The role of gastric accommodation in the pathophysiology of functional dyspepsia

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Abstract. – Background and Objectives: The pathophysiology of functional dyspepsia is not yet completely known. Several mechanisms have been suggested as having a role in symptom onset and impaired gastric accommodation to meal is one of the most frequent. This review will focus on the pathophysiological and clinical aspects of this abnormality.

Evidence and Information Sources: Medical peer-reviewed literature was considered to elucidate the role of gastric accommodation in the pathophysiology of functional dyspepsia.

State of the Art: Impaired gastric accommodation to meal is present in around 40% of patients with functional dyspepsia and it was shown to be associated with the presence of early satiety. Unfortunately, a definitive treatment of this abnormality with fundus-relaxing drugs is not yet available.

Perspectives: Further studies are needed to better clarify the role of each single pathophysiological mechanism on clinical manifestations of functional dyspepsia. Research is still ongoing to offer a valid therapeutic approach.

Key Words: Functional dyspepsia, Gastric emptying, Gastric accommodation, Barostat.

The pathophysiology of functional dyspepsia is not yet completely known and several mechanisms have recently been described as major topics for the onset of typical dyspeptic symptoms in subgroups of patients: dyspeptic patients may show a delayed gastric emptying, gastric hypersensitivity to mechanical distention of the stomach, or chemical stimulation of the duodenum, the presence of dysfunctions of central nervous system, abnormal small intestinal motility. The role of Helicobacter Pylori infection in the onset of dyspeptic symptom is still under debate, as evidence is available both in favour and against. A subgroup of dyspeptic patients also showed a defective accommodation to a meal of the stomach and this review will focus on the pathophysiological and clinical aspects of this abnormality.

Physiology of Gastric Accommodation

Gastric accommodation is represented by the reduction of gastric tone accompanied by an increased compliance induced by the ingestion of a caloric meal. From a functional point of view, the proximal stomach acts as a reservoir, having to accommodate the ingested meal and the accommodation reflex makes it possible to carry out this function, providing an appropriate gastric volume without an increased intragastric pressure. The first description of a modification of gastric volume, in response to its distention, was provided by Cannon and Lieb in 1911, the so-called “receptive relaxation”. Later, it was shown that an “adaptive relaxation” also occurs after food intake. The accommodation response is mediated via a vago-vagal reflex pathway which activates intrinsic non-adrenergic non-cholinergic neurons in the gastric wall. During fasting, both in animals and humans, gastric fundus tone is maintained by a vagally mediated cholinergic input and in animals a role for a continuous nitrergic input was also shown. In humans, fasting gastric tone is modifiable with nitric oxide donor as gastric relaxation was obtained, but negative data are also available. Several lines of evidence suggest a role for both NO and vasoactive intestinal polypeptide, VIP, as inhibitory neurotransmitters mediating gastric relaxation. In vivo studies both in animals and in humans gastric accommodation is significantly inhibited by NO-synthase inhibitors.
Evaluation of Gastric Accommodation

Our knowledge on gastric accommodation has been considerably improved during the last two decades with the adoption, first in experimental settings, then in clinical studies, of several techniques able to evaluate tonic and phasic activity of the stomach better than conventional manometric procedures. Among these, the adoption of gastric barostat has perhaps provided most of the data, first in dogs, then in humans. The barostat is an electronic device consisting of a computer-driven programmable volume-displacement device connected to a double lumen polyvinyl tube with an adherent, infinitely compliant plastic bag. The barostat maintains a constant preselected pressure within the bag, changing the bag volume of air, by an electronic feed-back mechanism. After the bag has been positioned in the viscus (stomach, duodenum, colon, rectum), the barostat monitors motor activity (contraction or relaxation) as changes in bag volume (reduction or increase, respectively) at a constant intrabag pressure. This is the only method that allows the simultaneous recording of pressure and volume, but the procedure is invasive, uncomfortable and difficult to use with solid foods. Nevertheless, up to now, the barostat test has provided the best results.

