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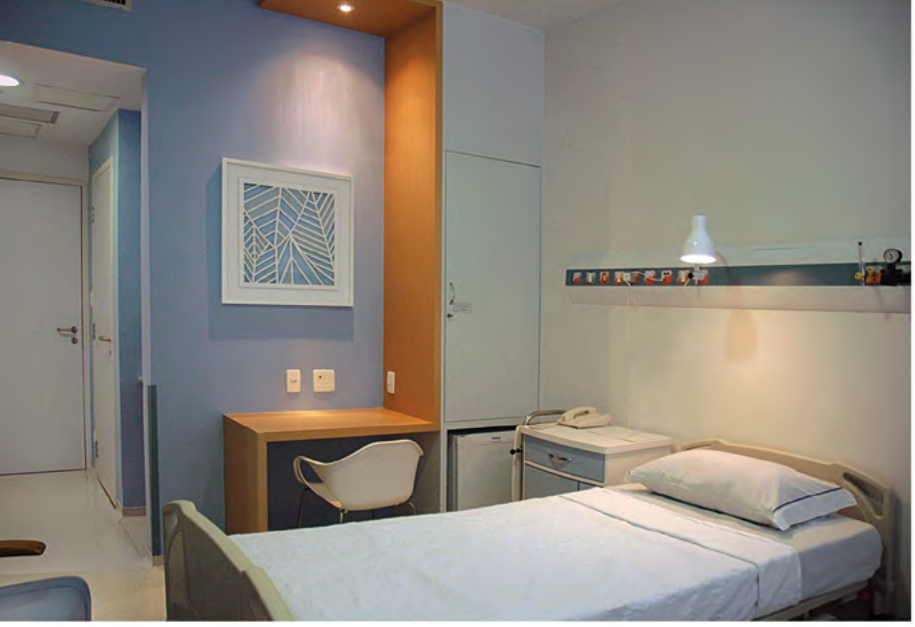

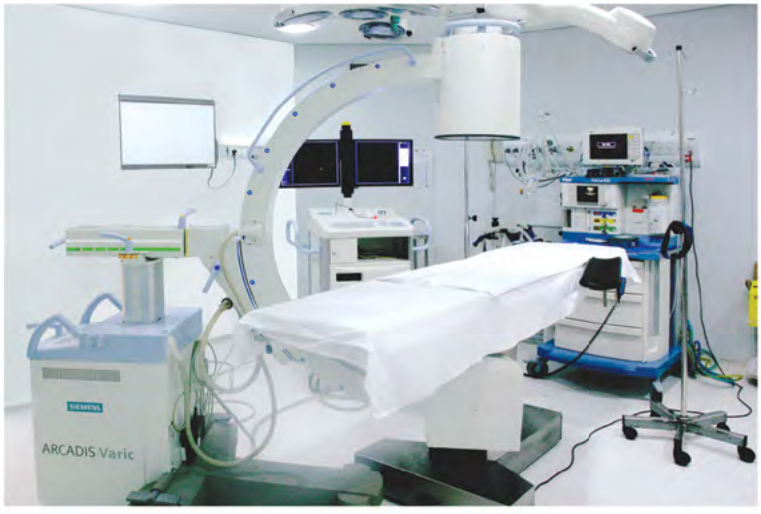

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Too much information. What to do?

Moraes-Filho JPP. Too much information. What to do? Arq Gastroenterol. 2018;55(Suppl 1):1.

It currently draws attention to the enormous amount of information available daily in the general media and on social networks, a phenomenon that has extended even to the medical area. In fact, it is peculiar the increase studies on prevalence, pathophysiology, diagnostic methods, therapeutic approaches and literature reviews that are available at the touch of the internet. Many of them have been carefully carried out following principles of evidence-based medicine and observing the principles of good clinical practice and can be said to be fully trusted.

Unfortunately, however, this is not always the case, because the information may not be reasonably correct and some publications may not be fully trusted. In fact, today's "scientific" journals are available, where there are papers of questionable quality regarding the methods of study, the therapeutic approach and the interpretation of the results. It has always been known that second- or third-line articles are accepted in second or third line medical journals but, the difference today is the availability. With the ease media, such publications are disseminated as if they were credible and actually create a problem: when and who we trust? How to avoid falling into the universe of scientific works/reviews/low quality updates that provide supposed knowledge and can induce bad medical practice?

Answering these questions, in the first place let's remember the more important sites and reliable as Pubmed (National Institute of Health), British Society of Gastroenterology, American Gastroenterology Association, American College of Gastroenterology, The New England Journal of Medicine, The Lancet, among others. Studies and scientific projects of great importance have traditionally been published in known international journals related to the sites above. In addition to the scientific content itself, it should also be considered the critical view about what is being published in terms of **diagnosis** and **therapeutic** which are the doctor's tools in front of the patient.

In addition to the International field, it is worth mentioning that some Brazilian scientific publications are highly representative and trustworthy. This is the case, for example, of the role played by **Archives of Gastroenterology (AG)**. Founded more than five decades ago, it has an interesting history of representation of medical societies related to gastroenterology and of publishing relevant works originating from national and international gastroenterological centers. The publication of good articles in **AG** constitutes an important differential and reflects the careful appreciation of the works that are submitted ("peer review").

This special edition of **AG** is a good demonstration of high quality articles that reflect the best in Latin American gastroenterology: thirteen outstanding, comprehensive and analytical works on the digestive tube. There are current themes that deserve attention from the specialist such as intestinal constipation, swallowing, diagnostic methods of gastroesophageal reflux, proton pump inhibitors, achalasia, anorectal function evaluation. The edition consists of four reviews/updates with critical analysis of the literature[1-4] and nine original works of research/standardization of study methods[5-13]. Particularly draws attention the medical centers involved (*Faculdade de Medicina de São Paulo* – USP; *Faculdade de Medicina de Ribeirão Preto* – USP; *Faculdade de Medicina de Botucatu* – UNESP; *Faculdade de Medicina da Universidade Federal do Ceará* – UFC; *Escola Paulista de Medicina* – UNIFESP; *Hospital Britânico de Buenos Aires* – Argentina; *Instituto de Ciências Biomédicas* – UFRJ; *Escola Bahiana de Medicina e Saúde Pública*; *Centro Médico de Diagnóstico Fleury* – SP; MoDiNe – *Instituto Brasileiro de Estudos e Pesquisas de Gastroenterologia e Outras. Especialidades* – SP). Also highlighted are the authors who, in turn, stand out in their respective areas of expertise in the specialty.

We therefore have varied, current and reliable substrate to wish to the colleagues "Good Reading"!

Joaquim Prado P. de **MORAES-FILHO***

Moraes-Filho JPP. Muita informação. Em quem confiar? Arq Gastroenterol. 2018;55(Supl 1):1.

