Lifestyle aspects in functional dyspepsia

Influence of relaxation and meals on vagal activity, gastric accommodation and symptoms

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List of publications

I. Hjelland IE, Hausken T, Svebak S, Olafsson S, Berstad A. Vagal tone and meal-induced abdominal symptoms in healthy subjects. Digestion 2002;65:172-176

II. Hjelland IE, Ofstad AP, Narvestad JK, Berstad A, Hausken T. Drink tests in functional dyspepsia: Which drink is best? Scand J Gastroenterol 2004;39:933-937

III. Hjelland IE, Oveland NP, Leversen K, Berstad A, Hausken T. Insulin-induced hypoglycemia stimulates gastric vagal activity and motor function without increasing cardiac vagal activity. Digestion 2005;72:43-48

IV. Hjelland IE, Svebak S, Berstad A, Flatabø G, Hausken T. Breathing exercises with vagal biofeedback may benefit patients with functional dyspepsia. Scand J Gastroenterol 2007;42:In Press

Introduction

Purpose of the introduction

The purpose of the introduction is to inform the reader about

- the background for this thesis

- functional dyspepsia; prevalence, pathologic findings and existing theories of pathophysiology

- the vagal nerve; mainlines of its role in normal gastrointestinal physiology and different methods to measure vagal activity

- methods for studying gastric function

- lifestyle and stress; definitions, lifestyle diseases and protecting factors

Background

The diagnosis functional dyspepsia is considered a heterogeneous disorder (1). There is no specific pathologic finding that is characteristic for all patients with this diagnosis, and there is no effective treatment available. Functional dyspepsia is often related to stress (2) and low vagal tone (3-5), and stress is implicated in several lifestyle diseases (6), giving the hypothesis that functional dyspepsia itself is a lifestyle disorder and that changes in lifestyle will improve the condition.

Functional dyspepsia

Definition of functional dyspepsia

Dyspepsia is derived from Greek and literally means "bad digestion" (dys=bad, peptein=digestion). Functional dyspepsia is by the Rome II declaration defined as: At least 12 weeks, which need not be consecutive, in the preceding 12 months of: 1. Persistent or recurrent upper, central, abdominal pain or discomfort. 2. No evidence of organic disease (including upper endoscopy) that is likely to explain the symptoms. 3. No evidence that

dyspepsia is exclusively relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome) (7).

Based on symptoms, functional dyspepsia has been sub-classified into ulcer-like (symptoms suggesting peptic ulcer), dysmotility-like (symptoms suggesting gastric stasis), reflux-like (retrosternal symptoms) and idiopathic (not fitting into any of the other groups). However, many patients belong to several of the subgroups, and the sub-classification has not proven useful with regard to therapeutic or prognostic implications (8, 9). Therefore, the patients were not sub-classified in this work.

Infection with *Helicobacter pylori* is not taken into consideration in this thesis, as it seems to have no impact on symptoms or gastric sensory-motor functions in patients with functional dyspepsia (10).

Prevalence, incidence and prognosis

Approximately 14-38% of the adult population in Western countries is affected by dyspepsia (11-13). Incidence of dyspepsia is approximately 11-20% (11, 12), however, about 13-18% have spontaneous resolution during a year (11, 12), leaving prevalence stable over time (11-13).

Patients with dyspepsia account for some 30% of consultations to specialist gastroenterologists (13-15). The prevalence of functional dyspepsia among patients with symptoms arising from the upper gastrointestinal tract is reported to range from 19-76% (14). Functional dyspepsia affects quality of life negatively (16). Hence, functional dyspepsia represents a substantial source of morbidity, as well as considerable financial burden on the healthcare system.

Pathophysiology

Patients with functional dyspepsia often experience epigastric pain or discomfort, early satiety, fullness and nausea in relation to meals. Epigastric discomfort may be perceived when

the tension in the stomach wall is increased as a consequence of inadequate relaxation (17-19). The fact that the symptoms often begin during the first 2-3 min of a meal (20), before maximal meal-induced relaxation has taken place (normally 5-12 min after a meal (21)), suggests that stretch-receptors in the muscularis propria of the gastric wall are activated (22).

Many of the patients with functional dyspepsia have indications of gastric motor or sensory dysfunctions, such as hypersensitivity to distension (23-25), impairment of accommodation to meals (23, 26, 27) or delayed emptying (15). Low vagal tone is found more often than normal in these patients (3-5). Vagotomy leads to impairment of fundic relaxation (28). Thus, the impairment of accommodation to meals in patients with functional dyspepsia might be due to low vagal tone.

The low vagal activity found in patients with functional dyspepsia might be a consequence of stress, because vagal tone decreases after acute mental stress in both patients with functional dyspepsia and healthy controls (4, 29), and patients with functional dyspepsia have more chronic stress than controls (30). Low vagal tone also has been suggested as a mediating mechanism by which psychological factors like neuroticism and anxiety induce dyspepsia in these patients (3, 4, 17). In patients with functional dyspepsia there is a significant negative correlation between neuroticism and low vagal tone (3). The patients have as a group more anxiety, depression, neuroticism, somatisation and experience more negative life events and chronic stress than controls (3, 30).

Thus, it seems like there might be a vicious cycle in functional dyspepsia (17), where psychological factors like anxiety, stress and neuroticism induces vagal suppression, which gives impaired gastric accommodation, inducing visceral hypersensitivity, which might produce central sensitisation maintaining physiological and psychological factors. Breaking this circle at any of the points might resolve the whole problem. In this project, the focus is on

the vagal nerve, as it, in this conceptual framework, is the connecting link between gut and brain.

The vagal nerve is a bidirectional connection between the brain and the immune system. In the intestine, mast cells and macrophages may be activated by stress and release histamine and inflammatory cytokines, which trigger sensory fibres of the vagal nerve lying close by (31, 32). The nerve conveys ascending signals to nucleus tractus solitarius in the brain stem (32). The brain processes the information and activates efferent vagal fibres. This vago-vagal reflex may influence the control of the peripheral immune system, by the so-called anti-inflammatory pathway. It has been shown that effector neurons originating in the dorsal motor nucleus of the vagal nerve can inhibit the production of pro-inflammatory cytokines of tissue macrophages through a mechanism dependent on the α7 nicotinic acetylcholine receptor (33, 34). Theoretically, an underlying defect in the activity of the cholinergic anti-inflammatory pathway, i.e. vagal nerve, might then trigger an over-production of cytokines from macrophages and other pro-inflammatory cytokine producing cells in response to an otherwise harmless immunological stimulation.

