal ingested from 1487 ± 94 to 994 ± 141 kcal ($p<0.05$). The drug significantly enhanced the average satiety scores for the same amount of kcal ingested ($p < 0.005$) (figure 4.1).

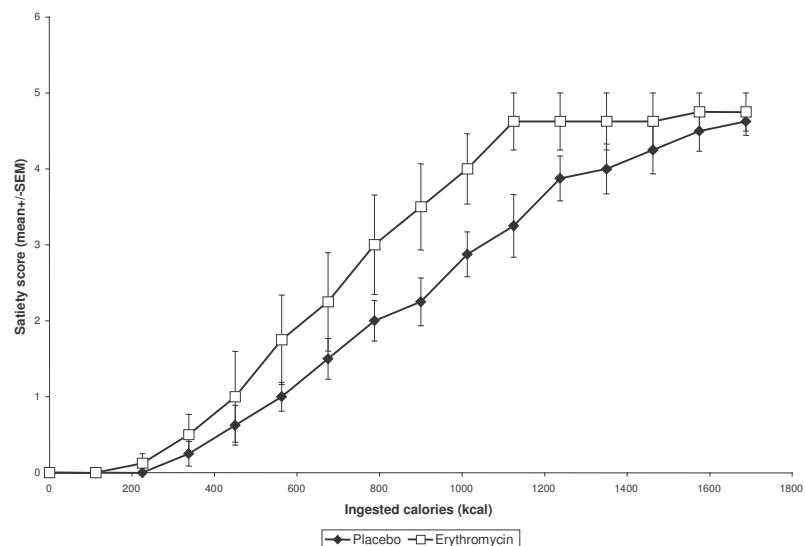
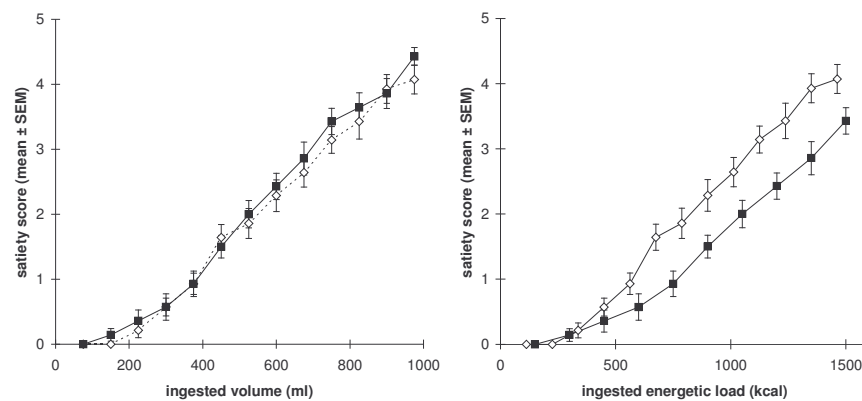


Figure 4.1: Influence of erythromycin (200 mg. IV) on satiety during a liquid meal satiety test.

Experiment 3: Influence of caloric content on satiety testing and CCK response

We found a highly significant correlation between satiety scores and the ingested volume and calories: $r = 0.97$ and 0.96 . The healthy volunteers could drink significantly more calories of the 2 kcal/ml meal before reaching full satiety: 1785 ± 84 during Nutri-40 vs. 1473 ± 71 kcal ($p=0.004$) during Nutridrink (figure 4.2 and 4.3). The subjects drank a similar volume of both types of meals: 893 ± 42 ml of Nutri-40 vs. 983 ± 48 ml (NS) of Nutridrink. The integrated CCK response over one hour did not differ in the two groups: 121 ± 23 fmol/ml X hour during Nutridrink vs. 176 ± 31 fmol/ml*hour (NS) during Nutri-40.



Figures 4.2 and 4.3: Relative influences of ingested volume and ingested energetic load on satiety during a liquid meal satiety test. Both figures represent the same tests with different X axes: mean satiety score (mean $\pm$ SEM) in function of the ingested volume (ml) (figure 4.2) and in function of the ingested energetic load (kcal)(figure 4.3). Open diamonds represent satiety test with Nutridrink (1.5 kcal/ml) and black squares represent satiety test with Nutri-40 (2 kcal/ml).

Experiment 4: Intra-gastric distribution pattern of a liquid meal during satiety testing

In this experiment, full satiety occurred at 1800 ± 281 kcal. Satiety correlated to the amount of liquid meal in the different parts of the stomach: r scores for

correlation with satiety were 0.89 for the proximal stomach, 0.86 for the total stomach and 0.75 for the distal stomach. The residual fraction in the stomach at full satiety represented $77 \pm 4\%$ (figure 4.4). A characteristic study is represented in figure 4.5.

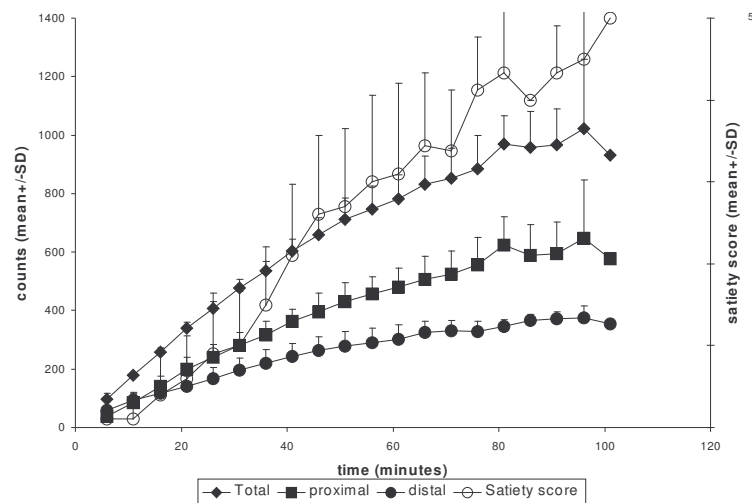


Figure 4.4: Total and regional intragastric distribution during a satiety test with a radiolabelled liquid meal. Satiety scores correlate best with the filling of the proximal stomach ($r=0.77$).

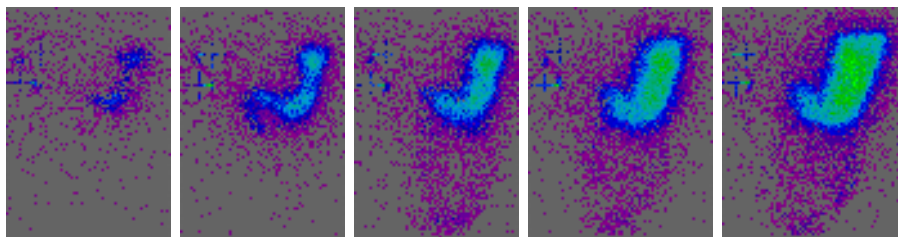


Figure 4.5: Characteristic study of the total and regional intragastric distribution during a satiety test with a radiolabelled liquid meal

4.2.4 Discussion

In this set of experiments, we have thoroughly investigated the clinical role and the mechanisms activated during satiety testing. This test has excellent reproducibility (Cuomo 1999). We have demonstrated the clinical usefulness

of this test, since in functional dyspepsia patients as a group there is a significantly impaired drinking capacity. The endpoint of the satiety test distinguishes most dyspeptic patients from healthy subjects (Tack 2003). In those patients, specifically presenting with early satiety, we found a good correlation between ingested volume (or caloric load) and the volume of the gastric accommodation as measured by gastric barostat (Tack 1998). Therefore, we have tried to ascertain our hypothesis that satiety in healthy volunteers, or the early satiety in patients with impaired accommodation, is generated by increased wall tension in the proximal stomach.

A first argument supporting this hypothesis was provided by the enhanced drinking capacity after pre-treatment with sumatriptan (Tack 2003, Tack 1997) or octreotide (Demedts 1997) in healthy volunteers. Secondly, in patients, we demonstrated the reversibility of the impaired drinking capacity after relaxation of the proximal stomach with sumatriptan (Tack 1998). Subsequently, experiment 2 indicated that, when the wall tension of the proximal stomach is enhanced using erythromycin (Bruley des Varannes 1995) satiety occurs at lower filling levels. These results are in line with the data presented in chapter 3 indicating the role of gastric tone in sensation arising from the stomach. Since sumatriptan inhibits (Coulie 1997) and erythromycin enhances gastric emptying (Sarna 1991, Peeters 1993) it might be postulated that the differences in satiety testing are related to their effect on gastric emptying. Additional studies have been performed by our group, using different drugs affecting gastric tone, gastric emptying and sensitivity in opposite ways, to demonstrate that satiety testing results correlate better with the effect of the drug on fundic tone compared to their effect on gastric emptying. For example, pre-treatment with cisapride, which speeds up gastric emptying, significantly enhanced the amount of food ingested from 1444 ± 78 kcal to 1684 ± 93 kcal ($p < 0.05$). Cisapride significantly decreased the average satiety scores for the same amount of kcal ingested ($p < 0.05$, ANOVA) (Tack 2003).

The chemoreceptors of the upper gastrointestinal tract sensing caloric and lipid load are supposed to be predominantly located in the duodenum.

Activation of these receptors leads to feedback inhibition of gastric emptying via the plasma CCK response and activation of intrinsic sensory neurones and reflex inhibitory pathways. Therefore, we wanted to quantify the importance of the activation of this duodenal brake by varying the caloric concentration of the liquid meal. These experiments have clearly shown that the main determinant of satiety is volume and not caloric load: volunteers drank the same volume, but more calories of the more concentrated formula. In this model, one might argue that there is an increased activation of the duodenal CCK brake, but we did not find any significant difference in the plasma CCK response. These data further suggest that the site of initiation of satiety during this test is located in the stomach and not in the duodenum. Additional support to this model was found in subsequent studies performed by our group indicating that when the pylorus is obstructed and the duodenal content is continuously aspirated, the results of the satiety test are unchanged.

Our next question was to locate the site of activation of perceived satiety during this test within the stomach. Our scintigraphic data, suggests the satiety score correlates best with the filling of the proximal stomach rather than that of the distal stomach. These findings support the idea that mechanoreceptors activated in the proximal stomach might trigger the satiety symptom. These data, however cannot firmly rule out a role for the antrum in the genesis of this symptom, since distension of both parts of the stomach occur simultaneously.

Interestingly, this study has revealed additional unexpected information. The analysis of the gastric emptying curves starting from the end of the satiety test indicates that although gastric emptying occurs during the filling phase, since about 1/4 of the ingested liquid has left the stomach by the end of the drinking period, this phenomenon is completely abolished when ingestion is halted. Based on these findings two possible explanations can be proposed: either the end of the emptying leads to excessive accumulation in the stomach, inducing distension of the (proximal) stomach above a threshold inducing full satiety, or the drinking activity (swallowing?) drives gastric

emptying through an unknown mechanism. To differentiate between these hypotheses, an additional study should be performed, in which volunteers would be asked to stop drinking before full satiety. In the case of a threshold distension, gastric emptying should still occur after the drinking period in opposition to the alternate proposition where gastric emptying should stop.