REFERENCES

1. Maffei HVL, Morais MB. Proposals to approximate the pediatric Rome constipation criteria to everyday practice. Arq Gastroenterol. 2018;55(Suppl 1):56-60.
2. Costa MMB. Neural control of swallowing. Arq Gastroenterol. 2018;55(Suppl 1):61-75.
3. Nasi A, Queiroz NSF, Michelsohn NH. Prolonged gastroesophageal reflux monitoring by impedance-pHmetry: a review of the subject pondered with our experience with 1,200 cases. Arq Gastroenterol. 2018;55(Suppl 1):76-84.
4. Azzam RS. Are the persistent symptoms to proton pump inhibitor therapy due to refractory gastroesophageal reflux disease or to other disorders? Arq Gastroenterol. 2018;55(Suppl 1):85-91.
5. Lasa JS, Altamirano MJ, Bracho LF, Paz S, Zubiaurre I. Efficacy and safety of intestinal secretagogues for chronic constipation: a systematic review and meta-analysis. Arq Gastroenterol. 2018;55(Suppl 1):2-12.
6. Del Grande LM, Herbella FAM, Katayama RC, Schlottmann F, Patti MG. The role of the transdiaphragmatic pressure gradient in the pathophysiology of gastroesophageal reflux disease. Arq Gastroenterol. 2018;55(Suppl 1):13-7.
7. Murad-Regadas SM, Regadas Filho FSP, Holanda EC, Veras LB, Vilarinho AS, Lopes MS. Can three-dimensional anorectal ultrasonography be included as a diagnostic tool for the assessment of anal fistula before and after surgical treatment? Arq Gastroenterol. 2018;55(Suppl 1):18-24.
8. Dantas RO, Cassiani RA, Santos CM, Alves LMT. Water ingestion dynamics in patients with achalasia: influence of sex and age. Arq Gastroenterol. 2018;55(Suppl 1):25-9.
9. Silva RMB, Herbella FAM, Gualberto D. Normative values for a new water-perfused high resolution manometry system. Arq Gastroenterol. 2018;55(Suppl 1):30-4.
10. Abreu GE, Dourado ER, Alves DN, Araujo MQ, Mendonça NSP, Barroso Junior U. Functional constipation and overactive bladder in women: a population-based study. Arq Gastroenterol. 2018;55(Suppl 1):35-40.
11. Viebig RG, Franco JTY, Araujo SV, Gualberto D. Water-perfused high-resolution anorectal manometry (HRAM-WP): the first Brazilian study. Arq Gastroenterol. 2018;55(Suppl 1):41-6.
12. Pinto RA, Corrêa Neto IJF, Nahas SC, Bustamante Lopes LA, Sobrado Junior CW, Cecconello I. Functional and anatomical analysis of the anorectum of female scleroderma patients at a center for pelvic floor disorders. Arq Gastroenterol. 2018;55 (Suppl 1):47-51.
13. Souza TF, Grecco E, Quadros LG, Albuquerque YD, Azôr FO, Galvão Neto M. Short-term results of minimally invasive treatment of gastroesophageal reflux disease by radiofrequency (Stretta): first Brazilian series of cases. Arq Gastroenterol. 2018;55(Suppl 1):52-5.

*Current President of Brazilian Society of Digestive Motility and Neurogastroenterolgy.

ORIGINAL ARTICLE

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Efficacy and safety of intestinal secretagogues for chronic constipation: a systematic review and meta-analysis

Juan Sebastian **LASA**, María Josefina **ALTAMIRANO**, Luis Florez **BRACHO**, Silvina **PAZ** and Ignacio **ZUBIAURRE**

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ABSTRACT – **Background** – Intestinal secretagogues have been tested for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. The class-effect of these type of drugs has not been studied. **Objective** – To determine the efficacy and safety of intestinal secretagogues for the treatment of chronic constipation and constipation-predominant irritable bowel syndrome. **Methods** – A computer-based search of papers from 1966 to September 2017 was performed. Search strategy consisted of the following MESH terms: intestinal secretagogues OR linaclotide OR lubiprostone OR plecanatide OR tenapanor OR chloride channel AND chronic constipation OR irritable bowel syndrome. Data were extracted as intention-to-treat analyses. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as Relative Risk of achieving an improvement in the symptom under consideration. **Results** – Database Search yielded 520 bibliographic citations: 16 trials were included for analysis, which enrolled 7658 patients. Twelve trials assessed the efficacy of intestinal secretagogues for chronic constipation. These were better than placebo at achieving an increase in the number of complete spontaneous bowel movements per week [RR 1.87 (1.24-2.83)], at achieving three or more spontaneous bowel movements per week [RR 1.56 (1.31-1.85)] and at inducing spontaneous bowel movement after medication intake [RR 1.49 (1.07-2.06)]. Similar results were observed when assessing the efficacy of intestinal secretagogues on constipation-predominant irritable bowel syndrome based on the results of six trials. **Conclusion** – Intestinal secretagogues are useful and safe therapeutic alternatives for the treatment of constipation-related syndromes.

HEADINGS – Constipation. Irritable bowel syndrome. Colon.

INTRODUCTION

Chronic constipation (CC) as well as constipation-predominant irritable bowel syndrome (IBS-C) are very common conditions that constitute a frequent reason for referral to the general practitioner and the gastroenterology specialist[1]. These conditions are associated with a significant morbidity and an impaired quality of life[2].

Even though they are classified as different entities according to Rome criteria[3], the physiological mechanisms behind CC and IBS-C share a common ground. Thus, a diminished contractile activity of the colonic muscular layer as well as alterations in water reabsorption or secretion through intestinal epithelium have been proposed as etiological mechanisms[4]. As a consequence, they have been regarded as potential targets for pharmacological therapy.

Conventional treatment for CC and IBS-C include changes in lifestyle, increase of fiber intake and the use of a myriad of laxatives[5]. It can also contemplate other therapies oriented to treat constipation-related symptoms, such as abdominal bloating or pain[6]. It is noteworthy that a significant proportion of patients will not experience an improvement with these measures. Over the last years, new therapeutic alternatives have been developed: new high-affinity 5-HT4 receptor agonists such as prucalopride have been successfully tested; however, previous experience with similar molecules may raise a concern regarding their safety[7].

Among these new alternatives, intestinal secretagogues have shown some promising results. These drugs are designed to increase intestinal fluid secretion, thus increasing bowel movement frequency as well as enhancing the amount of stool water[8]. These molecules can act at different points: linaclotide for instance is a guanylate cyclase-C agonist that activates the cystic fibrosis transmembrane conductance regulator in the intestinal epithelium[9], whereas lubiprostone activates type 2 Chloride channels in the aforementioned cells[10]. The common pathway of these mechanisms is an increased release of chloride – and water – to the intestinal lumen.

These drugs have now been tested in different clinical settings for the treatment of both CC and IBS-C, and the preliminary results have triggered the development of drugs with similar mechanism of action, such as plecanatide or tenapanor[11]. The class-effect of these type of drugs has not been extensively studied. As a consequence, we sought to determine the efficacy and safety of intestinal secretagogues for the treatment of CC and IBS-C.

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METHODS

Search strategy and study selection

A computer-based search of compatible papers from 1966 to November 2017 was performed using the following databases: MEDLINE-Pubmed, EMBASE, LILACS and The Cochrane Library. Search strategy consisted of the following MeSH terms: intestinal secretagogues OR linaclotide OR lubiprostone OR plecanatide OR tenapanor OR chloride channel AND chronic constipation OR irritable bowel syndrome.

Relevant paper's bibliographies were revised, as well as bibliographies from previously published meta-analyses. A manual search for potentially relevant abstracts from Digestive Disease Week and United European Gastroenterology Week from 2009-2017 was also undertaken.

Two authors performed bibliographic search in an independent manner. Potentially relevant abstracts were revised in order to check its inclusion. Inclusion criteria were: a) trials examining the efficacy of any intestinal secretagogue for CC and/or IBS-C treatment; b) randomized, placebo-controlled trials; c) trials performed on adults. There were no language restrictions.

Search findings were then compared. If there was disagreement on the inclusion of a particular trial, it was discussed and determined by consensus. If there was evidence of duplication of data, the main author would be contacted to determine its inclusion.

Methodological evaluation of included studies

Methodological assessment was done using the *Evidence-Based Gastroenterology Steering Group* recommendations[12]. A Jadad score of each trial was also calculated. If a significant difference in methodological quality among studies was observed, a sensitivity analysis would be undertaken by excluding those trials with less quality. If relevant data was missing in original manuscripts, authors would be contacted.

Outcome measures

The following outcomes were considered for analysis: three or more spontaneous bowel movements (SBM) per week, number of complete spontaneous bowel movements (CSBM) per week, SBM after medication administration, improvement in abdominal pain, global relief of symptoms. Since Rome IV criteria[3] disregard abdominal discomfort as a pivotal symptom for the definition of IBS, we decided that it should not be contemplated as an endpoint, even though most trials assessed this point in particular. Data were extracted as intention-to-treat analyses, in which all dropouts are assumed to be treatment failures, wherever trial reporting allowed this.

