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Review

Non-invasive method for the assessment of gastric acid secretion

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Summary. Methods for the measure of gastric acid secretion include invasive and non-invasive tests. The gold-standard to measure the acid output is the collection of gastric after in basal condition (Basal Acid Output, B.A.O.) and after an i.m. injection of pentagastrin (Maximal Acid Output, M.A.O.). However, direct measurement of gastric acid production is out of order in clinical practice, but many GI symptoms are claimed to be related with acid disorders and empirically cured. Hypochlorhydria is associated with precancerous conditions such as chronic atrophic gastritis (CAG). Acid measurement with non-invasive methods (pepsinogens) is supported by international guidelines. (www.actabiomedica.it)

Key words: acid measurement, atrophy, acid secretion, pepsinogens, aspiration test, maximal acid output

Introduction

Gastric acid secretion has a complex pathophysiological role in humans (1) being an important protective mechanism against ingested pathogens and being related to different diseases.

The measurement of acid secretion proves useful in the diagnostic workup and treatment of these conditions: increased gastric acidity is characteristic of duodenal ulcer (DU) and patients with Zollinger-Ellison syndrome; in contrast, low or even absent acid secretion is found in patients with pernicious anemia and atrophic gastritis (AG), which is the most important know risk condition for gastric cancer, and is characterized by a decrease of acid-producing parietal cells and the PG-secreting chief cells. Last but not least, AG is *per se* clinically silent but low acid secretion is also linked with non-neoplastic and "extra-gastric" diseases, even more important than the cancer burden from viewpoints of the public health, and frequent especially in the elder population; these "extra-gastric" conditions are for example risks of malabsorption of vitamin B12 and other micronutrients and the predisposition to enteric infections (e.g. E. coli, Clostridium difficile), being the stomach a natural defense against orale microbes (2-16). The overgrowth of bacteria and fungi in acid-free stomach results also in production of class I carcinogens (e.g. acetaldehyde and nitrosamines) that increase the likelihood of cancer promoting mutations in gastric epithelial cells (17, 18).

The importance of gastric acid in the 21st century, characterized by an evident decrease of peptic ulcer, is especially related to the possibility to detect precancerous conditions that result in a hypochlorhydric or acid-free stomach (19,20) and to the increasing use of proton-pump-inhibitors (PPIs). It could be useful an acid secretion examination prior the PPI medication, to ensure that the patient does not have atrophic gas-

tritis and hypochlorhydric or even achlorhydric stomach (21,22), and to detect people with a higher secretion, who could benefit from antisecretory therapy (23,24). Identification of hyperchlorhydria may have other significant clinical implications, even apart from extreme cases such as the Zollinger-Ellison syndrome. For example, some studies reported that individuals with hyperchlorhydria are at high risk of low-dose aspirin-induced gastropathy (25).

Furthermore, in daily clinical practice, a lot of symptoms, mainly aspecific, are claimed to be caused by an acid disorder and then empirically cured. This is the reason why the measurement of acid secretion remains highly relevant to practicing clinicians.

Methods of measuring gastric acid secretion

Aspiration tests

Methods for the measure of gastric acid secretion include invasive and non-invasive tests.

The gold standard for measuring gastric acid secretion remains the invasive method that is aspiration test (26), involving placing a tube (endoscopic or nasogastric tube) in the most lower part of the stomach. The right position of the tube is usually determined radiologically or with recovery test, which is performed administering 100 mL of water aspirated through the gastric tube.

After that, the basal acid output (B.A.O.) is measured using a pump with continuous suction at a subatmospheric pressure of 30 to 50 mmHg or manually by a syringe in 15 minutes periods. Pentagastrin, histamine or tetragastrin are used as stimulation to collect maximal acid output (M.A.O.), which is aspirated for four 15-minute intervals for a total of one hour. After collecting the samples, the volume and titratable acid are measured using alkaline solution and chemical indicators and the amount of acid in each specimen is calculated (27-31).

Gastric acid aspiration test may cause discomfort to the patient, is invasive and time consuming: for these reasons, it's no longer used in clinical practice, leaving a gap in the diagnostic possibilities: nowadays, considering the high prevalence of acid related diseases, the overuse of PPI (32) and the interest in detecting precancerous conditions such as AG, the absence of a validated tool to measure acid secretion is more evident than ever.