Ultrasound imaging is a non-invasive technique but its assessment of gastric accommodation is indirect, based on measurements of antral diameter, weakened by air presence which limits the view of the fundus.

Single Photon Emission Computed Tomography (SPECT) allows an assessment of the whole volume of the stomach and it was recently proposed as non-invasive measurement of gastric accommodation. Unfortunately, it uses radioactive isotope (99m Tc-pertechnetate) and, like ultrasonography, does not differentiate gastric content.

Magnetic Resonance Imaging seems the most promising technique for evaluating gastric motility. It is non-invasive, does not use radioactive isotopes, evaluates the anatomy of the organ, the motility of the fundus and antrum and gastric emptying; it also allows differentiation of gastric content into solid and liquid phases and air.

Gastric Accommodation and Symptoms

An abnormal gastric accommodation to food ingestion in patients with functional dyspepsia has been shown in several papers. In particular, impaired relaxation of the proximal stomach after the ingestion of a caloric meal was shown to be present in 40% of subjects of a group of consecutive functional dyspepsia patients. Moreover, this pathophysiological mechanism proved to be strictly associated with early satiety. Incomplete relaxation of the proximal stomach may induce an activation of mechanoreceptors in the gastric wall which, in turn, induces symptoms. It has been proposed that the gastric wall contains two types of mechanoreceptors. In animals, serosal mechanoreceptors arranged in parallel with muscular fibres respond to stimuli that elongate the stomach wall and mechanoreceptors arranged in series respond to stimuli that increase or decrease the tension of the stomach wall. Gastric distension in humans increases both elongation and wall tension of the stomach. Therefore, distension studies do not allow distinction between these mechanoreceptors for induction of perception. An alternative protocol for assessing the role of elongation versus tension in gastric sensation is the evaluation of an agent that contracts the stomach, activating this agent during volume clamping by fixed volume inflation of an intragastric balloon. When the proximal stomach contracts isometrically against the fixed volume, the stomach maintains its volume and the elongation of the stomach wall increases, resulting in increased perception.

Figure 1. Modification of gastric volume after meal administration evaluated by barostat. Panel A shows a normal gastric accommodation to meal. Panel B shows gastric accommodation to meal in a patient with functional dyspepsia and early satiety.
volume balloon, elongation is unchanged while changes in intraballoon pressure directly reflect changes in wall tension. Using this technique, spontaneous phasic changes in wall tension of the proximal stomach can indeed be perceived and increasing the intensity and frequency of the stimulus with erythromycin leads to a significant increase in the proportion of perceived contractions.

To better elucidate the patophysiological link between impaired gastric accommodation and symptoms, the demonstration of an improvement of early satiety after the normalization of gastric accommodation defect is needed. This topic was the target of a recent paper which, through the administration of a 5-HT1 receptor agonist, sumatriptan, obtained both an increased gastric relaxation after meal ingestion and an increased amount of calories ingested at maximum satiety. These results suggest that by improving accommodation, sumatriptan is able to improve the severity of satiety.

**Treatment Strategy for Impaired Gastric Accommodation**

However, the long-term use of sumatriptan in the management of functional dyspepsia is unacceptable due to costs and side effects but a promising alternative drug seems to be another serotoninergic agent, also acting as a 5-HT1A agonist, buspirone. Available preliminary data confirm this hypothesis. A double-blind, placebo-controlled, cross-over trial on buspirone in patients with functional dyspepsia showed a significant effect on symptom severity and an improvement of gastric accommodation to meal. However, no other paper has been published on this topic up to now, so these results are not yet confirmed and no application in clinical practice is available.

Several other serotoninergic agents were shown to improve relaxation of proximal stomach. A 7-day pre-treatment period with paroxetine enhances gastric accommodation to a meal. These data suggest that paroxetine may also be beneficial to patients with impaired post-prandial fundus relaxation. However, as in the case of buspirone, no results are yet available on long-term efficacy of paroxetine. Cisapride enhances both the perception of gastric distension and gastric accommodation to a meal. Oral administration of cisapride was also shown to improve gastric accommodation and it is therefore possible to hypothesise a benefit to patients with impaired postprandial relaxation of the fundus. However, its withdrawal from the market in several countries and, recently, even a halt in its production make these results of little importance.