Statistical analysis

Meta-analysis was performed using REVMAN software (Review Manager Version 5.2. Copenhagen: The Nordic Cochrane Collaboration, 2012). Heterogeneity among studies was evaluated by means of chi square and I2 tests. A random-effects model was used to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity among studies. Outcome measures were described as relative risk (RR) of achieving an improvement in the symptom under consideration. Also, 95% confidence intervals were calculated. Funnel plots were designed to evaluate possible publication bias. Numbers necessary to treat (NNT) were calculated.

RESULTS

Database Search yielded 520 bibliographic citations, as shown in FIGURE 1. Of these, 18 full texts were assessed for eligibility and 16 trials were finally included for analysis[13-27], which enrolled 7658 patients.

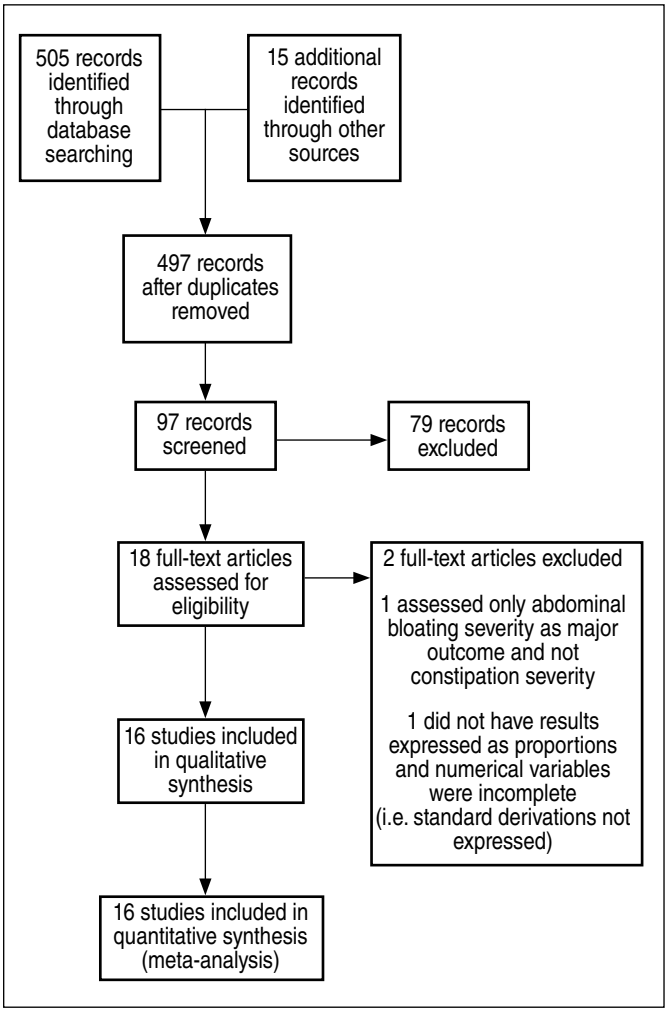

FIGURE 1. Flow chart showing the results of the bibliographic search and final selection of inc luded studies.

The main characteristics of included trials are described in TABLE 1. One of the most challenging aspects of this systematic review was the heterogeneity in the assessment of experimental drugs efficacy: as a consequence, not every trial was included in the assessment of each of the endpoints considered for meta-analysis. Patients were not similar: from an etiologic point of view, we divided trials evaluating the efficacy and safety of intestinal secretagogues on patients with CC and with IBS-C. Furthermore, CC patients also included patients with opioid-induced constipation as well as constipation associated with Parkinson disease[21] and diabetes mellitus[25].

Methodological evaluation of included trials is described in TABLE 2. No trial was excluded due to methodological limitations. No significant publication bias was found according to the Egger test (P>0.5).

TABLE 1. Main characteristics of included studies.

Author (Year)	Countrie	Age (median), Gender (%F) and Diagnosis	Outcome Measures	Number of Patients	Interventions	Co-Interventions
LINACLOTIDE						
Johnston 2010	USA/ Canada	44.4/92%; CIC+IBS-C	% of patients with CBM; % of patients with >3 BM during 75% of treatment period; % of patients with Bristol Score >3; % of patients without significant constipation; abdominal pain severity; abdominal bloating severity; % of patients with global relief	85 patients on placebo; 79 on linaclotide 75 ug; 82 on linaclotide 150 ug; 84 on linaclotide 300 ug; 89 on linaclotide 600 ug	Linaclotide once per day or placebo for 12 weeks	Bisacodyl or phosphate enema as rescue medication
Lembo 2010	USA	47.3/92%/ CIC	% of patients with CBM; % of patients with SBM; % of patients with Bristol Score>3; % of patients without significant straining; abdominal pain and bloating severity; % of patients with global relief	68 patients on placebo; 59 on linaclotide 75 ug; 56 on linaclotide 150 ug; 62 on linaclotide 600 ug	Oral linaclotide once daily or placebo for 4 weeks	Bisacodyl or phosphate enema as rescue medication
Lembo 2011	USA and Canada (2 clinical trials)	47.8/89.7%/ CIC	% of patients with >3 CSBM in 9 out of 12 weeks and/or increase in >1/week; % of patients with SBM after medication intake; % of patients with >2 SBM/week; % of patients with global relief	424 patients on placebo; 430 on linaclotide 145 ucg; 418 on linaclotide 290 ucg	Linaclotide or placebo for 12 weeks	Not clear
Chey 2012	USA	44.3/ 89.55%/ IBS-C	% of patients with pain severity improvement of >30% for at least 6 out of 12 weeks; % of patients with >1 CSBM/week for at least 6 out of 12 weeks; % of patients with >3 CBM/week; % of patients with CSBM after medication intake; % of patients with >2 SBM/week; % of patients with Bristol Score>3; % of patients with global relief	403 patients on placebo; 402 on linaclotide 290 ucg	Linaclotide or placebo for 26 weeks (assessment after 12 weeks of completion)	Not clear
Rao 2012	USA and Canada	43.5/90.5%/ IBS-C	% of patients with pain severity improvement >30% for at least 6 out of 12 weeks; % of patients with >1 CSBM/week for 6 out of 12 weeks; % of patients with >3 CBM/week; % of patients with SBM after medication intake; % of patients >2 SBM/week; % of patients with Bristol Score >3; % of patients with global relief	395 patients on placebo; 405 patients on linaclotide 290 ucg	Linaclotide or placebo for 12 weeks	Oral or rectal bisacodyl as rescue treatment
LUBIPROSTONE						
Johanson 2008	USA	48.27/90.55%/ CIC	% of patients with SBM; straining severity score; Bristol score; bloating and abdominal discomfort severity; % of patients who required rescue treatment	33 patients on placebo; 30 on lubiprostone 24 mcg; 32 on lubiprostone 48 mcg; 34 on lubiprostone 72 mcg	Lubiprostone or placebo T.I.D. for 3 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Drossman 2008	USA	46.6/91.6%/ IBS-C	% of patients with global improvement of IBS symptom severity: SBM, abdominal pain and bloating	385 patients on placebo; 769 on lubiprostone 8 mcg	Lubiprostone or placebo T.ID. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Fukudo 2011	Japan	39.4/90.58%/ CIC+IBS-C	P% of patients with SBM after medication intake; % of patients with global relief	42 patients on placebo; 41 on lubiprostone16 mcg; 43 on lubiprostone 32 mcg; 44 on lubiprostone 48 mcg	Lubiprostone or placebo for 2 weeks	Bisacodyl suppositories or glycerol enema as rescue treatment
Ondo 2012	USA	67.3/24.59%/ Constipation on Parkinson patients	% of patients with global relief; number of SBM/week with medication	31 patients on placebo; 30 on lubiprotsone 24 mcg	Lubiprostone or placebo B.I.D. for 4 weeks	Not clear
Cryer 2014	USA and Canada	50.4/64.35%/ opiod-induced constipation	% of patients with SBM after medication intake; % of patients with >3 SBM/week for at least 50% of treatment duration	208 patients on placebo; 210 patients on lubiprostone 24 mcg	Lubiprostone or placebo B.I.D. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Fukudo 2015	Japan	42.1/87.9%/ CIC	% of patients with SBM after medication intake; % of patients with >4 SBM/week; constipation severity	62 patients on placebo; 62 patients on lubiprostone 48 mcg	Lubiprostone or placebo for 4 weeks	Bisacodyl suppositories or glycerol enema as rescue treatment