Pain stimuli caused by stress is first transmitted upward through the brainstem to the perifornical area of the hypothalamus and from here into the paraventricular nucleus of the hypothalamus and eventually to the median eminence, where corticotrophin releasing factor (CRF) is secreted to the primary capillary plexus of the hypophysial portal system and then carried to the anterior pituitary gland, where it induces ACTH secretion. ACTH activates adrenocortical cells to produce cortisol. Mental stress also can cause ACTH secretion. This is believed to occur through the limbic system, especially in the region of the amygdala and hippocampus, both of these transmitting signals to the posterior medial hypothalamus. All these responses happen within a few minutes. (35)

Inhibition of gastric emptying and stimulation of colonic motor function are the commonly encouraged patterns induced by various stressors. CRF receptor 1 and 2 is found in human colon tissue (36), and CRF receptor 2 is found in human stomach (37), suggesting that activation of the CRF receptor 1 in the colon is stimulating its propulsive activity, while activation of the CRF receptor 2 in the stomach leads to inhibition of the gastric emptying rate (38). CRF is acting centrally as well, as it decreases gastric vagal outflow (39). Thus CRF delays gastric emptying via both central and peripheral mechanisms. Patients with functional dyspepsia have increased stress level, and possibly increased CRF secretion, and the central mechanism of CRF might explain their low vagal tone.

Thus, the pathogenesis of functional dyspepsia might be based on stress, leading to CRF induced low vagal tone, preventing the body to control inflammation in the gut released by triggering events like stress, inflammation or trauma. This might result in visceral hypersensitivity, and the patient may enter the vicious circle of functional dyspepsia.

The vagal nerve

Vagal nerve and gastrointestinal physiology

The motility of the gut and digestive secretory activity are regulated by the enteric nervous system in the gut wall, which constitutes a semiautonomous neural network control system. The enteric nervous system is composed mainly of two complexes; the Auerbach's plexus (or myenteric plexus) located between the circular and the longitudinal muscle layers, and the Meissner's plexus (or submucosal plexus) located in the submucosa. Auerbach's plexus mainly controls motility, and the Meissner's plexus mainly controls gastrointestinal secretion and local blood flow. The plexuses are innervated with postganglionic sympathetic nerve fibres from the splancnic nerves and with preganglionic parasympathetic nerve fibres from the vagal nerve. The sympathetic neurotransmitter is epinephrine, and the parasympathetic neurotransmitter is acetylcholine.

Sensory neurons transmit information from the gut to the enteric nervous system and to the central nervous system through the vagal nerve and sympathetic nerve fibres. Feedback responses to the gut go through efferent fibres from the central nervous system to the gut in the vagal nerve, and through sympathetic fibres from the prevertebral sympathetic ganglia back to the gastrointestinal tract. There are also feedback responses within the enteric nervous system itself. (40)

Vagal activity is of great importance for the regulation of the tone in the gastric wall. During fasting, gastric tone is maintained by cholinergic stimulation (40, 41). In response to a meal, the gastric musculature relaxes and the tone is reduced. This relaxation of the proximal stomach is controlled by nitrergic inhibition (nitric oxide as neurotransmitter) of cholinergic vagal efferent pathways (42, 43), also called a non-adrenergic, non-cholinergic vago-vagal reflex (44). The relaxation of the body and fundus enables the stomach to maintain a low balanced pressure and to continuously adapt its volume to its content (45).

Measurements of vagal activity
In man, only indirect methods for measuring vagal activity exist. Commonly used methods for measurement of gastric vagal activity are increase of gastric acid secretion (46) or pancreatic polypeptide level (47) in response to insulin-induced hypoglycaemia. Commonly used methods for measurement of cardiac vagal activity are various measures of heart rate variability (29, 48, 49).

Gastric vagal activity
Gastric acid is secreted by parietal cells which are located in the corpus and fundus areas of the stomach. The physiologic stimulation of acid secretion has been divided into three phases; cephalic, gastric and intestinal. The cephalic phase is activated by the thought, smell, taste and swallowing and is mediated through cholinergic/vagal mechanisms. The gastric phase is the responses to gastric distension and chemical effects of food, stimulating the gastrin cells/G-cells in the antral mucosa to release gastrin, which is transported via the blood to stimulate

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histamine release from the enterochromaffin-like (ECL) cells (50, 51) located in the corpus and fundus areas of the stomach in direct proximity to the parietal cells. ECL cell histamine is probably the major physiological mediator of acid secretion (52). The observation that H2 (histamine) receptor antagonists block the cephalic and gastric phases underscores the importance of histamine mediation of the stimulatory response (53), and illustrates the interdependence of the different phases. The intestinal phase accounts for only a small proportion of the acid secretory response to a meal, and its mediators remain controversial.

Pancreatic polypeptide is secreted from the duodenal part of the pancreas (54) in response to vagal cholinergic stimulation (47, 55). The response is abolished by vagotomy and atropine (47). Released pancreatic polypeptide enters systemic circulation and travels to the dorsal vagal complex in the brainstem, where it suppresses efferent vagal signals by negative feedback as digestion of the meal progresses (56).

Cardiac vagal activity
In animals, the non-invasive methods of cardiac vagal activity have shown nearly 100% linearity with invasive measures of efferent cardiac vagal activity (48).

For measuring heart rate variability, Sayers (57) performed spectral analysis and detected three peaks which were denoted very low-frequency (<0.05 Hz), low-frequency (0.05-0.15 Hz) and high-frequency (0.15-0.5 Hz). The very low frequency was considered to relate to body temperature. The low-frequency, also called the Mayer Wave-related sinus arrhythmia, is related to the regulation of blood pressure and reflects the combined activity of the sympathetic and parasympathetic nervous system (58, 59). The high frequency domain of heart rate variability, also called respiratory sinus arrhythmia, is caused by respiration and reflects the activity of the parasympathetic nervous system. In addition to using spectral analysis, respiratory sinus arrhythmia can also be measured as "peak-to-valley" differences. Studies by Grossman et al. (60) and Hayano et al. (61) have shown that the tests provide much the same information, and the results therefore can be considered almost interchangeable.