Intragastric pH measurement

A combined pH electrode (usually made of glass or antimony) is positioned transnasally in the gastric corpus and is connected with a recording device. Significant regional variations exist in intragastric pH, also related to post-prandial periods: therefore, it is necessary to check fluoroscopically that the intragastric electrode is maintained in a rather fixed position. This method was developed for esophageal pH studies but gained a popularity for its usefulness in the diagnosis and management of patients with acid-related disorders, in particular for the possibility to evaluate the effect of acid-suppressing drugs. However, this invasive technique gives a measure of intragastric pH and does not offer a quantitative measure of acid secretion.

Non invasive tests

Current interest lies in finding a rapid, reliable and inexpensive non-invasive test (33).

The determination of serum pepsinogen I (sPGI) is regarded as reliable gastric secretory parameter (34-36). sPGI has been reported by a lot of studies and comprehensive and high quality meta-analysis' as predictive of the histological status of the gastric mucosa (37-44), and has been proposed as marker of gastric atrophy and screening tool for gastric cancer, as recommended by international guidelines (45-46). Pepsinogens are aspartic proteinases from which derivate the active enzyme pepsin after exposure to hydrochloric acid, and they are responsible of initial protein digestion functioning between a pH of 1.5 and 5.0. Pepsinogens can be divided in two groups according to biochemical and immunological differences: pepsinogen I (PGA or PGI, pepsinogens 1-5) and pepsinogen II (PGC or PGII, pepsinogens 6,7). PGI is a product of the chief cells and the mucus neck cells in the fundus area (47-48) and reflects the structural and functional status of the stomach. PGI is stable in the individual but show differences based on some individual factors such as age, weight, gender, ethnicity, diet, and circadi-

an rhythm. Since high levels of this enzyme is present in the serum of duodenal ulcers patients (49-51) and it decreases in AG, it can be used in clinical practice as serum biomarker. In fact, the anatomical site of production of PGI underlies a large number of the studies on the relationship between serum pepsinogen levels and gastric acid secretion. PGI-II levels may change during different pathological conditions involving gastric mucosa and this reflects both functional and morphological status of stomach. If PGI/PGII ratio decreases, it might be an indication for precancerous disease such as atrophic gastritis. The plasma levels of fasting gastrin-17 are also able to give indirectly information of gastric acidity.

A diagnostic panel of biomarker tests, GastroPanel (including PGI, PGII, G17 and H. pylori serology) has been proposed to screen subjects at risk for gastric cancer, but also to evaluate patients with chronic stomach complaints. GastroPanel® provides a method to diagnose whether the stomach mucosa is healthy or not and if the atrophic gastritis is H. pylori positive or not (52).

The serologic profile of these atrophy markers in different combinations can be applied to population screening to detect individuals at risk for precancerous lesions to be further evaluated by endoscopy and biopsy (53). The usefulness of GastroPanel® has been demonstrated (54). A meta-analysis of 27 population-based screening studies (comprising 296,553 subjects) and 15 selected groups (with 4385 subjects) (55), indicated that pepsinogen test had a sensitivity of 77% in detecting GC, with negative predictive values ranging from 99.1 and 99.9%. It concludes that this method is useful in identifying high-risk subjects rather than cancer itself. A meta-analysis done in 2017 on 20 studies with a total of 4241 subjects assessed the performance of serum panel test for diagnosis of atrophic gastritis regardless the site in the stomach. It pointed out that sensitivity was 74.7%, specificity was 95.6% and negative predictive value was 91%.

Conclusions

Invasive and non-invasive tests are able to measure gastric acid secretion. Aspiration test is claimed to be the gold standard, but it's not currently used in clinical practice. Several studies recommend the measurement of serum PGI as a screening test for achlorydria (31-40), and as suggested in Kyoto (2014) and Maastricht V (2016) guidelines serological PGI levels are the best indicators of gastric atrophy. It is generally accepted that PGI serum levels reflects acid secretion, based on many studies assessing its correlation with histological findings of AG, which represents a hypochlorhydria of acid-free stomach.

The measure of serum PGI levels in gastric cancer screening and clinical practice is able to identify hypoclorhydria to figure out who of the patients are at high cancer risk and in whom the assessment of severe gastric disorders (such as ulcer disease) through the gastroscopy is mandatory. The possibility to evaluate gastric acid secretion levels by simple measurement a serum markers has significant clinical implications in daily practice.

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