Jamal 2015	USA and Europe	51.7/63.11%/ opioid-induced constipation	% of patients with SBM after medication intake	217 patients on placebo; 214 on lubiprostone 24 mcg BID	Lubiprostone or placebo B.I.D. for 12 weeks	Oral bisacodyl or sodium phosphate enema as rescue treatment
Christie 2017	USA	56.7/65.5%/ constipation on diabetic patients	% of patients with CSBM; average number of SBM/week	39 patients on placebo / 37 patients on lubiprostone 24 mcg BID	Lubiprostone or placebo B.I.D. for 8 weeks	Laxatives (including PEG) as rescue treatment
PLECANATIDE						
Miner 2017	USA and Canada	45.4/80.75%/ CIC	% of patients with >3 CSBM and/or increase in SBM/week in 9 out of 12 weeks of treatment; % of patients with SBM after medication intake	452 patients on placebo; 452 on plecanatide 3 mg; 441 on plecanatide 6 mg	Plecanatide or placebo once daily for 12 weeks	Bisacodyl as rescue treatment
TENAPANOR						
Chey 2017	USA	45.7/ 86.8%/ IBS-C	% of patients with >SBM/week for at least 50% of the treatment duration; % of patients with >30% decrease of abdominal pain severity for at least 50% of the treatment duration	89 patients on placebo; 85 on tenapanor 5 mg; 87 on tenapanor 20 mg; 84 on tenapanor 50 mg BID	Tenapanor or placebo B.I.D. for 12 weeks	Bisacodyl or suppositories as rescue treatment

CIC: chronic idiopathic constipation; IBS-C: constipation-predominant irritable bowel syndrome; CBM: complete bowel movement; SBM: spontaneous bowel movement; CSBM: complete spontaneous bowel movement; B.I.D: bis in die.

TABLE 2. Methodological features of included studies.

Study ID	Concealed allocation	Blinding of patients and healthcare personnel	Equalco-interventions between groups	Follow up report	Intention to treat analysis	Jadad score
LINACLOTIDE						
Johnston 2010	Yes	Yes	Yes	Yes	Yes	7
Lembo 2010	Yes	Yes	Yes	Yes	Yes	7
Lembo 2011	Yes	Yes	Yes	Yes	Yes	7
Chey 2012	Yes	Yes	Yes	Yes	Yes	7
Rao 2012	Yes	Yes	Yes	Yes	Yes	7
LUBIPROSTONA						
Johanson 2007	Not clear	Yes	Yes	Yes	Yes	6
Drossman 2008	Not clear	Yes	Yes	Yes	Yes	6
Fukudo 2010	Not clear	Yes	Yes	Yes	No	6
Ondo 2012	Yes	Yes	Yes	Yes	No	6
Cryer 2014	Yes	Yes	Yes	Yes	Yes	7
Fukudo 2014	Not clear	Yes	Yes	Yes	No	6
Jamal 2015	Yes	Yes	Yes	Yes	Yes	7
Christie 2017	Not clear	Yes	Yes	Yes	Not clear	6
PLECANATIDE						
Miner 2017	Yes	Yes	Yes	Yes	Yes	7
TENAPANOR						
Chey 2017	Yes	Yes	Yes	Yes	Yes	7

Efficacy of intestinal secretagogues for patients with chronic constipation

Twelve randomized controlled trials assessed the efficacy of three drugs for CC patients: linaclotide (Johnston 2010, Lembo 2010 and the two controlled trials published in Lembo 2011), lubiprostone (Johanson 2007, Fukudo 2011, Ondo 2012, Cryer 2014, Fukudo 2015, Jamal 2015 and Christie 2017) and plecanatide (Miner 2017). Efficacy endpoints are described in FIGURE 2. Overall, intestinal secretagogues were better than placebo at achieving an increase in the number of CSBM per week [RR 1.87 (1.24-2.83), NNT 9], also at achieving three or more SBM per week [RR 1.56 (1.31-1.85), NNT 6] and at inducing SBM after medication intake [RR 1.49 (1.07-2.06), NNT 6]. Additionally, patients treated with intestinal secretagogues experienced a more significant global relief of their symptoms compared to placebo [RR 1.78 (1.18-2.69), NNT 7]. In the cases where a significant heterogeneity was found, a sensitivity analysis was performed, showing no significant changes.

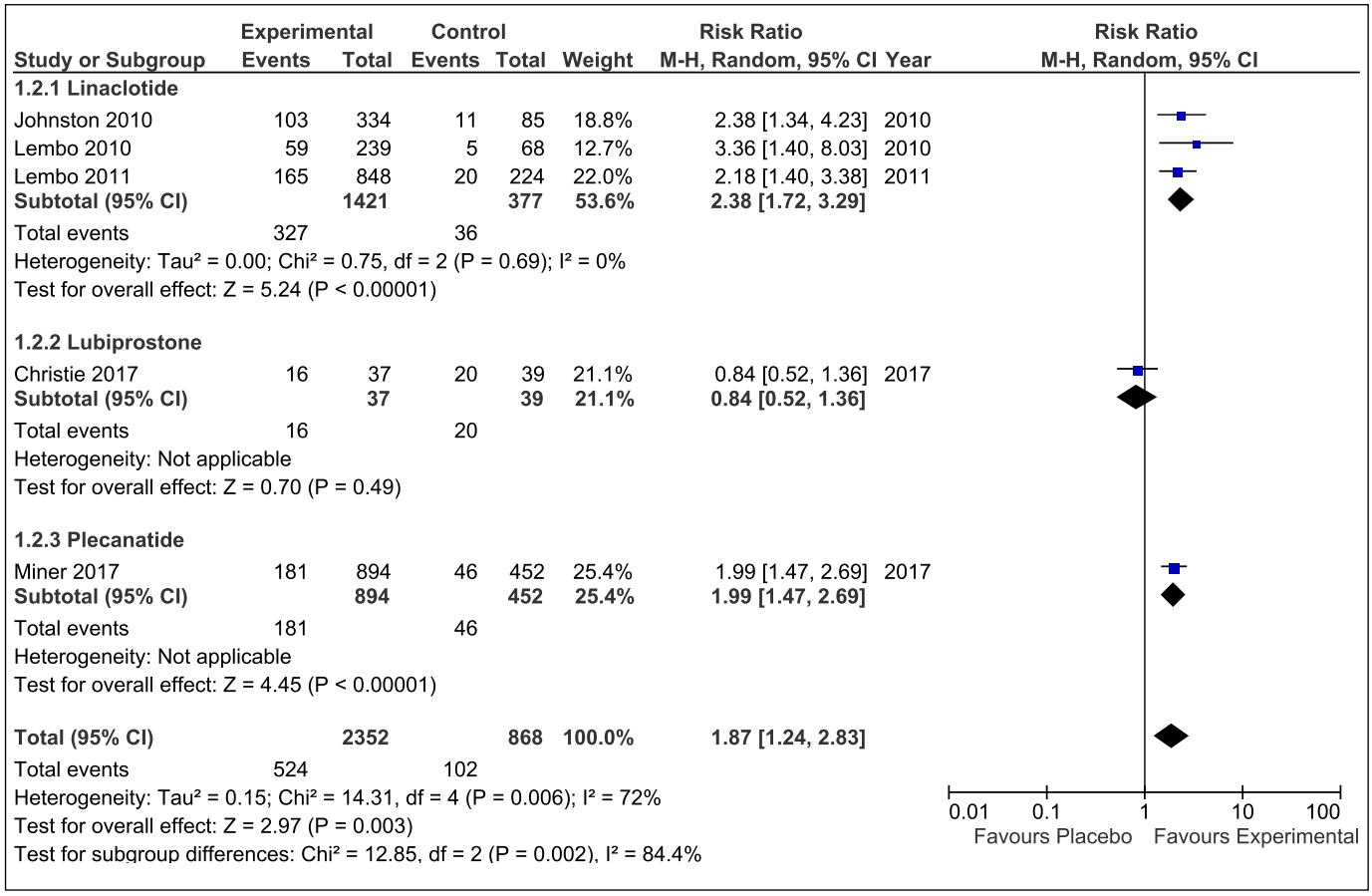

FIGURE 2. Efficacy of intestinal secretagogues on chronic idiopathic constipation patients, based on the following endpoints: A) Increase in the number of CSBM per week.