Spectral analysis is based on data-logged electrocardiographic (ECG) signals. From the ECG, the series of R-R intervals is calculated as a function of the beat number. In other words, the R-R interval measured in seconds is on the y-axis and the beat number on the x-axis. Then the frequency distribution of the R-R intervals is calculated, and from this the spectral analysis is composed (62).

The peak-to-valley (or peak-to-trough) method assesses, on a breath-by-breath basis, the difference between the shortest R-R interval/highest pulse corresponding to inspiration and the longest R-R interval/lowest pulse corresponding to expiration (29).

Different methods for measuring gastric accommodation

Gastric accommodation is a process by which the stomach adapts to a meal without increase in pressure by relaxing the proximal part of the stomach through non-adrenergic non-cholinergic vago-vagal reflexes. The reflexes are provoked by chemoreceptors in the duodenum and mechanoreceptors and tension receptors in the stomach.

The "gold standard" for studying gastric accommodation to a meal has been the barostat method (27). Thanks to its close contact with the gastric wall, the barostat bag adjusts to changes in proximal gastric pressure by changing the intrabag volume. Thus, changes in volume are believed to reflect changes in muscle tone of the wall. However, introducing the barostat balloon into the gastric lumen may influence the gastric motility patterns (21, 63-65), and the examination is invasive and unpleasant. Neither the barostat nor scintigraphy allows estimation of the size of the proximal stomach. On the contrary, ultrasound and single photon emission computer tomography (SPECT) scanning can detect changes in gastric volume in a non-invasive manner. Like ultrasound, SPECT scanning is a non-invasive alternative to the barostat in evaluating gastric relaxation. However, in comparison with meal induced volume increase, SPECT scanning failed to detect the profound gastric relaxation following glucagon infusion (66). These findings suggest that SPECT scanning is less suitable than the gastric

barostat in detecting gastric relaxation and rather detects the volume of the intragastric contents after meal intake. Imaging methods visualise directly the size of the gastric compartments, thus giving an indirect measure of relaxation and contraction. The volume change seen using imaging can thus be explained by additional secretion, air retention in addition to changes in gastric emptying.

An important question is whether measures obtained by imaging methods, such as SPECT or ultrasonography, can actually be compared to the measurements made by the barostat. The gastric meal accommodation process has two components: Passive meal distension of the gastric compartments and active muscle relaxation of the gastric wall. The first component is best measured with imaging methods whereas the barostat is best suited for studying the second component. Imaging methods at this stage do not distinguish between enlargement of the stomach due to reflex relaxation and that due to meal-induced distension; it just measures the totally accommodated volume. Accordingly, it may not be adequate to compare imaging methods and the barostat method for validation of gastric accommodation. Gastric accommodation depends on neuromuscular factors and hence also concerns the mechanical properties of the stomach. In this sense the barostat merely detects the existence of change in wall tone, but cannot, like imaging methods, provide data on the distribution of the volume and the normal behaviour of the gastric wall. It seems essential to carefully choose the most suitable method for the issue (distension or muscular relaxation) being studied.

Stress and lifestyle

In medicine, stress refers to a set of bodily reactions to physical, psychic, infectious and other natural aggressors capable of disturbing homeostasis. It is generally believed that biological organisms require a certain amount of stress in order to maintain their well-being. However, when stress occurs in quantities that the system cannot handle, it produces pathological changes (Taber's cyclopedic medical dictionary). Hans Selye, a pioneer in the study of stress

who recognised the mind-body connection and started studying stress biologically in 1936, named these pathological changes the General Adaptation Syndrome (GAS) or stress syndrome, and divided the GAS into three phases:

1) The alert or alarm reaction phase – the initial response to an aggressive agent.

2) The resistant phase – the body's attempt to adapt to the presence of the aggressor, producing organic changes.

3) The exhaustion or decompensation phase – the body fails to eliminate an aggressive agent (67).

Stress is a part of a modern lifestyle. Lifestyle is our relation to food, exercise, drugs, our attitudes and our self-created environments, and it is responsible for about 50% of death causes (68). Using 8 keys for health, (NEW START: Nutrition, Exercise, Water, Sunshine, Temperance, Air, Rest, Trust in God) Seventh-day Adventists live longer than the general population. In the Adventist Health study, studying mortality of 34 192 California Adventists from 1976 to 1988, men lived approximately 7.3 years longer than the average white California man, and women Adventists lived 4.4 years longer (69). No history of smoking, avoidance of overweight, regular physical activity, nut consumption and a vegetarian diet were each associated independently with longer median life expectancy (69). Vegetarian Adventists have lower risk for developing colon cancer, diabetes, coronary artery disease, hypertension, overweight and arthritis (70).

Using a questionnaire developed at our institute (71), we found that patients with FD had about similar lifestyle as healthy controls (unpublished data). In this work, we only studied the lifestyle factors related to general relaxation and meal ingestion.

Aims of the project

The overall aim of the project was to study whether simple changes of lifestyle (velocity of ingestion, breathing pattern, body position) can change vagal activity, accommodation of the stomach to a meal and meal-related discomfort.

The specific aims of the four papers included in this thesis were:

I. To study factors that influence vagal tone and whether vagal tone is related to abdominal symptoms in response to meal ingestion in healthy subjects.

II. To compare the diagnostic ability of various test meals in our drink test paradigm in functional dyspepsia.

III. a) To see if enhancement of vagal activity by insulin-induced hypoglycaemia in healthy subjects would influence gastric emptying and intragastric volumes as measured by three-dimensional ultrasonography.

b) To see if peak-to-trough method of heart rate variability, i.e. respiratory sinus arrhythmia, measured during hypoglycaemia would follow the increase in pancreatic polypeptide in healthy subjects.