An other unexpected finding is the observation of a progressive redistribution of the liquid meal to the proximal stomach after the end of the ingestion period, even although the volunteers were scanned in an upright position. A potential explanation for this phenomenon might be the progressive restoration of an antral phasic activity. It seems however difficult to imagine how even sustained postprandial antral phasic motor activity might pump the liquid content of the meal upwards. Stability test, performed in vitro, have shown excellent binding of the ^{99m}Tc to the liquid meal, however layering of the different phases of the meal and the gastric secretions is possible. In that case, one would expect to find a clear horizontal line in the gastric scans which was not the case.

4.3 Evaluation of intragastric distribution

Whereas evaluation of gastric emptying can be assessed non-invasively (Camilleri 1998, Ghoo 1993, Schwizer 1996), evaluation of gastric accommodation and hypersensitivity to distension still needs poorly tolerated gastric barostat studies (Azpiroz 1987, Tack 1998). There have been attempts to develop non-invasive techniques to assess gastric accommodation. Gastric single photon emission computed tomography (SPECT) is still not widely available and requires administration of considerable doses of radioactivity (Kuiken 1999). Gastric ultrasonography is limited by its operator dependency and the need for sophisticated devices to reconstruct volumetric data (Gilja 1997). These difficulties limit the assessment of gastric accommodation in functional dyspepsia patients in daily practice.

Abnormal intragastric distribution of the radiolabelled meal during scintigraphic gastric emptying studies has been reported in patients with

functional dyspepsia (Troncon 1994). In that study functional dyspepsia patients were taken as a group and correlations between specific symptom profiles and distribution patterns were not looked for.

The aim of the present study was to compare how, using conventional scintigraphic gastric emptying study, the intragastric distribution of the meal occurs in healthy volunteers and in functional dyspepsia patients. An additional aim was, in patients, to link a symptom pattern to the intragastric distribution profile.

4.3.1 Material and methods

Study subjects

Forty patients with functional dyspepsia (14 men, 26 women; mean age 50.9 ± 2.6 years) participated in this study. Twenty-nine healthy controls (20 men, 9 women; mean age 25.3 ± 3.0) had participated previously in a validation study of the scintigraphic evaluation of gastric emptying at our institution. None of the healthy subjects reported symptoms or a history of gastrointestinal disease or drug allergies, nor were taking any medication.

The patients presented to the outpatient clinic because of meal-related epigastric symptoms, and all underwent careful history taking and clinical examination, upper gastrointestinal endoscopy, routine biochemistry, and upper abdominal ultrasound. Inclusion criteria were the presence of functional dyspepsia according to the Rome II criteria, i.e. the presence of dyspeptic symptoms for at least 12 weeks in the last 12 months, in the absence of organic, systemic, or metabolic disease. Dyspeptic symptoms had to be present at least 3 days per week, with 2 or more symptoms scored as relevant or severe on the symptom questionnaire. Exclusion criteria were the presence of oesophagitis, gastric atrophy, or erosive gastro-duodenal lesions on endoscopy; heartburn as a predominant symptom; a history of peptic ulcer, major abdominal surgery, or underlying psychiatric illness; and the use of non-steroidal anti-inflammatory drugs, steroids, or drugs affecting gastric acid secretion. During upper gastrointestinal endoscopy, biopsy

specimens were taken from the antrum and the corpus to perform immunohistochemistry to detect the presence of *Helicobacter pylori*. In patients with relevant or severe epigastric burning on the symptom questionnaire (n 5), a 24-hour oesophageal pH monitoring was performed and found to be normal (<4% of time pH<4). A psychiatrist ruled out anorexia nervosa in patients with weight loss of at least 5% of the initial body weight. All drugs potentially affecting gastrointestinal motility were discontinued at least 1 week before the gastric emptying studies.

Symptom questionnaire

Before the studies, each patient completed a dyspepsia questionnaire as reported previously (Tack 1998). The patient was asked to grade the intensity (0–3; 0 = absent, 1 = mild, 2 = relevant, and 3 = severe, interfering with daily activities) of 8 different symptoms (epigastric pain, bloating, postprandial fullness, early satiety, nausea, vomiting, belching, and epigastric burning) over the last 3 months. Also, the amount of weight lost since the onset of the symptoms was noted.

Test procedure

Scintigraphic assessment of gastric emptying of both the solid and the liquid phase of a mixed meal was performed in all subjects. All studies were performed in the morning after an overnight fast. Patients or volunteers did not take any medication known to affect gastrointestinal motility 48 hours prior to assessment of gastric emptying. The test meal consisted of two scrambled eggs (50g each) to which had been added 22 MBq ^{99m}Tc sulphur colloid (600 μCi), two slices of white bread (35g each) and 10 g of butter. After ingestion of this solid phase, patients were asked to drink 170 ml of water labelled with 3.7 MBq ^{111}In DTPA (100 μCi). This test meal had a caloric content of 413 kcal (carbohydrate 36%, protein 18%, and fat 46%). The in vitro stability of this test meal had been confirmed previously. Anteroposterior (AP) and posteroanterior (PA) images were acquired during 1 minute in upright position using a gamma camera Diacam (Siemens

Gammasonics Inc, 1990 IL, USA) equipped with a medium energy all purpose collimator. Scintigraphic planar images were obtained immediately after intake of the meal and every 20 minutes for the next 2 hours. The images were transferred to a computer for further analysis.

Image analysis

A summation of all Tc images was used to draw a region of interest around the stomach. Matching this region of interest to all images, fine alignment was performed if necessary. Afterwards a summation of all images was computed. The final region of interest of the stomach was determined by the software using a pre-set threshold activity. All images were corrected for the difference of the tissue attenuation between the proximal and distal area of the stomach by computing geometric means of anteroposterior and posteroanterior images. The longitudinal axis of the stomach was indicated by the operator to the computer. The region of interest of the stomach was then separated in a proximal and distal compartment using a mid length separation (figure 4.6). The computer generated tables with total counts of both regions corrected for the isotopes' physical decay at each time point. Finally the counts were plotted as a residual fraction of the initial image (taken immediately after meal intake) and for the delay between initiation of the meal and the first image. The data points were fitted using the Siegel gastric emptying model $f(t) = (1 - (1 - e^{-kt})^\beta)$ and $t_{1/2}$ ($t_{1/2} = -\log(1 - 0.5^{1/\beta}) / k$) and t_{lag} (for solids; $t_{lag} = \log(\beta) / k$) were calculated (Siegel 1988)

The ratio of proximal over distal counts was computed at all time intervals for both phases.

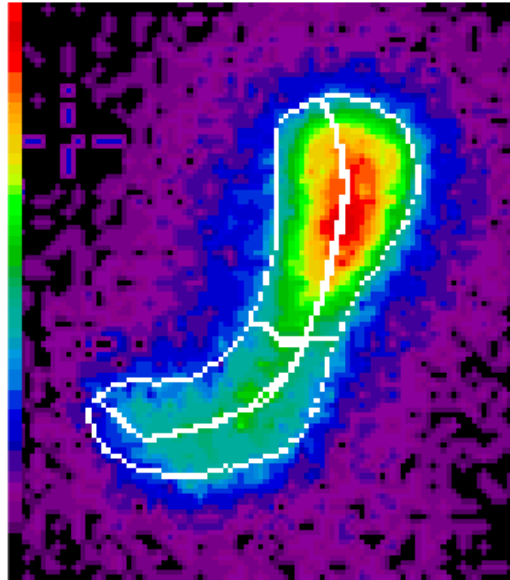


Figure 4.6: Representative image analysis of the solid phase of a meal in a healthy subject: all images at different time intervals have been summated. The white contour of the stomach has been computed automatically. The longitudinal axis of the stomach was indicated to the computer by the investigator. The stomach was divided in two parts based on the midlength of this axis.

Statistical analysis

Continuous variables were tested for normality and compared using Student's *t* test. Proportions between two groups were compared using χ^2 analysis. Time series of continuous variables were compared using ANOVA and Student's *t* test on the area under the curve. The influence of categorical variables (e.g. symptom grading) on continuous variables (e.g. distribution ratio) was assessed using multiple linear regression. The association between dichotomous independent and dependent variables was assessed using multiple logistic regression analysis with backward Wald's elimination procedure. In the stepwise procedure, the probability for entry was 0.05 and for removal 0.10. Odds ratios and the 95% confidence interval were computed. Differences were considered significant at the 0.05 level.

4.3.2 Results

Gastric emptying and intragastric distribution of a meal in healthy volunteers

The total gastric emptying characteristics of normal subjects were as follows: $t_{1/2}$ for solids: 91.8 ± 21.6 minutes; t_{lag} for solids: 61.2 ± 16.9 minutes; $t_{1/2}$ for liquids: 55.9 ± 20.9 minutes.

The intragastric distribution of the test meal could be assessed in all healthy volunteers. Table 4.1 represents the characteristics of this group. The distribution of the solid phase was initially more proximal, whereas for the liquid phase the distribution is more constant over time. There was however no significant correlation between time points and proximal/distal counts ratio for the solid phase (slope=-0.02; $r=0.21$). The 95% confidence interval determining the range of normal values was computed for both phases and for the different time points (see table 1). Over the whole test, the area under the curve of the intragastric distribution ratio over time was 247 ± 155 (mean $\pm$ SD, 95% CI 189-305) for solids and 210 ± 108 (mean $\pm$ SD, 95% CI 170-251) for liquids.

Time	Solid phase			Liquid phase		
	<i>prox/dist ratio</i>			<i>prox/dist ratio</i>		
	<i>mean</i>	<i>SEM</i>	<i>95%CI</i>	<i>mean</i>	<i>SEM</i>	<i>95%CI</i>
Postprandial	3.84	0.85	2.9-4.8	2.13	0.30	1.8-2.5
20'	2.69	0.50	2.1-3.3	2.05	0.31	1.7-2.4
40'	2.48	0.50	1.9-3.1	2.03	0.31	1.7-2.4
60'	2.21	0.57	1.6-2.9	1.78	0.30	1.4-2.1
80'	1.73	0.45	1.2-2.2	1.60	0.32	1.2-2.0
100'	1.28	0.33	0.9-1.7	1.47	0.34	1.1-1.9
120'	1.07	0.26	0.8-1.4	1.24	0.26	0.9-1.5

Table 4.1: Ratio of radioactivity counts from the proximal over the distal stomach in 29 healthy subjects after ingestion of a radiolabelled mixed solid/liquid meal.

Patient characteristics

Symptom patterns of functional dyspepsia patients

Table 4.2 summarises the grading of dyspeptic symptoms in the patient group. Relevant to severe nausea and epigastric pain were the most

prevalent symptoms, present in 28 (70%) and 27 (68%) patients respectively. Bloating (24 patients (60%)), fullness (21 patients (53%)) and early satiety (15 patients (38%)) were also frequently reported. Vomiting, belching and epigastric burning sensation were present in 8 (20%), 10 (25%) and 12 (30%) patients, respectively. Weight loss in excess of 5% was present in 8 patients (20%).