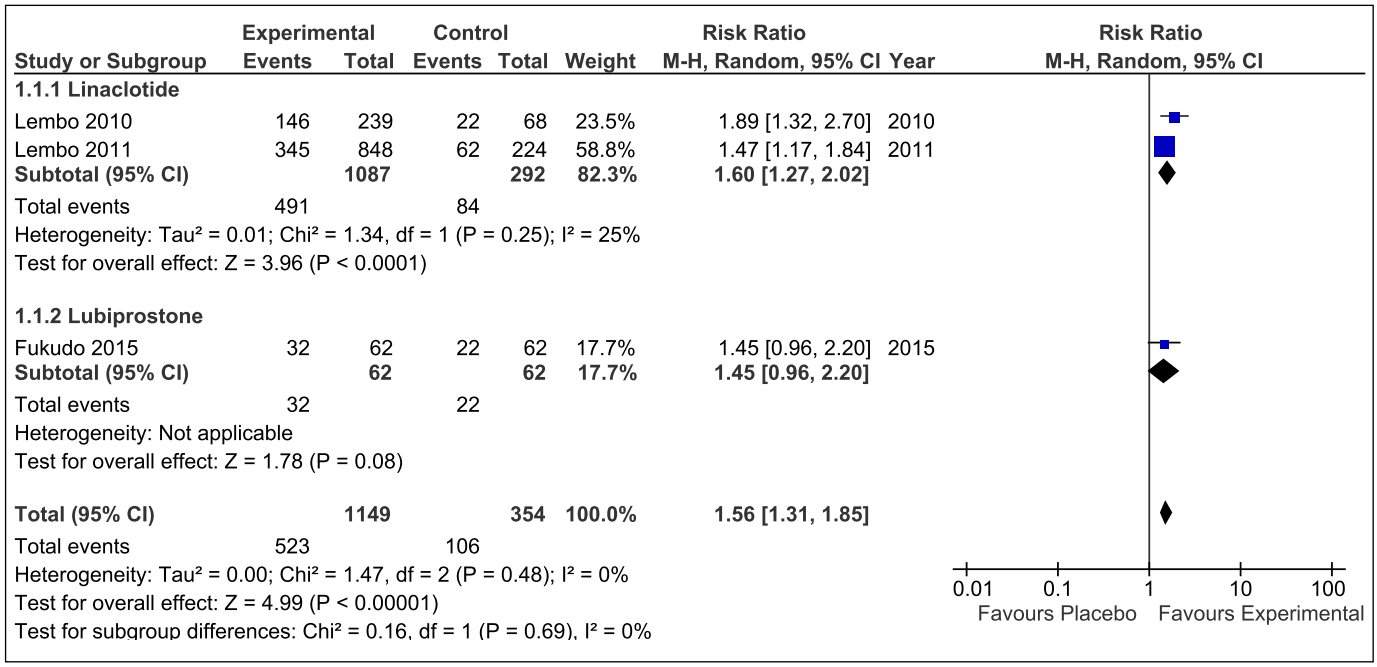

FIGURE 2. B) Achievement of >3 SBM per week.

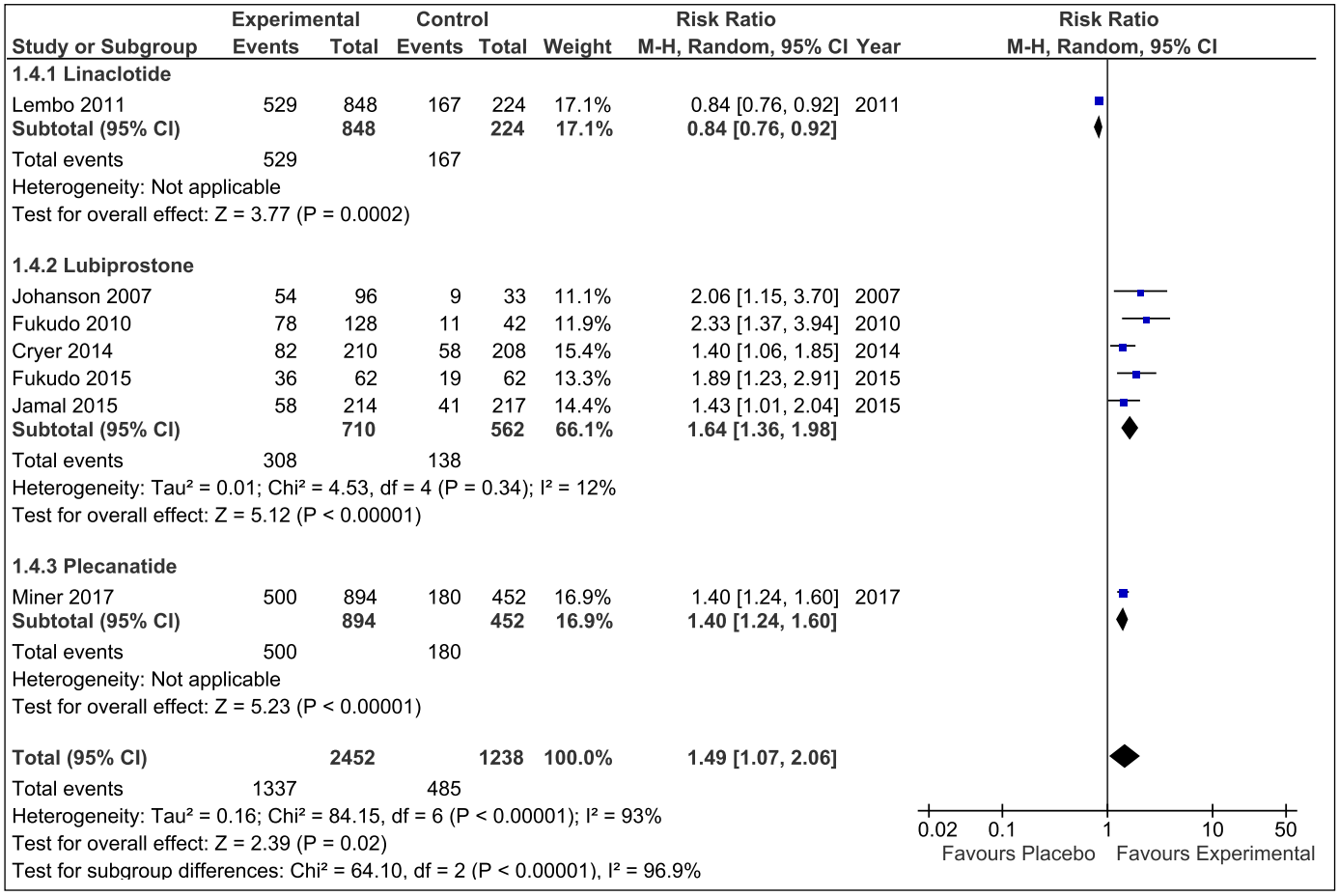

FIGURE 2. C) SBM after medication intake.