IV. To investigate whether enhancement of vagal tone by breathing exercises and vagal biofeedback would beneficially influence drinking capacity, intragastic volumes, gastric emptying, dyspepsia-related quality of life and baseline autonomic activity in patients with functional dyspepsia.

Materials and methods

An overview of study designs, interventions, subjects, test meals and measurements are given in table I. More details are outlined here and in the papers.

Ethics

The studies were approved by the Regional Committee for Medical Research Ethics, and were conducted in accordance with the revised Declaration of Helsinki. All participants gave a written, informed consent to participate in all the trials.

Subjects

In paper I, 40 healthy subjects, 20 men and 20 women, were recruited among university students in the city of Bergen in Norway. The median age was 23 years (range 19 to 38 years). In paper II, 10 healthy subjects (male/female 4/6, median age 29.5, range 19-37 years, mean BMI 21.2±1.7 kg/m^2) and 10 patients with functional dyspepsia (male/female 3/7, median age 31, range 18-40 years, mean BMI 23.3±2.8 kg/m^2) were included. In paper III, 20 healthy volunteers (male/female 10/10, median age 24, range 22-27 years, mean BMI 23.2±2.5 kg/m^2) were recruited among medical students in Bergen, Norway. In paper IV, 40 patients with functional dyspepsia were included (male/female 8/32, mean age 35.3±12.4 years, BMI 23.1±3.6 kg/m^2).

All patients fulfilled the Rome II criteria and were recruited from the out-patient clinic at Haukeland University Hospital in the city of Bergen in Norway. Healthy subjects were eligible if they defined themselves as healthy, were 18 years of age or older, were non-pregnant and did not abuse alcohol or drugs.

Methods

Table 1. Overview of study designs, interventions, subjects, test meals and measurements

	Paper I	Paper II	Paper III	Paper IV
Design	Prospective, ABA-design, non-blinded	Prospective, case-control, randomised, non-blinded	Prospective, randomised, non-blinded	Prospective, randomised, non-blinded, biofeedback group and control group
Intervention	Two different drinking speeds	Three different test meals	Insulin in saline and saline infusions	Breathing exercises and biofeedback
Healthy Volunteers	N=40	N=10	N=20	
FD Patients		N=10		N=40
Drink tests	500 ml Toro® clear meat soup	Nutridrink®, Toro® clear meat soup and water	Toro® clear meat soup	Toro® clear meat soup
Ingestion rate	1 and 4 min	100 ml/min	100 ml/min	100 ml/min
RSA	X		X	X
SC			X	X
Tree-dimensional Ultrasound		X	X	X
PP			X	
Questionnaires	Symptoms (VAS) nausea, discomfort, fullness, epigastric pain	Symptoms (VAS) nausea, fullness, epigastric pain	Symptoms (VAS) nausea, fullness, epigastric pain	SF-NDI, EPQ-N, TDS, SHQ-6, Music questionnaire

Abbreviations: ABA= test meal in 1 min, then 4 min and again in 1 min; FD = functional dyspepsia; RSA = respiratory sinus arrhythmia; SC = skin conductance; PP = pancreatic polypeptide; VAS = visual analogue scales; SF-NDI = short form Nepean dyspepsia index; EPQ-N = neuroticism subscale of the Eysenck personality questionnaire; TDS = telic dominance scale; SHQ-6 = sense of humour questionnaire

Respiratory Sinus Arrhythmia (RSA)

RSA was measured in paper I, III and IV. Cardiac vagal nerve function was evaluated non-

invasively by a computerised polygraph (Synectics® software and polygraph, Medinor®

Oslo, Norway) recording the RSA in beats/min. The R-R interval in the ECG was registered

by the computer and transformed into beats per minute. Three Ag/AgCl electrodes were attached to the thorax, two of them 2-3 cm under the right and left clavicular bones, and the third at the left 5th intercostal space in the midclavicular line. The computer recorded respiratory movements simultaneously using a pressure-sensible sensor attached to the thorax. Recordings were stored in digital format on a computer hard disk for off-line scoring. This method calculates the average of peak-to-valley changes of heart rate within 6 successive respiratory cycles (29, 49).

In paper I, time periods 15 min before the test meal and 2 min after the meal were chosen for assessment of RSA. In paper III and IV, RSA was assessed for 5 minutes immediately before and after the test meal, and RSA was calculated from the last 2 minutes of each assessed period.

Pancreatic Polypeptide (PP)

PP was measured in paper III. Blood samples were collected from a vein in the right elbow in 10 of the subjects before start of infusion of saline, before infusion of saline with insulin, after 30 minutes of saline infusion, and during the glucose clamp procedure. Because of the glycaemic threshold and lag time to response of PP, the samples were collected 15 minutes after reaching the 2.3 mmol/l level (72). The samples were immediately put on ice, and after blood clotting, the samples were centrifuged at $+4^{o}C$. Blood serum was then separated and kept in a freezer at $-80^{o}C$ until analysis. The blood samples were analysed when all samples from all the 10 subjects were collected. The samples were analysed by radioimmunoassay (Euro-Diagnostica AB SE-205 12 Malmø, Sweden). The coefficient of variation for the analysis was CV%=3.1% (n=8) and CV%=5.0% (n=7). The commercial controls run in the analysis were 19.2 pmol/l (expected value 17.1±3.4) and 94.8 pmol/l (expected value 94.0±15).

Skin Conductance (SC)

In paper III and IV, SC was evaluated non-invasively by a computerised polygraph (Synectics® software and polygraph, Medinor® Oslo, Norway). SC, expressed in microsiemens (μS), is recording ability to lead electricity on the skin by use of the constant current method, and is a measure of sweat secretion on the skin, stimulated by the sympathetic part of the autonomic nervous system. Two Ag/AgCl electrodes were attached on the palmar side of the third and fourth interphalang on the non-dominant hand. Recordings were stored in digital format on a computer hard disk for off-line scoring. SC was assessed concomitantly with RSA. Because of technical problems, SC was assessed only in nine subjects in paper III.

Ultrasonography

All ultrasound imaging was performed while the subjects were sitting slightly backwards in a wooden chair. The applied triplex scanner (System Five Ving Med A/S, Horten, Norway, with a 3.5 MHz curved array probe) allowed visualisation of real-time ultrasound images.