Nitricergic and α-adrenergic agents also have a role in the modulation of gastric activity. It was, in fact, shown that during fasting, clonidine relaxes the stomach, reduces gastric sensation and does not inhibit accommodation or emptying, while nitroglycerin relaxes the stomach without altering perception. Nitric oxide-induced smooth muscle relaxation involves activation of soluble guanylate cyclase, with cGMP production, which is then degraded by phosphodiesterase-5 (PDE-5). Accordingly, sildenafil, a selective PDE-5 inhibitor, significantly increases postprandial gastric volume and slows liquid emptying rate, confirming that meal-induced accommodation in humans involves the activation of a nitricergic pathway. The effect of sildenafil on gastric fundus therefore suggests a therapeutic potential for phosphodiesterase inhibitors in patients with impaired gastric accommodation. These results clearly suggest another putative therapeutic strategy, as sildenafil as such is unacceptable for long-term treatment; further studies are therefore needed to better clarify the putative role of these agents in the therapy of gastric dysfunctions and dyspeptic symptoms.

Several reasons make therapy a difficult task, but first of all the complexity of the pathophysiologic aspects of the individual patient is the main one: in fact, pathophysiology is often characterized by the presence of several mechanisms which interact and overlap with each other. In addition, the clinical history of dyspeptic patients is frequently characterized by the modification of clinical manifestations, the main symptom of which often changes over time, thus making additional diagnostic definitions and consequent therapeutic modifications necessary.

Second, another major problem is represented by the uncertainty about the site of origin of dyspeptic symptoms, which is still unknown. If we are not sure whether a fundus-directed therapy or an antrum-directed therapy is needed, the choice of incorrect treat-
ment is possible. A recent paper\(^4\) reporting the results of a double-balloon barostat test, consisting of the evaluation of sensorimotor response in both the antrum and fundus, showed that the distal stomach is less compliant than the proximal stomach to low level distension. Thresholds for both first perception and discomfort, and symptom profiles evoked by distensions do not differ between distal and proximal stomach and simultaneously applied low level distension of one gastric segment did not affect the mechanosensitivity of the other segment. Meal-induced relaxation is a phenomenon present in both the proximal and distal stomach and simultaneous low level antral distension decreases proximal gastric accommodation to a meal. Therefore, in comparison with the proximal stomach, the distal stomach is less compliant but its mechanosensitivity is not different, symptoms induced by gastric distension are not region-specific and meal induced relaxation occurs both in the proximal and distal stomach. These results represent an important basis for future investigations aimed at a better understanding of the pathophysiology of dyspeptic symptoms.

A more widespread use of the diagnostic methods will certainly allow a better definition of the problems connected with the relationships between impaired gastric accommodation and dyspeptic symptoms. An alternative method to the barostat, exploiting the principles of the breath tests\(^4\), has in fact recently been proposed: in the presence of impaired gastric accommodation, monitoring the excretion of \(^{13}\)CO\(_2\) after the sequential administration of two meals, both containing \(^{13}\)C-acetate, with a similar caloric content but a markedly higher volume of the second (800 ml) with respect to the first meal (200 ml), reveals lower emptying times of the second meal compared to the first. The non-relaxation of the gastric fundus is thus responsible for the reduction in emptying time of the more diluted meal. This test has the indisputable advantage of being non-invasive, not using radioactive isotopes and, therefore, of being repeatable without exposing the patient to particular risks. However, validation of this procedure in comparison to scintigraphy or barostat is not yet available.

In conclusion, the improvements in diagnostic and pathophysiologic terms are not yet matched by corresponding improvements in therapeutic terms and further studies are necessary to define both the true importance of the individual proposed mechanisms in the pathophysiology of dyspeptic symptoms and the best pharmacological approach to individual patients.

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