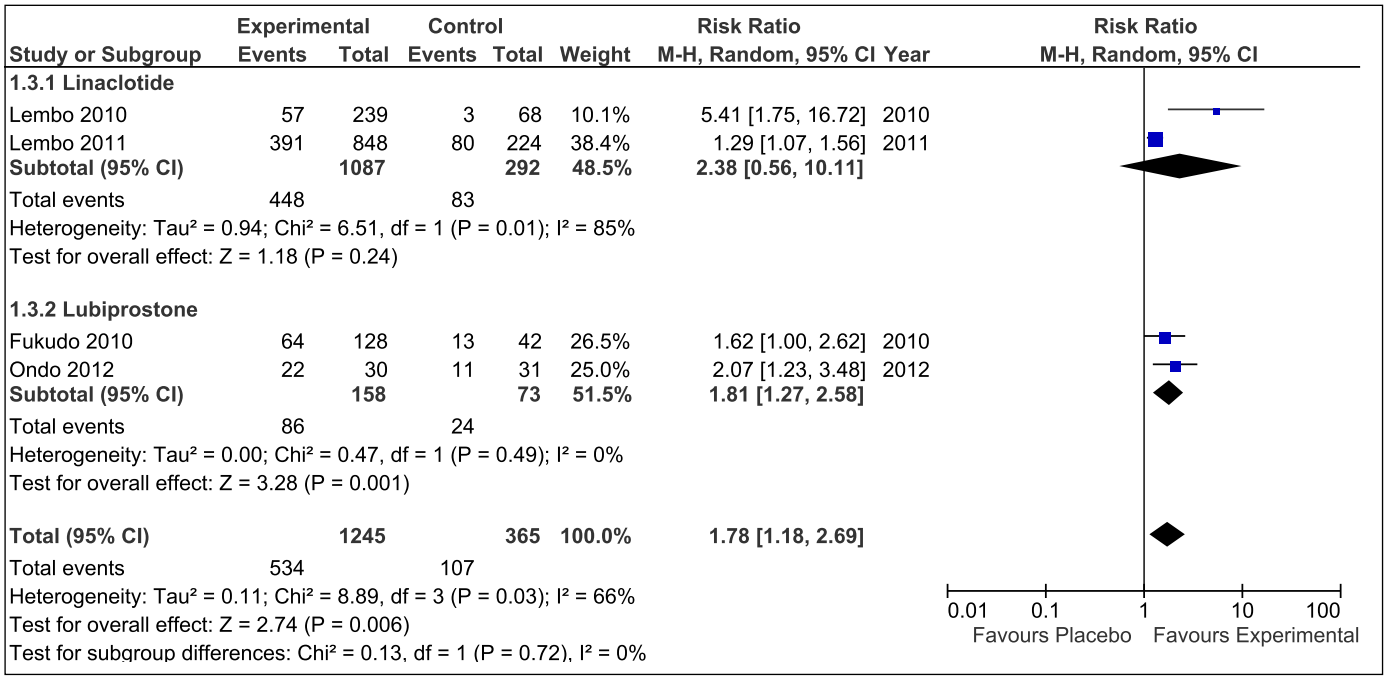

FIGURE 2. D) Achievement of global relief.

Efficacy of intestinal secretagogues for patients with constipation-predominant irritable bowel syndrome

Six randomized controlled trials assessed the efficacy of three drugs for IBS-C patients: linaclotide (Johnston 2010, Rao 2012, Chey 2012), lubiprostone (Fukudo 2011, Drossmann 2009) and tenapanor (Chey 2017). Efficacy endpoints are described in FIGURE 3. Intestinal secretagogues were not only better at achieving a relief in constipation-related outcomes such as increase in CSBM [RR 2.44 (1.51-3.93), NNT 5], three or more SBM per week [RR 1.97 (1.74-2.24), NNT 3], SBM after medication intake [RR 1.60 (1.44-1.79), NNT 4], but also a significant improvement in abdominal pain was observed versus placebo [RR 1.34 (1.21-1.48), NNT 9]. In the cases where a significant heterogeneity was found, a sensitivity analysis was performed, showing no significant changes.

Adverse events

A pooled analysis of the most frequent adverse events is detailed in TABLE 3. Overall, intestinal secretagogues showed to be safe drugs, without a significant proportion of serious adverse events reported. By far, the most common adverse event – which caused drop outs throughout most of the included studies – was diarrhea along with abdominal pain and nausea.

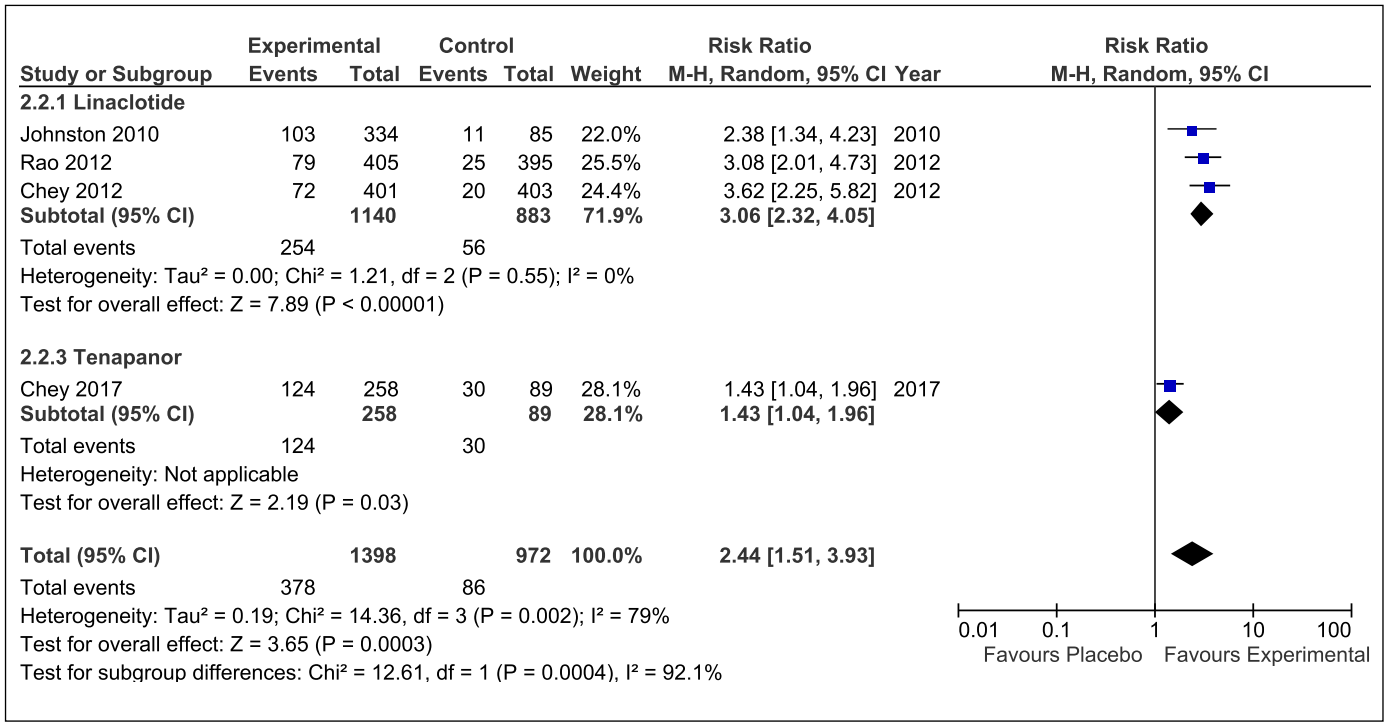

FIGURE 3. Efficacy of intestinal secretagogues on irritable bowel syndrome patients, based on the following endpoints: A) Increase in CSBM per week.