	0 (absent)	1 (mild)	2 (relevant)	3 (severe)
Fullness	15	4	9	12
Bloating	15	1	9	15
Epigastric pain	10	2	11	17
Early satiety	22	3	2	13
Nausea	11	2	12	15
Vomiting	29	3	5	3
Belching	22	8	5	5
Heartburn	18	10	6	6

Table 4.2: Frequency of severity grading for each of 8 dyspepsia symptoms in 40 patients with functional dyspepsia.

H pylori status

Seven patients (18%) were *H pylori* positive on gastric biopsies.

Total gastric emptying parameters

The total gastric emptying characteristics of the patients were as follows: (mean $\pm$ SD) $t_{1/2}$ for solids: 121 ± 49 min; t_{lag} for solids: 70 ± 38 ; $t_{1/2}$ for liquids: 53 ± 21 . These characteristics, although slightly outside normal ranges, were not significantly different when compared to the healthy controls. Twelve patients (30%) had a significantly delayed gastric emptying for the solid phase and eight patients (20%) for the liquid phase.

Intragastric distribution of a meal in functional dyspepsia patients

Intragastric distribution compared to volunteers

The intragastric distribution as evaluated by the proximal/distal counts ratio was not different for patients as a group when compared to the healthy volunteers (figure 4.7) nor was the area under the curve of the intragastric distribution ratio over time (mean $\pm$ SD) (256 ± 160 in patients vs. 247 ± 155 in

volunteers and 187 ± 95 in patients vs. 210 ± 109 in volunteers, for solids and liquids respectively, NS). Comparison of distribution ratios at the different time points was also not significantly different.

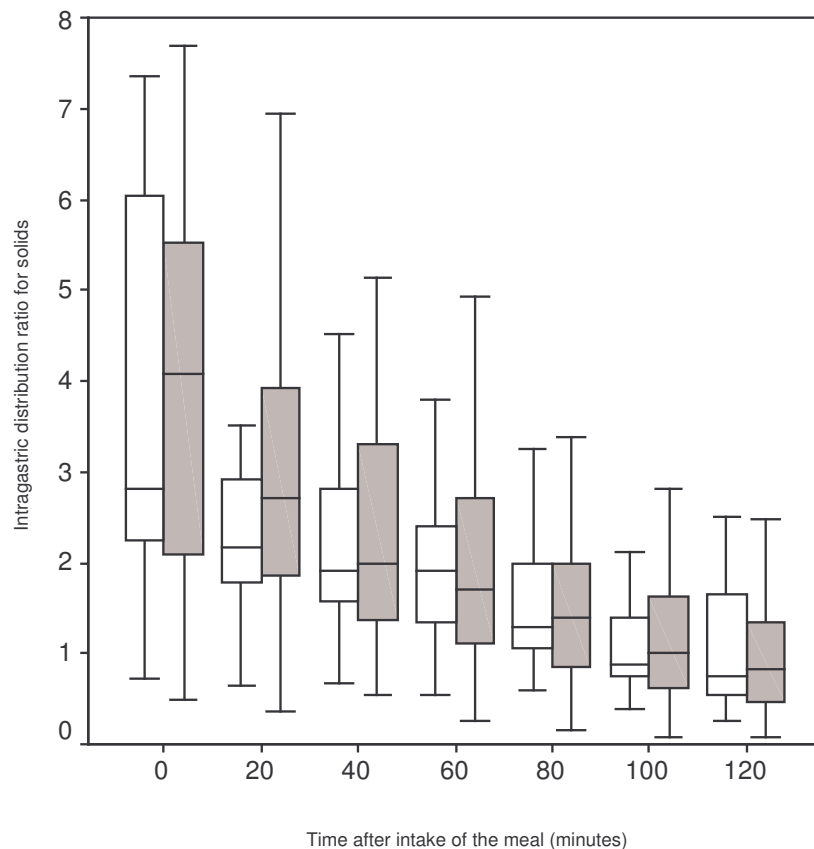


Figure 4.7: Boxplots of the ratio of counts of the proximal over the distal compartment of the stomach for the solid phase, in patients (grey boxes), compared to healthy volunteers (open boxes).

Integrated intragastric distribution comparison between patients

Using the 95% confidence interval of the area under the curve of the distribution ratio over time for solids as a cut-off, 18 patients (45%) had a distal redistribution of the solid phase of the meal and 13 patients (33%) had a proximal retention. Similarly, for the liquid phase, 20 patients (50%) had a distal redistribution of the liquid phase of the meal and 9 patients (23%) had

a proximal retention. Patients with proximal retention for solids were older (58 ± 14 year vs. 47 ± 15 year, $p < 0.05$) and had a higher $t_{1/2}$ for total gastric emptying (143 ± 51 min vs. 109 ± 43 min; $p < 0.05$). Patients with distal redistribution of the solid phase were younger (42 ± 13 year vs. 59 ± 13 year, $p < 0.01$), had a lower $t_{1/2}$ for total gastric emptying (101 ± 28 min vs. 136 ± 56 min, $p < 0.05$) and were more likely to be H pylori positive (11/18 vs. 6/32, $p < 0.05$). Patients with proximal retention of liquids were older (63 ± 14 year vs. 48 ± 14 year, $p < 0.05$). Finally, patients with distal redistribution of the liquid phase were younger (44 ± 14 year vs. 59 ± 13 year, $p < 0.05$). All other demographic correlates were not significant.

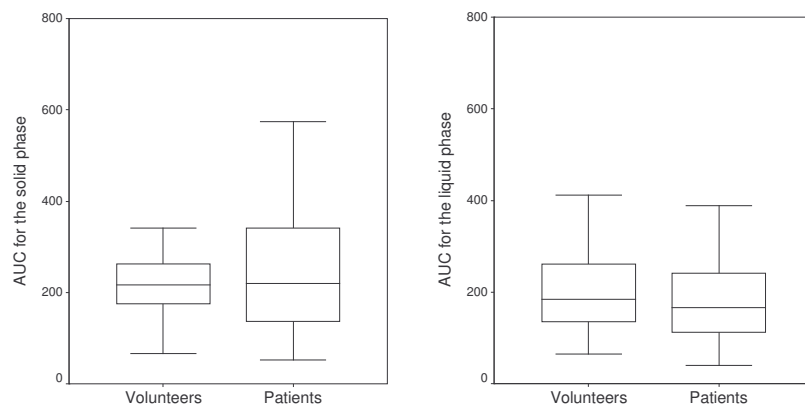


Figure 4.8: Boxplots of the area under the curve of the intragastric distribution ratio over time for solids (left panel) and liquids (right panel) in healthy volunteers ($n=29$) and functional dyspepsia patients ($n=40$)

Intragastric distribution at specific time points: comparison between patients

Using the lower range of the 95% confidence interval of the distribution ratio for liquids immediately after intake of the test meal in healthy volunteers as a cut-off, 20 patients (50%) had an abnormal initial intragastric distribution for liquids. Conversely, using the upper range of distribution ratio for solids as a cut-off, 16 patients (40%) had an abnormal intragastric distribution for solids at 80 min.

Correlation between intragastric distribution and symptoms in functional dyspepsia patients

Univariate analysis

When the patient population was divided, based on the presence of an abnormal integrated intragastric distribution pattern, no symptom appeared to be associated to any pattern.

Early satiety was significantly more prevalent in patients with distal redistribution of the liquid phase immediately after intake of the meal (12/20 vs. 3/20, $p < 0.01$) (table 4.3A). Conversely, when patients were grouped based on the presence or absence of relevant or severe early satiety, the intragastric distribution ratio was lower in the presence of early satiety (table 4.3B). This difference reached statistical significance for the liquid phase immediately after intake of the meal and at 20 minutes. Fullness was significantly more prevalent in patients with proximal retention of the solid phase at 80 minutes (12/16 vs. 9/24, $p < 0.01$) (table 4.4A). Similarly when patients were divided on the presence or absence of fullness, the intragastric distribution ratios at 80 and 100 min was significantly higher in the presence of relevant to severe fullness (table 4.4B). Representative studies are shown in figure 4.9.

Proximal/distal ratio of liquids immediately after the meal	Number of patients	
	Early satiety present	Early satiety absent
<1.8	12	8
≥1.8	3	17

	Proximal/distal ratio immediately after the meal	
	Solid phase	Liquid phase
Early satiety present	3.6±0.5	1.5±0.2
Early satiety absent	6.9±1.5	2.9±0.5

Table 4.3: Prevalence of relevant or severe early satiety in functional dyspepsia patients with distal redistribution of the meal immediately after intake (top) and mean ($\pm$ SD) intragastric distribution ratio in the presence of absence of relevant to severe early satiety (bottom).

Proximal/distal ratio of liquids at 80 minutes	Number of patients	
	Fullness present	Fullness absent
>1.5	12	4
≤ 1.5	9	15

	Proximal/distal ratio at 80 minutes	
	Solid phase	Liquid phase
Fullness present	2.0±0.3	1.6±0.2
Fullness absent	1.0±0.1	1.0±0.1

Table 4.4: Prevalence of relevant or severe fullness in functional dyspepsia patients with proximal retention of the meal 80 minutes after intake (top) and mean ($\pm$ SD) intragastric distribution ratio in the presence of absence of relevant to severe fullness (bottom).

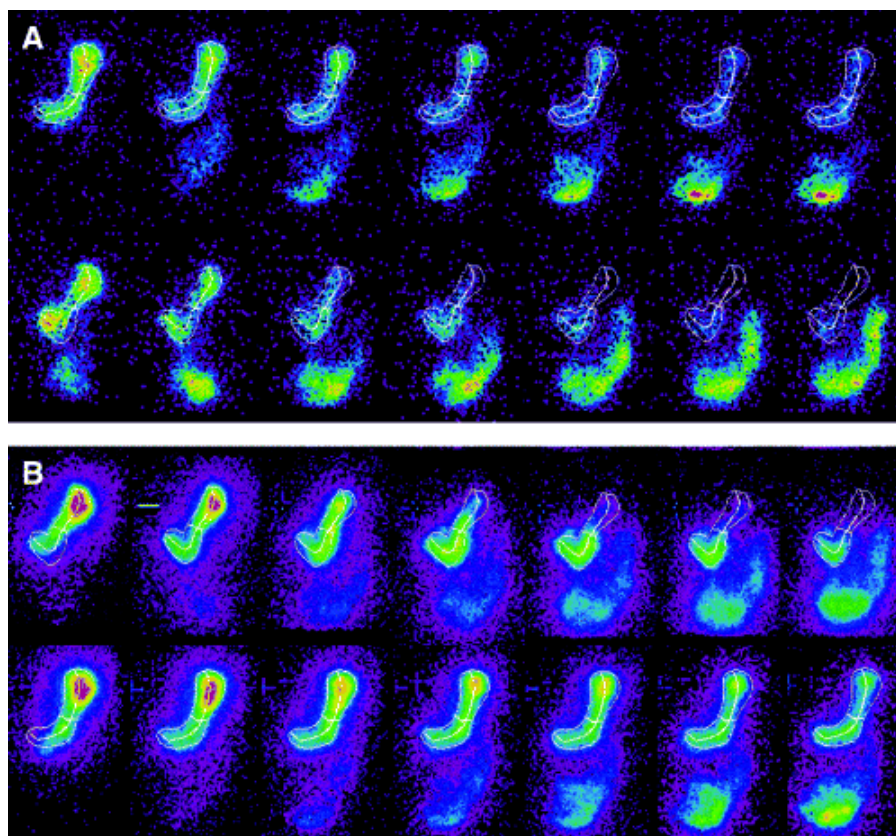


Figure 4.9: Panel A: Scintigraphic images of the liquid phase in representative patients with functional dyspepsia. The top series depicts the intragastric distribution in the absence (top series) or presence (bottom series) of relevant or severe early satiety at 0, 20, 40, 60, 80, 100 and 120 minutes after intake of the meal. Panel B: Scintigraphic images of the solid phase in representative patients with functional dyspepsia. The top series depicts the intragastric distribution in the absence (top series) or presence (bottom series) of relevant or severe early fullness at 0, 20, 40, 60, 80, 100 and 120 minutes after intake of the meal.