Three-dimensional (3D) ultrasound imaging was performed using previously validated methods (73). In the volume range 100 to 700 ml, the 3D system showed excellent agreement between estimated and true intragastric volumes with low inter-observer variation (73). The 3D ultrasound system consisted of the ultrasound scanner (System Five, VingMed Sound A/S, Horten, Norway) with a built-in position and orientation measurement (POM) system (Flock of Birds Model 6D FOB, Ascension Technology Corp. Burlington, Vermont, USA). The POM system is based on a transmitter which produces a spatially varying magnetic field, and a small receiver containing three orthogonal coils to sense the magnetic field strength (74). Detailed description of the POM system and the calibration procedure is previously reported (75).

The 3D ultrasound acquisition was performed after the test meal, and the subjects were instructed to hold their breath and to avoid moving their body. The scanning time normally was about 6-7 seconds. The stomach was scanned along its long axis by a continuous

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translation movement, and scanning started proximally at the left subcostal margin and moved distally to the gastroduodenal junction. In this manner, transversal sections of the entire stomach were recorded. For each scan approximately 100-130 ultrasound images were stored.

Gastric emptying was defined as fraction of the test meal emptied from the stomach during the meal ((drinking capacity minus intragastric volume) x 100% / drinking capacity).

Intragastric distribution of the meal was assessed by the ratio of proximal to distal volume (75).

Test meals

In paper I, the test meal was 500 ml commercially available meat soup ingested in 1 or 4 minutes (Toro® clear meat soup, Rieber & Søn A/S, Bergen, Norway). It contained 1.8 g of protein, 0.9 g of fat, 1.1 g carbohydrate and non-soluble seasoning (0.2 g) per 500 ml. The pH of the soup varied between 5.4 and 5.7, and the osmolarity was 350 mOsm/kgH$_2$O. The soup was first boiled and then cooled to 37°C.

In paper II, the test meals were Nutridrink®, Toro® clear meat soup and water ingested at a rate of 100 ml/minute until maximal drinking capacity. Nutridrink® (Nutricia Norway as, Oslo, Norway), a high-caloric meal (150 kcal/100 ml) tasting vanilla, containing 5 g protein, 18 g carbohydrate and 6.5 g fat per 100 ml, was ingested room-tempered. The water was tapped from the tap, and ingested lukewarm. Toro® clear meat soup was prepared as in paper I.

In paper III and IV the test meal was Toro® clear meat soup ingested at a rate of 100 ml/minute until maximal capacity. The test meal was prepared as in paper I.

Biofeedback

"Freeze-Framer" is computer software that visualizes and evaluates changes in heart rate variability in real time. The Freeze-Framer was developed by the Institute of HeartMath under the direction of Doc Childre in Boulder Creek, California. The Freeze-Framer monitors the

beat-by-beat changes in heart rate with its electronic sensor, which reads the pulse from the finger. It plots the speeding and slowing of the heart rate, and analyses the heart rhythm pattern. In general, a smoother heart rhythm pattern indicates a balanced nervous system whereas an irregular, jagged pattern indicates a less balanced nervous system. The Freeze-Framer records the degree of smoothness or jaggedness of the heart rhythm and, based on a mathematical algorithm, assigns a score. It is possible to increase the smoothness of the heart rhythm pattern. This is mainly done through teaching the subjects how to relax, using breathing techniques.

The probe was put on the subject's second finger, on the non-dominant hand. When the breathing exercises were correctly performed, a warm-air-balloon started flying. With deterioration of performance, the balloon lost height, and it even landed on the ground if performance did not improve. The evaluation of performance, or entrainment ratio, was summarized in a red (low entrainment ratio), blue (medium entrainment ratio) and green column (high entrainment ratio) with a percentage scale. The training criterion was that the patients had, in sum, at least 70% high and medium entrainment ratio. Those who did not reach training criterion had to practice breathing technique using the Freeze Framer once a week until training criterion was reached, or the treatment period was completed.

Questionnaires

In paper I, a questionnaire with visual analogue scale (VAS) for nausea, discomfort, fullness and epigastric pain was applied before and after the test meal. Scoring was made on a 10 cm unmarked line where a mark at 0 cm expressed "no symptom" and a mark at 10 cm expressed "excruciating symptoms". The total score was the sum of scores for these four symptoms.

In paper II and III, nausea, fullness and epigastric pain were assessed at maximal drinking capacity, using VAS as in paper I, but measured in mm. Sum of scores for nausea, fullness and pain at maximal drinking capacity was denoted "pooled symptom score". The

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rate by which a symptom was induced was calculated as symptom score at maximal drinking capacity divided by ingestion time.

In paper IV, Norwegian versions of the "Short Form Nepean Dyspepsia Index" (SF-NDI) (76), "Sense of Humor Questionnaire" (SHQ-6) (77), "Telic Dominance Scale" (78) and the Neuroticism subscale of the "Eysenck Personality Questionnaire" (EPQ-N) (79) were filled in before investigations at visit 1. At visit 2, SF-NDI was filled in once more. In addition, the patients in the biofeedback group filled in a questionnaire to assess liking of the music.

SF-NDI is a disease specific measure of quality of life, with ten questions divided into five subscale scores (tension, interference with daily activities, eating/drinking, knowledge/control, work/study) and one total score. Each question has five options giving 1-5 points (1=not at all, 5=extremely). The lowest possible score is 10, and the maximal possible score is 50. Arslan et al. found that the score in the general Norwegian population (n=70) was 13.5±6.8 (80).

SHQ-6 is measuring the patients' sense of humour, ability to discover humoristic hints and situations, and attitude to humorous others. There are 6 questions, and each question has four answer alternatives giving scores 1-4, when summarised gives the total SHQ-6 score. The lowest possible score is 6, and the maximal possible score is 24, with a normal value of 15.5 in urban areas (rural areas 18.8).

"Telic Dominance Scale" is analysing serious-mindedness, planning orientation and arousal avoidance through 42 questions, with 14 questions for each subscale. Mean, or normal value of serious-mindedness is 6.4±1.9, planning orientation is 5.6±2.1, and arousal avoidance is 6.4±2.3.