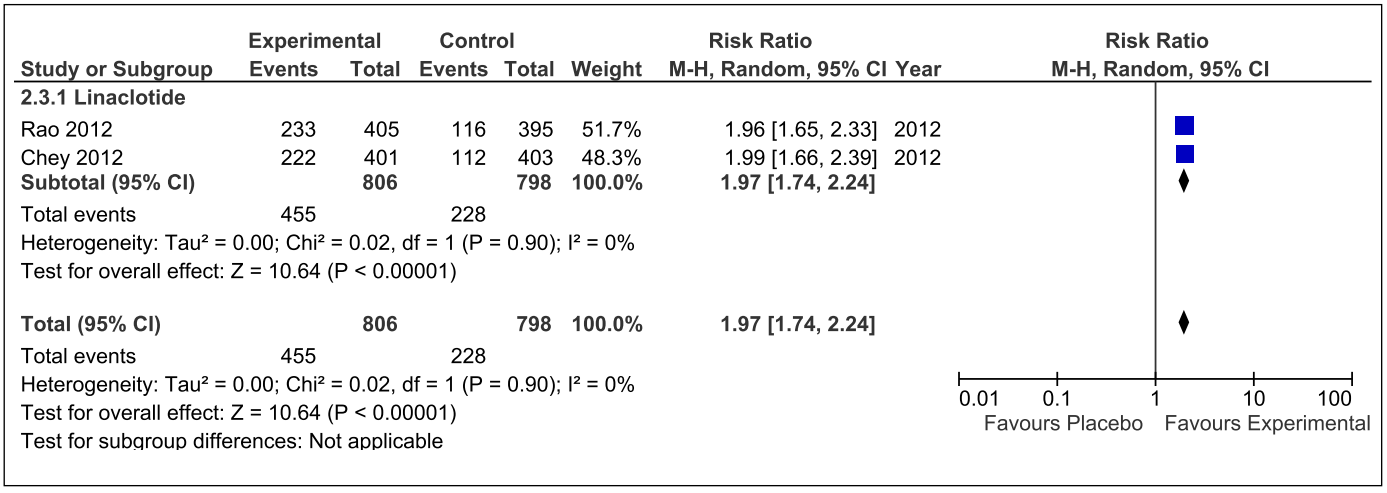

FIGURE 3. B) Achievement of >3 SBM per week.

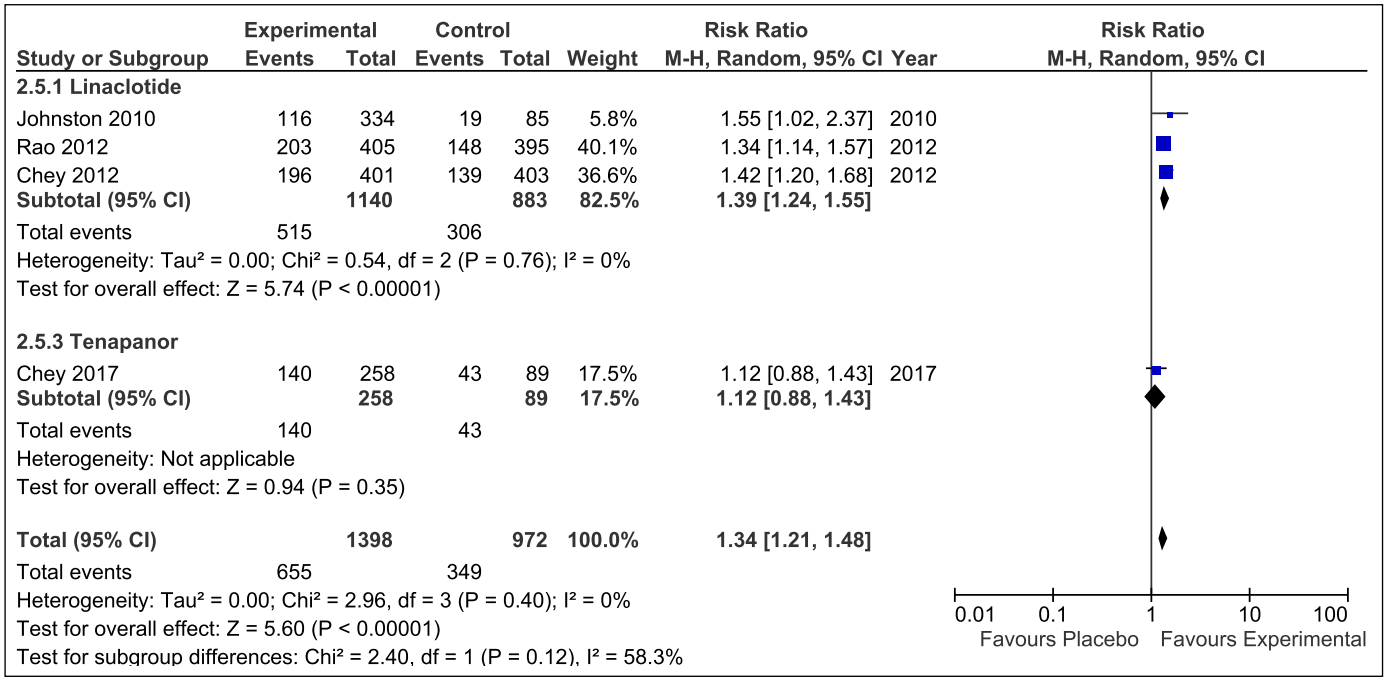

FIGURE 3. C) Improvement of abdominal pain; D) SBM after medication intake.

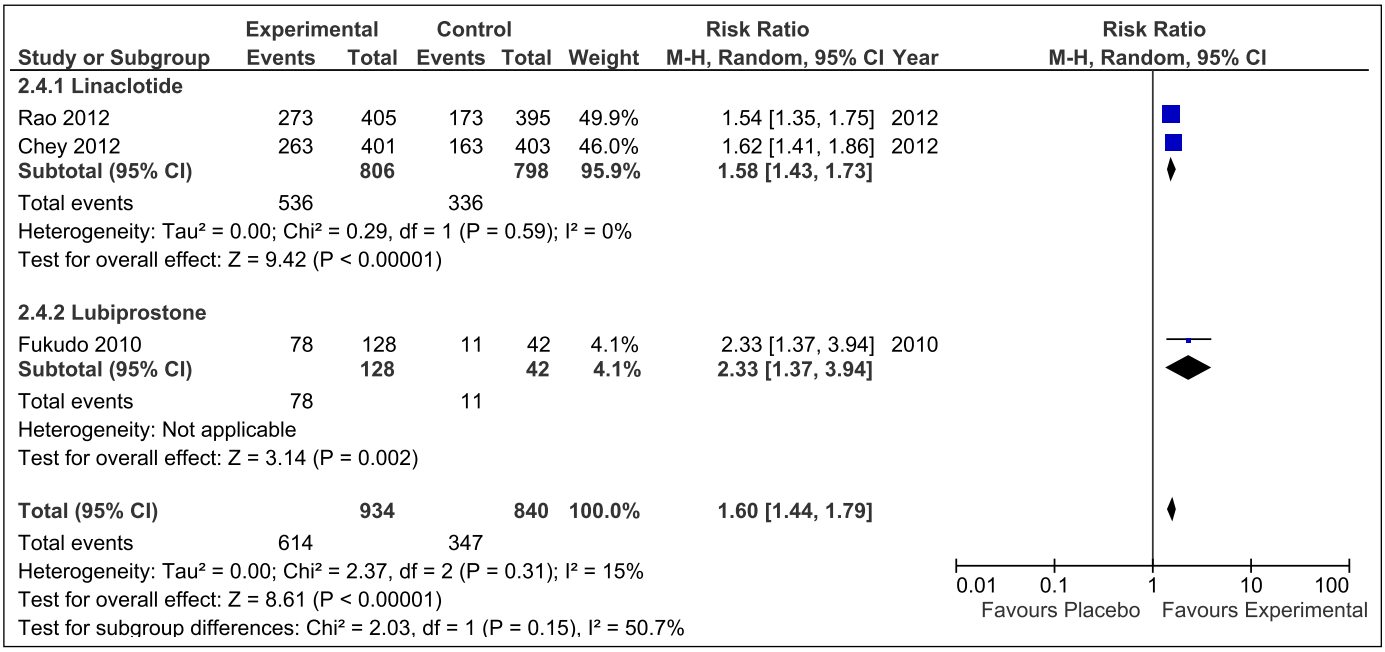

FIGURE 3. D) SBM after medication intake.