Multivariate analysis

Linear regression analysis was used to identify an association between the presence of distal distribution or proximal retention (evaluated by the area under the curve of the distribution ratio over time) and the grading of specific symptoms. None of these predictor variables (symptoms) was associated with one of both distribution patterns. Using multiple logistic regression analysis with backward Wald's elimination procedure, the association

between the risk of early distal redistribution of liquids and the presence of relevant or severe specific symptoms was studied. The presence of relevant or severe early satiety was significantly associated with the risk of early distal redistribution of liquids (Odds ratio 5.04, 95% CI 1.05-28.00; $p=0.05$). The presence of relevant or severe fullness was significantly associated with the risk of late (100 min) proximal retention of solids (Odds ratio 0.067, 95% CI 0.003-0.429; $p<0.05$). When the cut-off value for the presence or absence of a symptom was changed to mild or severe, similar associations were identified, but these did not reach statistical significance.

4.3.3 Discussion

In these studies we have shown that the evaluation of the intragastric distribution of the solid and liquid phase of a standard test meal can be assessed using a conventional scintigraphic emptying test.

From a methodological point of view, we have elaborated an image analysis protocol, which lead to reproducible analyses and which minimised the intervention of the operator, leading to more objective compartmentalisation of the stomach. Indeed, in previous studies (Kuiken 1999, Troncon 1994), the gastric area was divided in two parts on visual appreciation of the incisura. We believe however, that this subjective division may lead to false and subjective results, mainly in view of the poor spatial resolution of these scintigraphic studies, which hampers correct identification of the anatomical landmarks. Kuiken et al. reported that in a significant proportion of subjects the incisura is not clearly visible (Kuiken 1999). In some studies the stomach was divided in two parts of equal surface on AP or PA projections (Troncon 1994). This method seemed inappropriate, since the outcome measure, namely the distribution of the meal within the area of the stomach, may strongly influence the way the stomach is subdivided. We experienced that the least subjective parameter of the morphology of the stomach was the identification of its longitudinal axis. Using powerful computer algorithms, it might even be possible to reconstruct this axis mathematically. In our hands, our method to divide the stomach in a proximal and a distal part was very

reproducible, but a formal assessment of reproducibility was not performed. Moreover, when visually comparing the calculated region of interests to the actual images, we found excellent agreement, even in individuals with unusual stomach shape.

Since we wanted to evaluate gastric accommodation without interference of gastric emptying we used the intragastric distribution ratio (activity of the proximal stomach (counts)/activity of the distal stomach (counts)) as an objective measurement.

Our primary aim was to thoroughly evaluate and compare the intragastric distribution pattern of a meal in health and functional dyspepsia.

First, in our healthy volunteers' studies, we carefully documented the characteristics of the normal intragastric distribution pattern of a meal. Analysis of distribution curves over time confirmed the role of the proximal stomach as an early postprandial reservoir. Confirming the data obtained by Collins et al. we found a more diffuse distribution of the liquid phase of the meal, when compared to the solid phase (Collins 1991). Based on our findings, however we cannot infer whether the proximal stomach has a driving force in the emptying of the solid or liquid phases of a meal or only a storage function (Ropert 1993, Azpiroz 1994). The age range in our healthy volunteers was insufficient to identify the age-related modifications of the total gastric emptying parameters which have been previously described (Horowitz 1984), nor any age-related change in the intragastric distribution patterns. Due to the set-up of our studies we did not evaluate the symptoms in healthy volunteers using the patient's questionnaire. However, healthy controls were required to report absence of abdominal symptoms to be eligible for the studies. In a combined scintigraphic and ultrasound study in healthy volunteers, postprandial satiation was correlated to the antral area (Jones 1997).

In patients we found a proportion of patients with delayed total gastric emptying but we did not find a different intragastric distribution pattern compared to volunteers. This last observation is in contrast to Troncon's small (n=11) scintigraphic (Troncon 1994) and to Gilja's ultrasonographic

observations (Gilja 1996). In an earlier large (n=75) study, Scott did find abnormal intragastric distribution of a radiolabelled mixed meal only in a small subset of functional dyspepsia patients (13% for solids and 9% for liquids) (Scott 1993). Our findings might be explained by methodological differences, which we already alluded to. But, although we cannot rule out an influence of group differences such as the older age and higher prevalence of women in our patients' group, the use of a distribution ratio corrects our distribution data for differences in gastric emptying, bearing in mind that functional dyspepsia patients may have delayed gastric emptying in one third of the cases and that the gastric emptying rate for solids is significantly lower in functional dyspepsia patients as compared to controls (Stanghellini 1996). Like in Stanghellini's study, in patients there was no correlation between age and gastric emptying parameters. Finally, Troncon did not observe any influence of gender on intragastric distribution of food in patients or volunteers (Troncon 1994). In our patients we found a dispersion of intragastric distribution patterns, both for the solid and the liquid phase, indicating the disease might interfere with this parameter in opposite directions.

Interestingly in contrast to volunteers' data, age was a significant determinant of intragastric distribution within the patients' group. In these, proximal retention of both phases was associated with delayed gastric emptying and ageing. Both observations might be linked, since, at least during the earlier phases of the gastric emptying process, the antral filling is known to be less variable over time. The filling of the proximal stomach is then correlated to the total gastric emptying. As already mentioned, our control group has an insufficiently large age-range to evaluate whether the variations of intragastric distribution with age is a phenomenon related to the disease or if this phenomenon is also observed in health. A gastric barostat study has found a decreased postprandial gastric tone in older healthy volunteers (Rayner 2000). In line with these findings, in our previous studies, we observed that the age of patients with impaired gastric accommodation tended to be lower than those with normal accommodation, although this

difference was statistically not significant. (34 ± 4 years vs. 41 ± 2 year) (Tack 1998).

An other interesting finding is the higher prevalence of *Helicobacter pylori* in patients with distal redistribution of solids. An association between *Helicobacter pylori* infection and impaired accommodation was reported in healthy volunteers (Thumshirn 1999b), but we did not find any correlation between defective accommodation and Hp status in previous gastric barostat studies in patients (Tack 1998, Tack 2001a).

Our secondary aim was to link different intragastric distribution patterns to symptoms. When studying the integrated intragastric distribution patterns over a whole 2-hour postprandial period we found no correlation with symptoms. The reason for this may be that initial small differences in intragastric distribution might be corrected during the later phases of the gastric meal processing or that the process of emptying dominates later phases. However, when we looked at the distribution ratios at specific time points, we found early satiety being associated with early (immediately after intake of the meal) distal redistribution and fullness being associated with late (at 80 and 100 minutes after the meal) proximal retention. Early satiety is a symptom that has been linked to defective gastric accommodation (Tack 1998). It is therefore likely that patients presenting with early satiety have more frequently defective accommodation. In turn, defective accommodation may lead to disturbed intragastric distribution of the meal, particularly at the start of the postprandial period when early satiety is most prominent. Our previous studies indicated that increased gastric wall tension might lead to symptoms (chapter 3). In our hypothesis, patients with defective accommodation would have increased wall tension both in the proximal stomach, due to the absence of the normal relaxation, and/or in the antrum because of a driving force to distend the antrum. In these scintigraphic assessments it is impossible to distinguish between both potential origins of symptoms. Data in healthy volunteers tend to indicate that the increased wall tension in the proximal stomach may be predominant (chapter 3).

In conclusion, using conventional scintigraphic emptying studies, we characterised the intragastric distribution pattern in health and in functional dyspepsia. These findings allowed us to reveal an association between specific intragastric distribution patterns and symptom profiles. Early distal redistribution of the liquid phase and late proximal retention of the solid phase might be related to different pathophysiological mechanisms.

4.4 Measurement of gastric accommodation using SPECT

In previous chapters we have described the gastric accommodation reflex and its importance in functional dyspepsia. The standard way to measure gastric accommodation is, using a gastric barostat, to measure the increase of the intrabag volume at constant pressure, after administration of a liquid meal. This method however carries several drawbacks which may hamper its use in clinical practice, outside well-defined clinical and research studies. First this technique needs an oral intubation with a finely folded balloon mounted on a double lumen gastric suction tube. This assembly is not only poorly tolerated during placement of the device in the stomach, but may also lead to intolerance (repeated swallowing, nausea, ...) due to continuous pharyngeal stimulation during the procedure. This last phenomenon may interfere with the results of the procedure, since e.g. pharyngeal stimulation may induce reflex vagal stimulation leading to modifications in gastric motor and secretory physiology and repeated swallowing may lead to receptive relaxation (chapter 1). Second, there is a need for fluoroscopic control of the placement of the device in the proximal stomach. In addition, even if the tube is correctly positioned in the proximal stomach, due to the necessary oversize of the bag, during the procedure, the investigator cannot ascertain where the air is trapped and if the majority of the inflated air really stays trapped in the proximal stomach. Third, the intragastric bag may interfere with the normal processing of a meal. Some attempts have been made to use a solid meal as a trigger for the gastric accommodation, but due to poor tolerance this is no longer used. Therefore, the stimulus, although well standardised (most often 200 ml of Nutridrink), may not be the most

physiological and its emptying may be hampered by the presence of a balloon. The site of triggering of the gastric accommodation may be predominantly in the stomach (Vanden Berghe 2001) but the presence of lipids in the duodenum may certainly interfere with the process (Feinle 1997). Finally, this test is time consuming.

On the other hand, gastric barostat studies may yield additional information, such as sensitivity to mechanical distension, which cannot be obtained without invasive procedures.