EPQ-N is scoring neuroticism through 12 Yes/No questions. Answering "Yes" to any of the questions gives 1 point, and the possible range of score is 0-12. Normal values are varying with sex and age from 4.14 to 6.7.

The questionnaire to assess liking of the music in the biofeedback group was filled in at the first and last day of the treatment, using a ten-step scoring format (1= I strongly dislike the music, and 10=I liked the music very much).

Summary of results

Paper I
Vagal tone and meal-induced abdominal symptoms in healthy subjects
Scores for nausea and discomfort were higher when the soup was ingested in 1 min as compared with 4 min (nausea: $P = 0.02$; discomfort: $P = 0.04$). There was no difference in fullness or abdominal pain. RSA was unrelated to meal-induced symptom scores. RSA varied with respiration and body position: It was highest while breathing deeply in the sitting position (24.0 beats/min). With normal breathing RSA was highest in the supine position (9.0 beats/min), lower while sitting (7.0 beats/min) and lowest while standing (6.2 beats/min).

Paper II
Drink tests in functional dyspepsia: Which drink is best?
Drinking capacity ($P < 0.05$) and intragastric volume ($P < 0.01$) were significantly lower in the patients than in the controls with the meat soup meal, but not with Nutridrink® or water. Gastric emptying distinguished significantly ($P < 0.05$) between patients and controls only with Nutridrink®. Gastric emptying of Nutridrink® was significantly correlated to the rate by which nausea was induced ($P = 0.02$), while gastric emptying of meat soup was significantly negatively correlated to the rate by which fullness was induced ($P < 0.05$). ROC analysis indicated that optimal discrimination between patients and controls was obtained by the combined test result of symptoms per intragastric volume using meat soup as test meal.

Paper III
Insulin-induced hypoglycemia stimulates gastric vagal activity and motor function
without increasing cardiac vagal activity
Insulin-induced hypoglycemia increased drinking capacity ($P =0.002$), gastric emptying ($P =0.02$), pancreatic polypeptide ($P =0.004$) and SC ($P =0.004$), while intragastric volume was unchanged ($P =0.7$) and RSA decreased ($P =0.03$).

Paper IV
Breathing exercises with vagal biofeedback: beneficial for patients with functional dyspepsia?
Drinking capacity and quality of life improved significantly more in the biofeedback group than in the control group ($P =0.02$ and $P =0.01$) without any significant change in baseline autonomic activity (RSA and SC) or intragastric volume. After the treatment period, RSA during breathing exercises was significantly correlated to drinking capacity (r=0.6, $P=0.008$).

General discussion

Important findings in this project were that rapid ingestion of a meal evoked symptoms in healthy subjects, and that vagal activity depended on body positions. Vagal activity was highest in the supine position, intermediate in the sitting position and lowest during standing. In healthy subjects, breathing exercises with slow and deep breathing greatly improved vagal activity. The meat soup meal was the best test meal to discriminate between patients with functional dyspepsia and healthy controls. In healthy subjects, drinking capacity increased significantly during invasive vagal stimulation. Likewise, in patients with functional dyspepsia, vagal stimulation using vagal biofeedback with deep breathing improved drinking capacity. There was a strong relationship between vagal tone during deep breathing and drinking capacity after four weeks of daily breathing exercise.

Lifestyle factors like general relaxation and speed of meal ingestion seem to impact dyspeptic symptoms, quality of life, vagal activity and gastric function. Because vagal activity might be a mediating mechanism, people suffering from stomach complaints ought to practice deep and calm breathing during the day – if possible in the supine position, as vagal activity is highest in this body position, consistent with the fact that parasympathetic activity dominates at rest and is lower during labour. In addition, deep breathing may be easier when lying down. In this way the vagal nerve increases its activity or ability to fluctuate, for better control of stomach function. Then symptoms decline and quality of life increases.

Dyspeptic patients in general and vagal reflexes in these patients in particular are very sensitive to psychological stress. Because functional disorders are so strongly associated to psychological factors, we chose to measure gastric function with minimal stress. Ultrasonography is a non-invasive procedure that in itself does not distort the physiological response in stress-responsive individuals. The examination is also normally performed in a quiet and relaxing atmosphere with a minimum of distress. The "stress-factor" is thus minimal

with ultrasound, and we chose ultrasonography for studying gastric accommodation in this work.

A non-invasive drink-test for assessment of visceral sensitivity and gastric accommodation is a much more convenient diagnostic tool than the invasive and unpleasant procedure of the barostat. In patients with functional dyspepsia, early satiety during meals is related to impaired gastric accommodation (27). Impaired drinking capacity in patients with functional dyspepsia (81-83) may thus be an expression of impaired gastric accommodation. However, this is controversial, as Boeckxstaens et al. did not find any relationship between drinking capacity and fundic accommodation or visceral hypersensitivity as measured by barostat (81), whereas Tack et al. did (84). Boeckxstaens et al. used an ingestion rate of 100 ml/min (81) while Tack et al. used 15 ml/min (84). The gastric accommodation reflex is elicited both by distension of the stomach and by nutrients in the duodenum, and the reflex takes some time (21). Thus, some of the explanation of the disagreeing results might be the use of different ingestion rates. Another variant of the drink test is the water load test where the subjects drank tap water *ad libitum* over a five-minute period until reaching fullness (83). There is no standard way of performing a drink test, and the ideal drinking rate is not known.

Healthy subjects get very little symptoms when drinking the 500 ml meat soup meal in 4 minutes, but drinking the test meal in 1 minute evokes more symptoms (85). In healthy subjects, the maximal meal-related gastric relaxation is induced after 5-12 minutes (21). From this perspective, it can be assumed that the stomach of healthy individuals adapts so well to a meal that they experience few meal-related abdominal symptoms when drinking 500 ml test meal in 4 minutes. However, during rapid meal ingestion, the adaptive capability was stretched towards its limit, producing symptoms even in healthy subjects. Rapid distension may more intensely activate stretch receptors in the muscularis propria of the gastric wall,

thereby explaining the higher symptom scores found with rapid than with slow soup ingestion.