In view of this, there is a need for a non-invasive method for the evaluation of gastric accommodation. Some authors have proposed the use of ultrasonography to evaluate not only gastric emptying and transpyloric flow, but also to measure gastric accommodation. This technique however is highly time consuming and necessitates the use of sophisticated devices to calculate intragastric volume (Berstad 1996, Gilja 1996). In 1999 the Mayo group has proposed the use of Single Photon Emission Computed Tomography (SPECT) in this setting (Kuiken 1999). They used the selective uptake of Tc pertechnetate by the gastric mucosa to obtain a radioactive labelling of the stomach inner layers and reconstruct volumetric data of the stomach. The gastric SPECT has been extensively studied and validated. It has been compared to the gold standard gastric barostat (Bouras 2002) and pharmacologically induced variations of the gastric tone both pre- and postprandially were recorded (Liau 2001). The SPECT technique although very appealing has some limitations and needs thorough understanding of the gastric motor and secretory physiology for correct interpretation.

One of the limitations of this technology is the narrow safety margin of the injected radio-active tracer at the dose originally published at the time we planned our studies (20 mCi=740 MBq)(Kuiken 1999). Following intravenous injection, 70-80% of Technetium-99m pertechnetate ($^{99m}\text{TcO}_4^-$) is weakly bound to serum proteins (Owunwanne 1995). Unbound $^{99m}\text{TcO}_4^-$ diffuses slowly through the capillary membranes to the interstitial fluids, from where it is cleared by various organs such as stomach wall, intestines, salivary glands, thyroid, choroid plexus, sweat glands, kidneys and mucous

membrane. The thyroid uptake of $^{99m}\text{TCO}_4^-$ is by active transport and represents approximately 2-4%. In the kidneys, $^{99m}\text{TCO}_4^-$ is filtered in the glomeruli, but 86% of it is reabsorbed in proximal tubules. Therefore only, 30% of the injected dose is excreted in urine in 24h. Table 4.5 represents the estimated radiation absorbed dose of $^{99m}\text{TCO}_4^-$. Additional information provided by the Mayo group (Liau 2001) can be found in table 4.6. The signal to noise ratio can be derived from these figures and represents approximately a factor 4 when compared to the neighbouring intestines. This is the reason why large doses of $^{99m}\text{TCO}_4^-$ (20 mCi/740MBq initially and later 10 mCi/370MBq) are necessary for these studies. Therefore the dosis is limited by the uptake of the thyroid (2.6 cGy if 20 mCi is injected). It is probable that thyroid blocking agents should preferably be avoided, since the uptake by the gastric mucosa is probably very similar to the active transport in the thyroid. In Meckel scans, which use the same tracer, anti-secretory agents, such as H_2 -blockers are used to block the radioactive marker in the gastric mucosa and mucous layers. In gastric studies, however this method cannot be used since inhibition of gastric secretion may interfere with the motor behaviour of the stomach (Parkman 1998). It has been shown previously that proton pump inhibitors may modulate gastric accommodation and sensitivity to distension (Mearadji 1999). Due to the poor signal to noise ratio, long acquisition times have been necessary reaching up to 16 minutes, which in turn may lead to decreased spatial resolution of the method and hampering measurement of transient changes in gastric volumes. Finally, the labelling of the mucosa decreases over time hampering longer studies (personal observations). Recent studies have shown that lower doses as low as 5.6 mCi/200 MBq can be successfully used and acquisition times shortened to 10 minutes (Liau 2001, van den Elzen 2003). In this part of the thesis we tried to develop a method to improve the signal to noise ratio of this procedure, while increasing the safety. To achieve this goal we wanted to evaluate the feasibility of per-oral labelling of the gastric mucosa with a radiolabelled muco-adherent compound. Previous studies, aimed at the development of gastric topical treatment for

Helicobacter pylori eradication, have revealed that cholestyramine has a long adherence to the gastric mucosa, even in the presence of a meal (Thairs 1998). We therefore evaluated the use of cholestyramine labelled with ^{99m}Tc in gastric SPECT studies.

Organ	MGy/MBq	Rad/mCi
Thyroid	0.035	0.13
GI tract		
Stomach (wall)	0.068	0.25
Upper large intestine	0.018	0.068
Lower large intestine	0.016	0.061
Testes	0.035	0.13
Bladder wall	0.014	0.053
Ovaries	0.006	0.022
Red bone marrow	0.005	0.019
Total body	0.004	0.014

Table 4.5: Estimated radiation absorbed dose of $^{99m}\text{TcO}_4^-$ (from Owunwanne 1995)

Organ	Exposure in mrem
Body (effective dose)	0.4
Gonads	0.1
Breast	0.24
Red Marrow	0.24
Lung	0.1
Thyroid	0.02
Liver	0.1
Oesophagus	0.05
Stomach	0.1
Colon	0.24

Table 4.6: Radiation exposures (organ doses and effective dose) from SPECT imaging for gastric accommodation after IV injection of 10 mCi/370MBq of $^{99m}\text{TcO}_4^-$ (Adapted from Delgado-Aros 2003).NB: 1mSv=100 mrem

4.4.1 Material and methods

Study subjects

Four healthy volunteers were included. None of the subjects had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Informed consent was obtained from each participant.

Radio-labelling and in vitro stability testing of cholestyramine

Prior to each study, cholestyramine (Questran, Bristol-Myers Squibb) was radio-labelled with Technetium^{99m} according to Jackson et al. (Jackson 2000). The required activity was added to the cholestyramine so that 1mCi labelled 1 g of cholestyramine. Following a 5-min incubation, 20 ml of distilled water was used to rinse any unbound activity from the resin, and as much liquid as possible was decanted from the solid. The stability of the radio-labelled resin was investigated over 6 hours. Samples of 25 ml of the suspension were filtered every hour. The masses of the fractions were calculated and the activity in each sample recorded using a gamma camera. The percentage of radio-label bound to the resin was then deduced.

Study protocol

After an overnight fast of at least 12 hours, the volunteers ingested 1g in 20 ml of radio-labelled cholestyramine suspension.

After 1 and 3 hours and immediately after ingestion of 200 ml of Nutridrink, tomographies of 1 min were acquired in the supine position using a SPECT (Single Photon Emission Computed Tomography) camera (Trionix, Triad XLT20) equipped with 3 LEUHR collimators.

Image analysis and reconstruction

The tomographies were reconstructed using an iterative reconstruction algorithm (OSEM Technology Ltd). The region of interest of the stomach was extracted using an activity threshold and the 3D shape was computed with the different tomographies. A dedicated software program was used to

calculate gastric volumes. After correction for decay, the total radio-activity of the gastric wall was computed and compared to the ingested activity.

4.4.2 Results

In vitro evaluation of the stability of the labelling

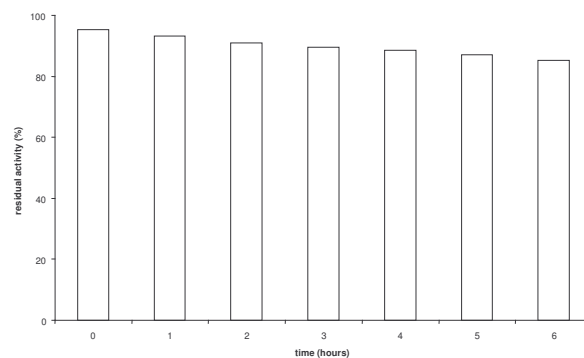


Figure 4.10 shows the percentage activity bound in vitro to the cholestyramine at different time points in a single experiment.

In vivo experiments

Thirty $\pm$ 5.6 percent at 1 hour and 22 $\pm$ 8.2 % at 3 hours of the ingested radio-activity was still adherent to the gastric wall. The marking of the stomach wall was sufficient in both experiments to reconstruct accurately the stomach wall. An example of a 3D reconstructed view of the stomach is represented in figure 4.11.

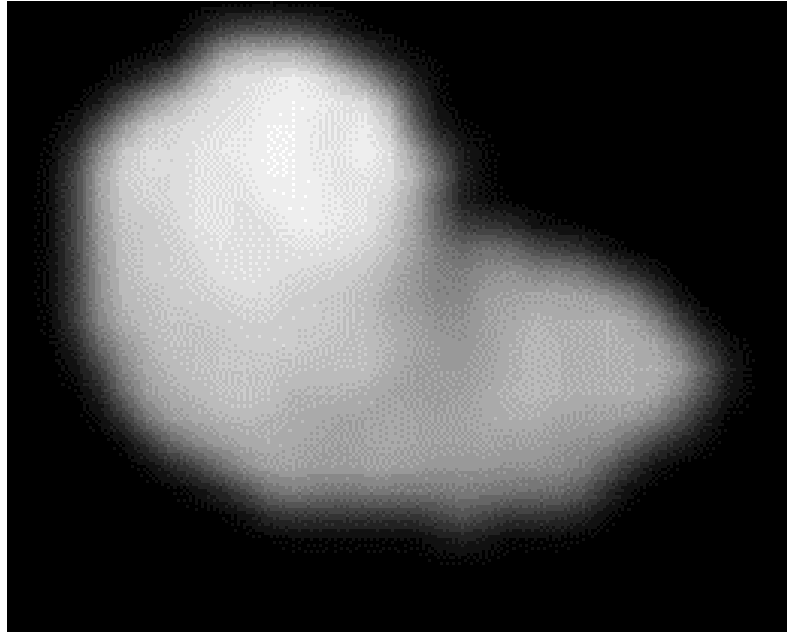


Figure 4.11: Postero-anterior view of the stomach after ingestion of a meal, after marking of the gastric mucosa with radio-labelled Technetium^{99m}.

4.4.3 Discussion

These preliminary studies have showed that SPECT imaging of the stomach to measure gastric accommodation can be improved. We have shown that using oral mucosal labelling with radio-labelled cholestyramine instead of intravenous injection of Tc it is possible to achieve excellent marking of the gastric mucosa. In our in vitro experiments we confirmed the data published by Jackson et al. (Jackson 2001) indicating that cholestyramine is easy to radio-label and that the stability of the bound is very high. The stability of the radio-labelling in gastric juice had been previously demonstrated (Jackson 2001). We believe therefore, that it is unlikely that the label becomes dissociated from the resin during the course of the experiments. Thairs et al. have shown that after ingestion of 250 mg of cholestyramine a significant proportion of the resin is still adhering to the stomach up to 6 hours later. In addition, they had demonstrated that ingestion of a meal did not significantly decrease the mucoadhesion properties of the resin (Thairs 1998). In our

experiments we reproduce very similar findings with good gastric mucoadherent properties of cholestyramine, leading to excellent marking of the mucus layer on top of the gastric mucosa. In contrast to SPECT studies performed after intravenous injection of Tc pertechnetate, due to the absence (or very low levels) of circulating Tc in adjacent vascular structures or highly vascularized organs the noise adjacent to the stomach wall is almost absent. In our experience the combination of lower noise levels and excellent signal intensity lead to improved spatial resolution of the technique. The gain in signal to noise ratio has lead to decreased acquisition times by a factor 10 when compared to the initial Mayo studies (Kuiken 1999) and by a factor 5 when compared to the most recent experiments (Delgado-Aros 2003). In addition this innovative method, leads to a significant decreased systemic and thyroid exposure to radioactivity at least by a factor 10. We believe these technical improvements, might improve the acceptability of SPECT technology to measure gastric volumes non invasively.