Patients with functional dyspepsia get dyspeptic symptoms when drinking 500ml Toro® clear meat soup in 4 minutes (4), and symptoms precede the maximal adaptive relaxation response (20, 21). This suggests that 4 minutes is close to a threshold in these patients. Most of the patients with functional dyspepsia would probably not be able to drink 500 ml meat soup during 1 minute. For further refinement of the drink test, we figured that approaching the limits of drinking capacity would make the test more robust in discriminating between patients with functional dyspepsia and healthy subjects. Hence, we chose a drinking rate of 100 ml/min.

The test meals used by others have been water or high-caloric drinks (81, 83, 84). A slow high-caloric drink test induces proximal gastric relaxation, while a rapid low-caloric test using the meat soup meal, which is a weak stimulus of nutrient induced accommodation, is mainly a test of distension induced accommodation and sensitivity to gastric distension, and not of nutrient induced gastric accommodation. (21, 82, 84).

We have used a low-caloric meal, Toro® clear meat soup, and combined the test with ultrasonography to study gastric volumes and emptying in addition to the meal-related symptoms {Hjelland, 2004 83 /id;Hjelland, 2005 85 /id;Hjelland, 2007 117 /id}. The meat soup meal is eminent for ultrasound investigation. Nutridrink® and water are much more difficult to see using ultrasonography. In paper II we compared the test meals Nutridrink®, water and Toro® clear meat soup. ROC (receiver operating characteristic) analysis indicated that drinking capacity, intragastric volume and pooled symptom score after drinking meat soup, and gastric emptying of Nutridrink®, discriminated significantly between patients and healthy persons. Drink tests with water had poor discriminatory power regardless the variable analysed. Pooled symptom score divided by intragastric volume at maximal drinking capacity

turned out to be the variable best distinguishing patients from controls. This former measure was not used in paper III and IV, as data collection of these studies started before data analysis of paper II was completed.

We found that the perception of nausea was related to the rate of gastric emptying of Nutridrink® so that the more Nutridrink® that emptied into the duodenum, the more nausea (82). Gastric emptying is inhibited by long chain fatty acids acting on duodenal chemoreceptors (88). Teleologically, the slow gastric emptying of Nutridrink® could be a consequence of enteric reflexes aiming to avoid nausea. With meat soup the perception of fullness was significantly negatively correlated to gastric emptying, i.e., the less meat soup emptied into the duodenum, the more fullness. The results suggest that fullness is related to distension of the stomach, as also indicated in earlier studies using the gastric barostat (89). Water was well tolerated by both patients and controls, but its fast emptying from the stomach made intragastric volume assessment difficult, contributing to the poor discriminatory power of the test. It thus appears as if the ideal test meal should be something between water and Nutridrink®. In fact, our meat soup meal fits this requirement very well. In spite of its low caloric density (40 kcal/L), it induces fed state motility and empties from the stomach at a rate slow enough to allow accurate ultrasonographic assessment of intragastric volumes.

A surprising finding is that intragastric volume did not increase during vagal stimulation, neither in healthy subjects during hypoglycaemia, nor during vagal stimulation using breathing exercises and vagal biofeedback in patients with FD. Intragastric volume of FD patients drinking Nutridrink®, water and meat soup also was remarkably similar. In healthy subjects intragastric volume of water and meat soup was about the same, but intragastric volume was lower when drinking Nutridrink, possibly due to the high caloric load activating chemoreceptors giving nausea. Thus, it seems as if there is a constant individual intragastric volume that triggers activation of stretch- and mechanoreceptors of the stomach

that via the vagal nerve induce symptoms, encouraging the subject to stop intake of more food or liquid.

The relation between vagal activity and gastric/intestinal motility is complex. There are indications of a relationship between poor vagal activity and abnormal gastric motility (3, 4). There is a positive correlation between vagal activity and proximal gastric size, and a negative correlation between vagal activity and antral area (90). Correlation between vagal tone and electrogastrogram dominant power, i.e. the myoelectric activity of the intestines, has also been found (91). Our findings are consistent with prior studies, as drinking capacity and quality of life improved in those receiving vagal stimulation {Hjelland, 2005 85 /id;Hjelland, 2007 117 /id} and there was a strong relationship between drinking capacity and vagal tone during breathing exercises when correct breathing technique was learnt {Hjelland, 2007 117 /id}.

It has been suggested that central activation of efferent vagal activity has a parallel influence on the heart and the stomach (92). Stimulation of the afferent cardiac vagal nerve can induce reflex gastric relaxation and vomiting in the cat, resistant to both atropine and guanethidine but not vagotomy (93). RSA increases considerably with deep, calm breathing (85), and may also be increased by biofeedback techniques using respiratory techniques to influence RSA amplitudes (94). Jokerst et al. found that increasing the parasympathetic nervous system activity as measured by RSA by slow diaphragmatic breathing prevented development of gastric dysrythmias and decreased symptoms of motion sickness (95). During hypoglycaemia, we found that RSA was positively correlated to drinking capacity and negatively correlated to nausea while pancreatic polypeptide was not correlated to any of these measures (86). This suggests that RSA, and not pancreatic polypeptide, is related to perceptions of stomach function. Interestingly, Uijtdehaage et al. found that high levels of

cardiac vagal tone were associated with low motion sickness scores (96). The results suggest that RSA, as an index of cardiac vagal tone, is related to abdominal vagal tone.

We found, on the contrary, no correlation between our measures of cardiac (RSA) and gastric (pancreatic polypeptide) vagal activity in response to hypoglycaemia (86). The result is consistent with prior studies where no correlation was found between RSA and acid output in response to insulin-induced hypoglycaemia (97, 98). In prior studies, vagal tone as indexed by RSA, decreased after acute mental stress in both patients with functional dyspepsia and healthy controls (4, 29). Reduced heart rate variability during vagal stimulation by hypoglycaemia could therefore, in part, be due to stress-induced sympathetic activation (5).

Similarly, increased skin conductance (a measure of sympathetic activation) both during glucose clamp hypoglycaemia and during saline infusion, suggests that the procedure was perceived stressful, even in the absence of hypoglycaemia (86). Reduced RSA and increased pancreatic polypeptide during hypoglycaemia might be consequences of stress-induced sympathetic activation inhibiting the cardiac but not the gastric vagal drive. Also, both hypoglycaemia and insulin may itself release adrenaline and stimulate sympathetic activity (99). The net result (the balance between sympathetic and parasympathetic activation) might thus seriously depend on the experimental conditions. Schächinger et al. (100) used less insulin, a higher glucose level and a longer baseline (and possibly less stress) then we did. Contrary to us, they found increased heart rate variability during hypoglycaemia (100). The divergent results might be due to different sympathetic activation by the different experimental conditions in our study and in the study of Schächinger et al..

In patients with functional dyspepsia vagal activity, as measured both by RSA and pancreatic polypeptide in response to hypoglycaemia, is assumed to be low (4, 101). As low vagal tone might be a key factor for motility disturbances and symptom development in these patients, we figured that stimulation of vagal activity might improve symptoms by improving

gastric motility. In healthy subjects, vagal stimulation using hypoglycaemia improved gastric motility (86). It was, however, a very stressful procedure, not suitable for treatment of patients with functional dyspepsia. Stimulation of vagal activity using vagal biofeedback and breathing exercises in patients with functional dyspepsia improved quality of life and increased drinking capacity {Hjelland, 2007 117 /id}. RSA during breathing exercises was positively correlated to drinking capacity solely after the treatment period, not before, suggesting that learning correct breathing technique is important. However, although vagal tone improved during breathing exercises, "baseline" vagal tone as measured by RSA remained unchanged, suggesting no persistent effect on cholinergic control of cardiac rhythmic activity. The mechanism by which biofeedback treatment exerted its beneficial effects is therefore not clear.

Lack of maintenance of improvement in vagal tone might be due to too short-lasting biofeedback treatments (five minutes a day). Short treatment periods were chosen to improve compliance. A prior study, using 1 hour sessions once a week with daily home exercises (thermal feedback with breathing exercises + relaxation program) during 8 weeks, has shown longer lasting clinical improvement (102). Leahy et al. reported some benefit of treating patients with irritable bowel syndrome using 30 min sessions with mental relaxation once a week for four weeks, with daily home exercises (103). Denis claimed that the duration of feedback sessions cannot be standardised because of the variability of the subjects' ability of learning, their motivation, the pathology and the investigators' practice (104).

However, it may be that even increasing duration of treatment does not give persistent increased vagal activity. In a small, open study in patients with congestive heart failure, Freeze-Framer was used in eight 75 min sessions during 10 weeks with improvements in emotional coping and functional capacity, but without any persistent increase in heart rate variability (105). We cannot exclude that the increased drinking capacity and quality of life of

our patients treated with vagal biofeedback and breathing exercises {Hjelland, 2007 117 /id} might be due to other mechanism than increased cardiac vagal activity.

The quality of life scores improved significantly in the biofeedback group compared with the control group {Hjelland, 2007 117 /id}. Sub-analysis revealed that it was only for eating/drinking subscale the improvement was significant. Being included in a study improved scores for the subscale knowledge/control, independent of group identity. When adding vagal biofeedback, eating capacity as well as the ability to enjoy eating and drinking were improved.

Quality of life is influenced by psychological factors such as anxiety and depression, which are common in functional dyspepsia and might be part of its pathophysiology (106, 107). Experimentally induced anxiety inhibits gastric accommodation and increases symptoms after a test-meal (108). Respiratory control evokes feelings of peacefulness and rest, i.e., the opposite to anxiety (94, 109). Hence, the beneficial influence of our feedback therapy on quality of life in patients with functional dyspepsia could be due to anxiety relief and not necessarily effects of improved vagal tone.

Patients with functional dyspepsia do not constitute a uniform group of patients. In paper IV, most patients did not have very low vagal tone {Hjelland, 2007 117 /id} as compared to other studies using identical method for measuring vagal tone (3-5). In future projects using vagal biofeedback and breathing exercises, it might be advantageous to select patients with low vagal tone, as they possibly would benefit more from the treatment. Learning correct breathing technique seems important, because, after four weeks of practice, there was a strong relationship between vagal tone during breathing exercises and drinking capacity.

Vagal activity is reduced during stress, giving physiological consequences similar to vagotomy; reduced antral motility and impaired gastric accommodation (3, 4). Pancreatic

polypeptide is reduced in patients with functional dyspepsia and in patients with diabetic autonomic neuropathy (92, 101). After vagotomy, there is very low pancreatic polypeptide secretion in response to meals (92). Vagotomy and diabetic autonomic neuropathy are irreversible conditions, while attenuated vagal activity due to stress may be reversible. Some patients with functional dyspepsia might have come to the third phase of stress reaction, the phase of exhaustion (67), making improvements hard to take place. The treatment of vagal biofeedback with breathing exercises thus might be most effective early in the progression of the functional dyspepsia disorder.

Summary and Conclusions

Paper I suggests that breathing exercises for increasing vagal activity would benefit patients with functional dyspepsia. In paper II a drink test was developed to discriminate between healthy subjects and patients with functional dyspepsia, and the drinking capacity was an effect variable that could be used for evaluating the influence of vagal stimulation on gastric function. In paper III, invasive vagal stimulation was tested in healthy subjects, using the drink test developed in paper II. Paper IV was the realisation of the idea that improving the low vagal tone found in patients with functional dyspepsia using breathing exercises and vagal biofeedback would increase their low drinking capacity. The non-invasive drink test, using a meat soup meal with an ingestion rate of 100 ml/min until maximal satiety, seems promising for characterisation of functional dyspepsia and for evaluation of treatment. However, for use in clinical practice, further validation of the test is warranted.

Is functional dyspepsia a lifestyle disorder? Lifestyle is more than general relaxation and the rate by which a meal is ingested as investigated in this work. Thus a complete answer to this question cannot be given. However, stress is important in many lifestyle diseases, and stress might be one of the factors that induce functional dyspepsia. The link between stress, vagal activity and stomach function is not new (4). The new in this work is that treatment, aiming to lower tension and stress, using simple breathing exercises without any adverse events, does improve stomach function and quality of life in these patients. Hence, functional dyspepsia might be considered as a lifestyle disorder.

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