The interpretation of the obtained volumetric measurements was not done in these studies, but we would like to emphasise that the link between volumetric findings and accommodation should be interpreted with caution. Indeed, we believe that a limitation of the SPECT technique as described by the Mayo group, is the correct interpretation of the data. Kuiken et al. have claimed that the difference in gastric (either total or proximal) volume from baseline represents the gastric accommodation. We believe changes in gastric volume should be interpreted with caution. During gastric barostat studies, the intragastric pressure is maintained constant at a predetermined level which is above minimal distending pressure (MDP) (most often $MDP + 2$ mmHg). This means that the intragastric volume is determined by the difference in pressure between the lumen and the intra-abdominal pressure and the mechanical characteristics of the gastric wall. When a gastric relaxation takes place, leading to changed mechanical characteristics of the stomach wall, the intragastric volume increases to a new equilibrium. During SPECT studies however the influence of adequate or inadequate relaxation may be less prominent, because there is no driving force leading to

expansion of the stomach except for the ingested liquid volume and the gastric secretions. We therefore believe that the gastric volume load, i.e. the difference between the ingested plus the secreted volume minus the emptied volume, must be a major contributor to SPECT measured gastric volumes. There is ample evidence from morphological evaluations of the gastric accommodation reflex that it is taking place in the proximal stomach. It is logical to assume that impaired accommodation may lead to a different intragastric distribution. One can thus use the differential changes in mechanical characteristics of the gastric wall between the proximal and the distal stomach leading to different gastric shapes to semi-quantitatively evaluate gastric accommodation. We expect that, after ingestion of a liquid meal, the intragastric distribution of the meal leading to different shapes of the stomach will reflect these differences in mechanical properties. Studies observing different intragastric distributions of a test meal were published previously and are reported in section 4.3 (Troncon 1994, Gilja 1996, Piessevaux 2003). We would propose to confirm this hypothesis to use repeated studies with both barostat and SPECT studies, since the placement of a balloon in the stomach will interfere with the intragastric distribution of the liquid meal and will interfere with the muco-adhesive properties of cholestyramine.

Finally, it must be mentioned that these studies are performed in the supine position, which might interfere with gastric accommodation. It is known that gastric emptying might be influenced by posture (Horowitz 1993; Anvari 1995; Hebbard 1995).

In conclusion, the findings of this part of the thesis indicate that measurement of gastric accommodation using SPECT can be improved both in terms of signal to noise ratio and in terms of tolerability.

CHAPTER 5: QUANTIFICATION OF TOTAL AND REGIONAL WALL TENSION OF THE STOMACH DURING GASTRIC DISTENSION STUDIES

5.1 Introduction

It has been repeatedly shown that gastric distension studies both in healthy subjects and in functional dyspepsia patients elicit symptoms comparable to those perceived postprandially in these patients. These observations support the idea that activation of mechanoreceptors in the stomach may be the trigger to the perceived symptoms. Two types of mechanoreceptors have been functionally identified in animal models: in series receptors sensing gastric wall tension and in parallel receptors sensing gastric elongation (figure 5.1). Based on the findings of the previous chapters and on the literature there is evidence suggesting that wall tension might be more important for the genesis of perceived symptoms (Distrutti 1999, Chapter 3). Until now, the in vivo evaluation of the wall tension of a hollow organ has always been based on calculations using the simplified Laplace's law. In the case of a spheric organ, the law can be written: $T = \Delta P(r/2)$ (Gregersen 1996). The requirements to allow the use of this law are: that the organ indeed matches a spherical shape, that the wall thickness is very thin and that the organ structure is isotropic, i.e. that the mechanical properties are uniform along the whole organ wall. These assumptions are not met in the case of the stomach and therefore it remains doubtful if Laplace's wall can be used, as is, to calculate total gastric wall tension. If however, one knows the shape of the stomach, the wall tension at every surface point of the stomach can be calculated or approximated. Indeed, the wall tension at point x of the stomach wall can be formulated $dT(x) = dP(x)(gastric - extragastric)(r^{(x)}/2)$. During isobaric gastric

distension studies the intragastric pressure can be measured and is clamped at each distension step. This pressure is similar for the whole surface of the stomach in close apposition with the balloon. It can be postulated that the extragastric (intraperitoneal) pressure is constant over time. This suggests that dP is constant at each distension step in distension studies or in barostat mode. The curvature radius at point x can be calculated, providing the shape of the balloon or the stomach wall in contact to it is known. Each point of the stomach surface can be fitted to a sphere element with radius $r(x)$. Finally, since in barostat mode or during an isobaric distension step, the pressure is maintained constant, one can say that the local wall tension is proportional to the curvature radius: $T(x) \approx r$.

We therefore aimed to simultaneously record the balloon or the stomach shape during isobaric distension studies.

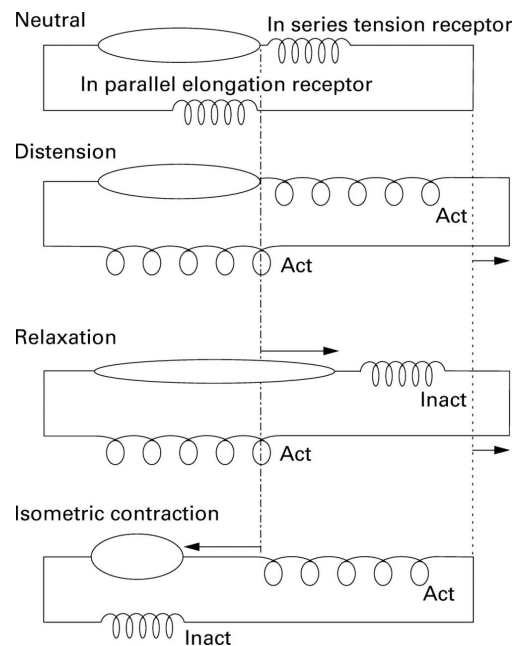


Figure 5.1: Schematic model of the proximal stomach wall with muscular component, in series tension receptor and in parallel elongation receptor. The four panels represent the behaviour of the model in various experimental conditions.

5.2 Pilot study assessing the shape of the balloon during gastric barostat studies

5.2.1 Materials and Methods

In vitro validation studies:

A dummy stomach made of piled water bottles and wet pads was constructed and positioned on the table of the SPECT camera (Trionix, Triad XLT20). A barostat balloon made of a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) was introduced in the middle of the dummy and connected to the barostat device (Synectics Visceral Stimulator, Synectics, Stockholm, Sweden). The barostat pump was then connected in closed circuit with a reservoir filled with 1.5 l of air radiolabelled with 9 mCi of Xe^{133} (figure 5.2). Isovolumetric distension series were applied with increments of 100 ml for 2 min up to 1l, while continuous acquisitions of 20 seconds were performed.

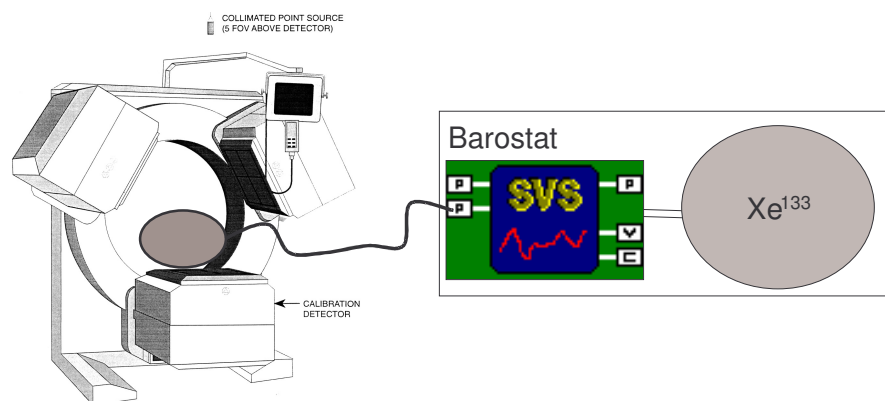


Figure 5.2: Schematic representation of the experimental set-up during in vivo and in vitro studies evaluating the balloon shape during gastric barostat studies.

Study subjects

Two healthy volunteers were included (2M, age 36 and 32). None had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. Informed consent was obtained from both participants.

Protocol

After an overnight fast of at least 12 hours, the volunteers were orally intubated with a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded. The position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube with the bag was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Synectics, Stockholm, Sweden). To unfold the intragastric bag, a fixed volume of 500 ml air was inflated during two minutes with the study subject in a recumbent position. After a 10 minute equilibration period, the subjects were positioned supine on the table of the SPECT camera. Subsequently, a standard isobaric distension protocol was applied (see chapters 2 and 3). During the distension, continuous acquisitions of 20 sec were performed.

Image analysis

The raw data was reconstructed using an OSEM algorithm. The balloon shape was identified and calibrated using an activity threshold chosen to obtain the best correlation between the actual volume inflated by the barostat pump and the SPECT measured volume, during the in vitro studies.

5.2.2 Results

In vitro validation studies

During the in vitro validation studies, we obtained excellent correlation between the inflated volumes by the barostat pump and the measured

radioactivity (linear regression analysis, $r > 0.9$). Volumetric reconstruction and calculations were not performed at this stage.

In vivo studies

Confirming our in vitro studies we obtained an excellent correlation between the inflated volume recorded by the gastric barostat and the radioactivity counts in the SPECT scans (figure 5.3). In addition, the 3D shape of the intragastric balloon could be reconstructed in both cases (figure 5.4). The shape and the supposed location of the balloon was variable during the distension procedure. The shape of the balloon was complex, far from spherical or ellipsoidal and at higher volumes extended towards the antrum.

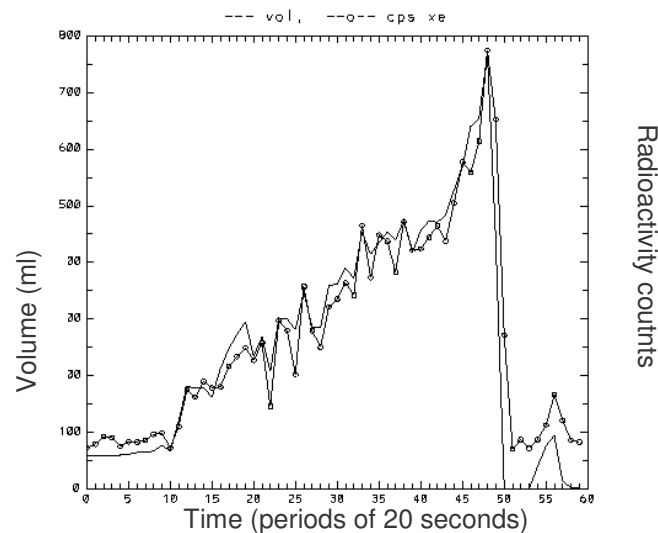


Figure 5.3: Correlation between intragastric volume and radioactivity counts during an isobaric distension study. (intragastric balloon volume in (ml), radioactivity in arbitrary units, time periods of 20 seconds). The intragastric volume measured by the barostat device is depicted with a line without marks. The radioactivity in the balloon measured by SPECT is represented with a line with white circles.

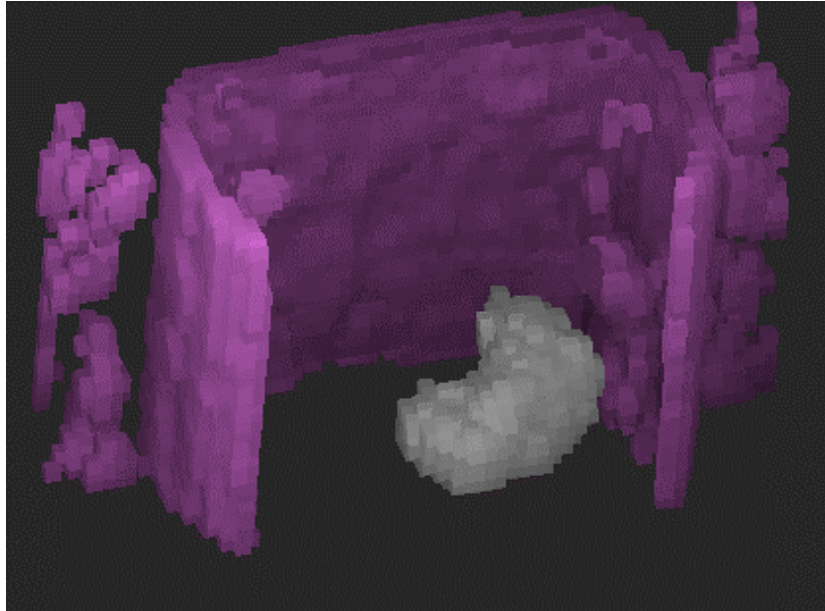


Figure 5.4: Morphology of an intragastric balloon at full inflation during an isobaric distension. Note the extension of the balloon towards the antrum.

5.3 Pilot study assessing the gastric shape and the variability of the local wall tension during gastric distension studies

5.3.1 Materials and methods

Study subjects

Two healthy volunteers were included (1M, age 36 and 31). None had symptoms or a history of gastrointestinal disease or drug allergies, nor were they taking any medication. The female volunteer was taking oral contraception. Informed consent was obtained from both participants.

Protocol

After an overnight fast of at least 12 hours, the volunteers were orally intubated with a double lumen polyvinyl tube (Salem sump tube 14 Ch.,

Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded. The position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube with the bag was then connected to a computer-driven programmable volume-displacement barostat device (Synectics Visceral Stimulator, Synectics, Stockholm, Sweden). To unfold the intragastric bag, a fixed volume of 500 ml air was inflated during two minutes with the study subject in a recumbent position. After a 10 minute equilibration period, the subjects were positioned supine on the table of the SPECT camera. Twenty mCi of Tc^{99m} pertechnetate was injected intravenously. Subsequently, a standard isobaric distension protocol was applied (see chapters 2 and 3). During the distension, continuous acquisitions of 1 min were performed using LEUHR collimators.

Image analysis

All the image analysis procedures were performed on in-house developed software. The raw data was reconstructed using an OSEM algorithm. The gastric mucosal activity was identified using an activity threshold. The obtained gastric volumes were then processed by a specially developed software routine to fit each edge point and its 8 neighbouring voxels to an arc segment (Figure 5.5). The curvature radius was calculated for each of these voxels and expressed graphically using a colour code on the 3D shape of the stomach. Finally, to determine the variability of the local gastric wall tension a histogram of the frequency of the curvature radius was plotted.

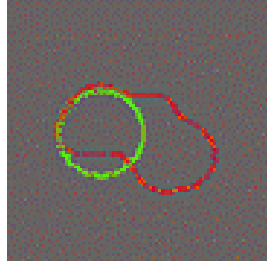


Figure 5.5: Two dimensional representation of the fitting of the stomach wall to an arc segment.; the gastric mucosa is depicted by the red line and the fitted circle by the green line

5.3.2 Results

Confirming the observations from the Mayo group (Kuiken 1999), the uptake of Tc by the gastric mucosa was sufficient to obtain volumetric data on the stomach. Using this mucosal uptake of Tc pertechnetate, we could reconstruct the gastric shape at various points of the gastric distension. A curvature radius/local tension mapping of the stomach wall was performed. A representative example is reproduced in figure 5.6. The considerable variations in curvature radius along the gastric wall are represented in figure 5.7.

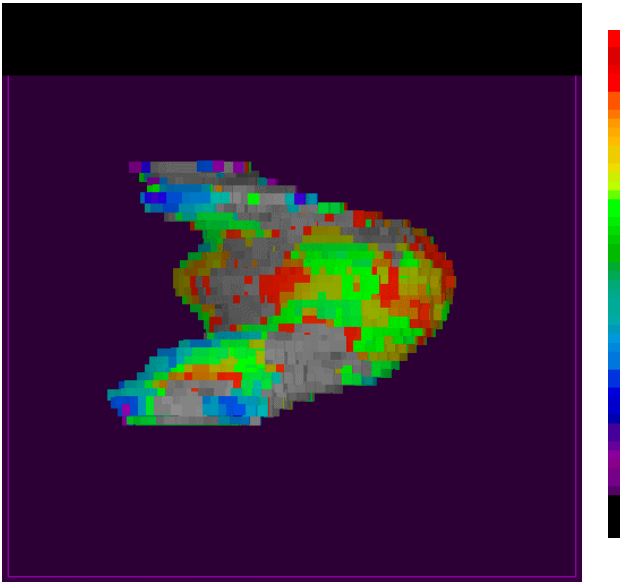


Figure 5.6: Three dimensional representation of the stomach wall during a isobaric distension study. The fitted curvature radius at each voxel is depicted using a colour code.

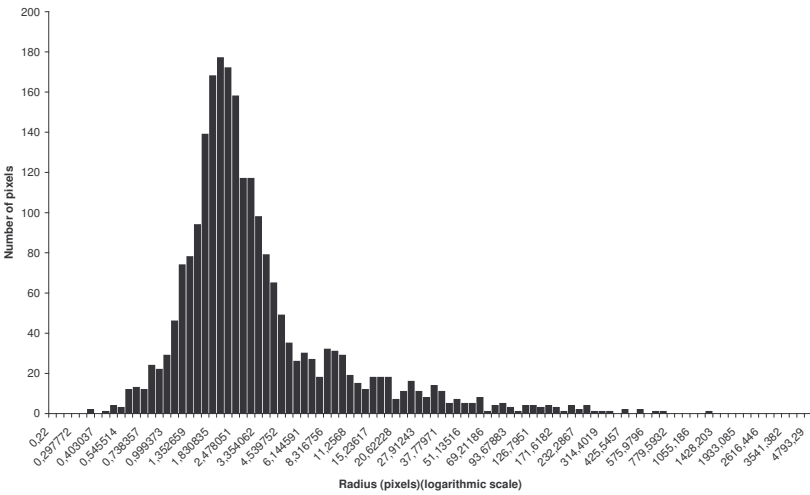


Figure 5.7: Distribution of the curvature radius (logarithmic scale) along the surface of the stomach during an isobaric distension

5.4 Discussion

This set of pilot experiments revealed that during gastric distension studies, the shape of the intragastric balloon is far from spherical or ellipsoidal. This observation is important as several studies have used the simplified Law of Laplace to calculate the wall tension of the stomach, assuming the intragastric balloon was approximately spherical. This observation also questions the pertinence of the tensostat device, which uses Laplace's law to calculate online the hollow organ wall tension to control the inflation of a balloon (Distrutti 1999). Some attempts to correct for the shape of the organ have been proposed such as the use of impedance planimetry, which allows determining the cross-sectional area during a distension (Gregersen 1991). This last method however is more suited for the study of cylindrical organs such as the oesophagus. Another interesting observation is that during isobaric distensions, especially at higher volumes, the balloon, which is supposed to be located in the proximal stomach, may extend to the antral area. This may hamper correct interpretation of distension data, for two reasons. First, the site of the activation of mechanoreceptors at higher distension levels may be different comparatively to lower levels of distension. Secondly, the reflex activation of the phasic activity of the antro-duodenal region during gastric distensions may also influence the intra-balloon pressure and secondarily the intragastric balloon volume (Piessevaux 1998).

In the second study, we observed large variations in regional wall tension. This structural heterogeneity of the stomach, which is responsible for its shape, may be indicative of different mechanosensitivity according the sub-area of the stomach. The development of this tool may help to detect if very high wall tensions at one point, or the summation of lower levels of wall tension in a larger area of the stomach are predominantly responsible for the genesis of symptoms during gastric distension studies or during the mechanical distension of the stomach occurring postprandially.

CONCLUSIONS AND PERSPECTIVES

Summary

About 20 to 30% of the patients in a gastroenterological practice present with functional dyspepsia. It is increasingly apparent that this syndrome is very heterogeneous. Recent research has focused on the characterisation of these patients in terms of symptomatic pattern and their pathophysiological correlates. This work was aimed at characterising one of the pathophysiological defects in this syndrome, at studying how this mechanical dysfunction may lead to symptoms and at the development of new modalities to quantify symptoms and to explore gastric motor physiology.

We first thoroughly investigated a group of patients with functional dyspepsia using a gastric barostat and compared them to healthy volunteers. This study showed that impaired gastric accommodation to a meal is a frequent finding in patients with functional dyspepsia, and that this defective mechanism is associated to the presence of early satiety in the symptomatic pattern, which in turn may lead to weight loss. This finding is of clinical relevance, since, to date, treatment of functional dyspepsia has been disappointing. Most therapeutic standards in this condition include the use of prokinetics, acid lowering therapy or medications aimed at increasing the sensitivity thresholds. The presence of defective gastric accommodation to a meal may open new therapeutic perspectives with special emphasis on drugs aimed at restoring this defect, such as 5HT₁ agonists. Preliminary evidence of the effectiveness of this approach has been obtained.

Consequently we wanted to study how defective gastric accommodation to a meal can lead to dyspeptic symptoms in functional dyspepsia patients. Previous studies had shown that gastric tone determines the sensitivity to distension, but precise analysis of these results could not clearly identify, whether elongation of the gastric wall, increased tension of the gastric wall or both may lead to symptoms during gastric distension. In a first set of

experiments we found increased sensitivity to distension after enhancement of gastric tone, further supporting the link between gastric tone and sensitivity to distension. Then we elaborated a new study protocol in which changes of elongation and wall tension could be separately evaluated. In this study we could clearly demonstrate that changes in wall tension without changes in elongation could lead to perception of epigastric symptoms. These findings might explain how symptoms can arise in patients with functional dyspepsia with defective gastric accommodation to a meal: defective accommodation leads to a deficient reservoir function of the proximal stomach, where increased wall tension is generated, which in turn leads to early postprandial symptoms. These findings also support a role for fundus-relaxing drugs in the treatment of some of the symptoms in functional dyspepsia.

Since in the first parts of the work it appeared that defective gastric accommodation plays an important role in pathophysiology of functional dyspepsia, we then focused on the development of non invasive tools to measure accommodation and to quantify symptoms. We developed and validated a satiety test, which was designed to quantify satiety during a slow ramp drinking test. Our findings indicated a nice correlation between the amount of calories ingested and the satiety score. Manipulation of the tone of the proximal stomach leads to changes in satiety scores which were in line with the proposed association between satiety and wall tension of the proximal stomach. In patients with defective gastric accommodation, which had impaired drinking capacity, restoration of the accommodation led to correction of the drinking capacity. More extensive study of this test revealed that the ingested volume was the predominant factor in the induction of satiety even when compared to the ingested amount of calories. Finally, scintigraphic control during the satiety test confirmed, in volunteers, that satiety correlated best with the filling of the proximal stomach, further supporting the hypothesis that increases of the wall tension at that level leads to symptoms.

In the search for surrogate, non invasive markers of gastric accommodation, we studied whether the intragastric distribution of a meal during a conventional scintigraphic gastric emptying test was influenced by gastric accommodation. We therefore developed a new protocol to analyse scintigraphic gastric emptying studies with a mixed solid/liquid meal. After thorough description of the findings in healthy volunteers, we studied patients with functional dyspepsia and compared their intragastric distribution of the meal to the symptomatic patterns. We found significant associations between specific symptoms and distribution patterns, which perfectly fit in our pathophysiological model of functional dyspepsia.

Recently, gastric SPECT has been advocated as a non invasive tool to measure gastric accommodation. This technique, however, has limitations in terms of spatial and temporal resolution and in terms of exposure to radiation. We therefore developed a new protocol which leads to improved signal to noise ratio while simultaneously decreasing the radiation exposure.

Finally, in the last chapter, we have presented some preliminary data, which show that calculations of the total gastric wall tension is not licit, but that changes in the regional wall tension can be assessed during combined gastric barostat and SPECT studies.

Conclusions

This work has tried to provide better insight in some pathophysiological factors involved in functional dyspepsia. We have identified several experimental evidences supporting the hypothesis that activation of transducers of wall tension at the level the proximal stomach might be the key to the genesis of at least some of the symptoms. One of the mechanisms by which this activation may be enhanced in patients is the presence of defective accommodation of the proximal stomach in response to a meal. This abnormality was present in a large subgroup of patients and was associated to the presence of early satiety. Pharmacological modulation

of the gastric wall tension resulted in concomitant changes in symptom severity, both in health and in functional dyspepsia patients.

Special attention has been given to provide the clinician with better tools to investigate his patient, in the perspective of the prescription of a treatment aimed at restoring a defective mechanism.

Perspectives

The data presented in this thesis, of course represents only a tiny part of the puzzle of functional gastrointestinal diseases.

First, although we describe new insights in the pathophysiology of functional dyspepsia, the search for the aetiology of this syndrome still deserves attention. The recent finding that, similarly to irritable bowel syndrome, a subgroup of patients with functional dyspepsia develops their syndrome as a consequence of a severe gastrointestinal infection opens many new perspectives in the search for etiological factors. Large epidemiological studies, evaluating symptoms prior to and after gastrointestinal infections and identifying specific germs should be carried out. Histopathological and neurophysiological changes affecting the submucosal, and myenteric plexuses as well as the lamina propria should be looked for in these patients, although it is clear that access to human material will remain problematic. Once clearly identified, animal models of post-infectious functional dyspepsia can be created. In view of the tremendous heterogeneity of the syndrome, it appears that different aetiologies should be looked for and maybe correlated to specific pathophysiological mechanisms.

More specifically in the prolongation of this work, some questions remain unanswered. What are the respective role of antrum and proximal stomach in the genesis of symptoms? If increases of gastric wall tension induce symptoms, is this true for the whole stomach? Is the symptom related to the maximal gastric wall tension at one point or to the average wall tension of the whole stomach? Future studies should also explore if our findings can be

extended to other areas of the gastro-intestinal tract such as the oesophagus or the colon.

On the other end of the medical research field, this work opens new perspectives to the therapeutic approach of the syndrome. Not only restoration of defective gastric accommodation, but also visceral hypersensitivity will be a target in the near future. The choice between a therapeutic approach based on a symptom pattern or on the identified pathophysiological mechanisms, will need clarification once reasonably effective diagnostic and therapeutic tools will be available.

RÉSUMÉ ET CONCLUSIONS

De 20 à 30 % des patients se présentant en consultation de gastro-entérologie souffrent de dyspepsie fonctionnelle. Il apparaît de plus en plus clairement que ce syndrome est extrêmement hétérogène. La recherche dans ce domaine s'est récemment focalisée sur la caractérisation des profils symptomatiques chez ces patients et les corrélations de ces profils avec des mécanismes physiopathologiques. La présente thèse a visé à caractériser un de ces mécanismes dans ce syndrome, à étudier comment un dysfonctionnement mécanique peut générer des symptômes et à développer de nouvelles modalités pour quantifier les symptômes et explorer la physiologie de la motricité gastrique.

D'abord, nous avons étudié en détail un groupe de patients souffrant de dyspepsie fonctionnelle en utilisant un barostat gastrique et nous l'avons comparé à des volontaires sains. Cette étude a mis en évidence que le défaut d'accommodation gastrique est une constatation fréquente chez les patients souffrant de dyspepsie fonctionnelle et que cette dysfonction est associée à la présence de satiété précoce dans le tableau symptomatique, ce qui secondairement peut engendrer une perte de poids. Cette donnée est importante car il n'y a à ce jour de traitement satisfaisant pour cette affection. Les traitements standards comportent principalement l'utilisation de prokinétiques, d'anti-sécrétoires ou de médicaments visant à relever les seuils de sensibilité. La présence d'un défaut d'accommodation gastrique après ingestion d'un repas ouvre de nouvelles perspectives thérapeutiques. On pense en particulier à des médicaments visant à restaurer ce défaut, tels les agonistes des récepteurs 5HT₁. Nous avons obtenu des données préliminaires soutenant cette approche.

Ensuite, nous avons voulu étudier comment un défaut d'accommodation gastrique au repas peut générer des symptômes chez ces patients. Des études préalables avaient déjà montré que la sensibilité à la distension gastrique est déterminée par le tonus gastrique, mais il n'apparaissait pas

clairement si c'est plutôt l'étirement de la paroi gastrique ou l'accroissement de la tension pariétale ou encore une combinaison des deux facteurs qui est responsable des symptômes pendant une distension gastrique. Dans une première série d'expériences nous avons mis en évidence un accroissement de la sensibilité à la distension gastrique après renforcement du tonus gastrique. Ensuite nous avons élaboré un protocole permettant d'évaluer séparément les modifications d'étirement ou de tension. Dans cette étude nous avons clairement pu démontrer que des modifications de la tension pariétale gastrique, sans modification concomitante de l'étirement pouvaient être perçues au niveau de l'épigastre. Cette constatation peut expliquer comment des symptômes peuvent être générés en cas de défaut d'accommodation gastrique: le défaut d'accommodation perturbe la fonction de réservoir de l'estomac proximal après la prise d'un repas, causant un accroissement de la tension pariétale elle-même responsable de l'apparition des symptômes. Ces constatations sont en faveur d'un rôle pour des médicaments visant à relâcher l'estomac proximal dans le traitement de la dyspepsie fonctionnelle.

Etant donné que dans la première partie du travail il est apparu que le défaut d'accommodation gastrique après un repas joue un rôle important dans la physiopathologie de la dyspepsie fonctionnelle, nous nous sommes concentrés sur le développement d'outils non invasifs de mesure de l'accommodation gastrique et de quantification des symptômes. Nous avons développé et validé un test de satiété, conçu pour quantifier la satiété au cours d'un test de remplissage de lent de l'estomac par un repas liquide. Nous avons obtenu une belle corrélation entre les scores de satiété et le nombre de calories ingérées. Les manipulations pharmacologiques du tonus de l'estomac proximal au cours de ce test ont modifié les scores de satiété compatibles avec notre modèle qui postule une association entre la satiété et la tension pariétale de l'estomac proximal. Chez les patients souffrant d'un défaut d'accommodation gastrique, qui se caractérisent par une capacité d'ingestion moindre au cours de ce test, la correction du défaut d'accommodation a restauré le résultat du test. Des études plus

approfondies ont montré que c'est principalement le volume ingéré plutôt que le nombre de calories qui détermine la satiété. Enfin un contrôle par scintigraphie a confirmé chez les volontaires sains que la satiété corrélait le mieux avec le degré de remplissage de l'estomac proximal. Cette observation est toujours compatible avec notre hypothèse de départ.

A la recherche de marqueurs alternatifs non-invasifs pour la mesure de l'accommodation gastrique, nous avons étudié si la distribution intragastrique d'un repas isotopique au cours d'un test de vidange gastrique conventionnel était influencée par l'accommodation gastrique. Pour cela nous avons développé un nouvel outil d'analyse des scintigraphies de vidange gastrique pour les solides et les liquides. Après description approfondie de la distribution intragastrique chez le volontaire nous avons étudié les patients et avons comparé leur profil symptomatique à la distribution intragastrique du repas marqué. Nous avons trouvé des associations entre symptômes spécifiques et type de distribution, qui s'insère parfaitement dans notre modèle de dyspepsie fonctionnelle.

Récemment, la technique du SPECT gastrique a été proposée comme outil de mesure non invasive de l'accommodation gastrique. Toutefois cette technique connaît des limites en terme de résolution spatiale et temporelle et en termes d'exposition aux radiations ionisantes. C'est pour cela que nous avons développé un nouveau protocole améliorant le rapport signal bruit tout en réduisant l'exposition aux radiations.

Enfin, dans le dernier chapitre, nous présentons des données préliminaires qui démontrent que le calcul de la tension pariétale gastrique totale n'est pas licite, mais que des variations de la tension pariétale régionale peuvent être identifiées en combinant l'utilisation de SPECT et barostat.

En conclusion, ce travail a tenté d'améliorer la compréhension de certains mécanismes physiopathologiques de la dyspepsie fonctionnelle. Nous avons identifié plusieurs arguments expérimentaux soutenant l'hypothèse disant que c'est l'activation de mécanorécepteurs sensibles à la tension pariétale qui est responsable d'au moins un des symptômes de l'affection. Un des mécanismes par lesquels cette activation peut accrue chez les patients est

la présence d'un défaut de l'accommodation gastrique post-prandiale. Cette anomalie a été retrouvée dans une large proportion des patients et est associée à la présence de satiété précoce. Les modifications du tonus gastrique ont résulté dans de modifications concomitantes des symptômes aussi bien chez les volontaires que chez les patients atteints de dyspepsie fonctionnelle.

Une attention particulière a été portée sur le développement de nouveaux outils permettant de caractériser les patients dans la perspective de la prescription d'un traitement visant à corriger un mécanisme défectueux.

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