DISCUSSION

Constipation – in the context of CC or IBS-C – can be a very challenging condition to treat, leading to an impaired quality of life in a non-neglectable proportion of patients[2]. One of the reasons for this difficulty in the treatment is the paucity of therapeutic alternatives available. Most of the treatment options consist of laxatives as well as bulky agents such as fiber, which constitute a heterogeneous group of medications directed towards increasing the amount of water in stools or increasing colonic wall motility. A meta-analysis by Lee-Robichaud et al.[28] showed that, among the afore-mentioned options, polyethylene glycol was the laxative that showed more consistent results in terms of both efficacy and safety for the treatment of CC. Nevertheless, available alternatives other than laxatives are not abundant.

TABLE 3. Adverse events rates versus placebo.

AE	Number of studies	Number of patients on experimental drug	Number of patients on experimental drug and AE (%)	Number of patients on placebo	Number of patients on placebo and AE (%)	RR	CI 95%
LINACLOTIDE							
Diarrhea	6	2235	722	1377	47	9.46	7.1-12.61
Abdominal pain	6	2235	106	1377	45	1.45	1.03-2.04
Flatulence	5	1900	89	1292	41	1.47	1.02-2.18
LUBIPROSTONE							
Diarrhea	8	1691	131	1055	14	5.83	3.38-10.1
Nausea	7	1663	162	1029	42	2.38	1.71-3.32
Abdominal pain	6	779	51	626	19	2.15	1.28-3.61
PLECANATIDE							
Diarrhea	1	931	54	458	6	4.42	1.91-10.21
Nasopharyngitis	1	931	15	458	8	0.92	0.39-2.15
Sinusitis	1	931	13	458	3	2.13	0.61-7.44
TENAPANOR							
Diarrhea	1	266	28	90	0	N/A	N/A
Nausea	1	266	13	90	1	4.39	0.58-33.15
Abdominal pain	1	266	11	90	2	1.86	0.42-8.23

AE: adverse event.

Agents that promote adequate colonic motility such as 5-HT agonists have not been widely used until recently, mainly due to the concerns related to their potential cardiac side effects – as shown by the cisapride experience[7]. Prucalopride – a selective 5-HT4 agonist – has been approved by the European Medicines Agency for the treatment of CC due to its safety profile, showing no cardiac adverse events. Although prucalopride has expanded the therapeutic horizons for the treatment of CC or IBS-C, it may not be suitable or effective for every case that do not respond to laxatives or dietary measures.

Intestinal secretagogues are a type of medications whose mechanism of action implicates an increased amount of water excreted through the colonic epithelium. This is achieved by different means: linaclotide is a guanylate-cyclase agonist, whereas lubiprostone activates CIC-2 chloride channels, leading to the above-mentioned effect. Both plecanatide and tenapanor have been recently tested: plecanatide is also a guanylate-cyclase agonist like linaclotide[26]; tenapanor in change inhibits sodium intake by intestinal epithelial cells, by inhibiting the sodium-proton exchanger NHE3[27]. According to our result, regardless of the molecular approach these drugs have, intestinal secretagogues are more effective than placebo for the treatment of CC and IBS-C. This conclusion becomes relevant since evidently the mechanism exerted by these drugs is an effective one, thus it may provide significant information towards the design of new drugs with a similar mechanism. Moreover, these drugs seem to have acceptable safety profiles: there is a logical increase in the risk of gastrointestinal symptoms, which do not seem to represent a major threat to the patients under treatment.

Some interesting points should be mentioned when analyzing this systematic review. First of all, even though all of the clinical trials involved showed high quality from a methodological point of view, a non-neglectable heterogeneity in terms of outcome measurement was observed. With the exception of two trials[16,17] which adopted Food and Drug Administration's suggested endpoints, none of the included studies evaluated the outcomes in a uniform fashion – this is a relevant point when it comes to comparing the results of different trials and when meta-analyses are performed. An effort should be made for future trials to reach a consensus regarding endpoint consideration and measurement.

On the other hand, there is relevant information which has not been exhaustively assessed. As highlighted in TABLE 1, the vast majority of patients were allowed to receive rescue medications; and even though intestinal secretagogues showed a better performance in every single endpoint under consideration, the comparison of the amount of rescue medicine needed in both therapeutic arms becomes a valuable piece of information in a clinical scenario in which most endpoints are subjective – this information is not present in most of the clinical trials.

According to our results, it becomes clear that intestinal secretagogues are a useful tool for the treatment of CC and IBS-C. However, the exact place in the therapeutic algorithm of constipation-related syndromes is not clear. Placebo-controlled trials do not answer the question of whether these drugs are suitable to become first-line therapies. For this purpose, head to head comparisons between experimental drugs and standard of care treatments (such as polyethylene glycol for instance) are needed. There is a noticeable lack of evidence involving head to head comparisons: a network meta-analysis (with its obvious limitations) did not find any advantage among therapeutic alternatives for CC[29]. This network meta-analysis can arguably replace the need for non-inferiority clinical trials comparing different therapeutic approaches – prokinetics, laxatives, intestinal secretagogues.

In conclusion, intestinal secretagogues are both useful and safe for the treatment of both CC and IBS-C. A significant heterogeneity in terms of outcome measurement was observed, which can be detrimental for pooled analysis and therefore efforts should be made towards unifying endpoint selection criteria. Finally, head to head comparisons are necessary in order to establish a stepwise algorithm for the management of patients with CC and IBS-C.

Authors' contribution

Lasa JS: study design, bibliographic coordination, statistical analysis. Altamirano MJ: bibliographic search, data input. Bracho LF: bibliographic search, data input. Paz S: bibliographic search, data input. Zubiaurre I: study design, critical review of draft.

Lasa JS, Altamirano MJ, Bracho LF, Paz S, Zubiaurre I. Eficiência e segurança de secretagogos intestinais para constipação crônica: uma revisão sistemática e meta-análise. Arq Gastroenterol. 2018;55(Suppl 1):2-12.

RESUMO – **Contexto** – Os secretagogos intestinais têm sido testados para o tratamento da constipação crônica e síndrome do intestino irritável com constipação predominante. O efeito classe desses tipos de drogas ainda não foi estudado. **Objetivo** – Determinar a eficácia e a segurança de secretagogos intestinais para o tratamento da constipação crônica e síndrome do intestino irritável de constipação predominante. **Métodos** – Realizada pesquisa baseada em banco de dados de trabalhos publicados entre 1966 e setembro de 2017. A estratégia de pesquisa consistia dos seguintes termos MeSH: secretagogos intestinais OU linaclotide OU lubiprostona OU plecanatide OU tenapanor OU canal de cloro E constipação crônica OU síndrome do intestino irritável. Os dados foram extraídos como análises de intenção de tratar. Um modelo de efeitos aleatórios foi usado para dar uma estimativa mais conservadora do efeito das terapias individuais, permitindo a qualquer heterogeneidade entre os estudos. Os desfechos foram descritos como risco relativo de alcançar uma melhoria no sintoma em consideração. **Resultados** – A busca no banco de dados rendeu 520 citações bibliográficas: 16 ensaios foram incluídos para análise, que incluiu 7658 pacientes. Doze trabalhos avaliaram a eficácia de secretagogos intestinais para constipação crônica. Estes foram melhores do que placebo, alcançando um aumento no número de evacuações completas espontâneas por semana [RR 1,87 (1,24-2,83)], para a aquisição de três ou mais evacuações espontâneas por semana [RR 1,56 (1,31-1,85)] e na indução espontânea do movimento intestinal após a ingestão de medicação [RR 1,49 (1,07-2,06)]. Resultados semelhantes foram observados ao avaliar a eficácia de secretagogos intestinais na síndrome do intestino irritável de constipação predominante com base em resultados de seis ensaios. **Conclusão** – Os secretagogos intestinais são alternativas terapêuticas úteis e seguras para o tratamento de síndromes relacionadas à constipação.

DESCRITORES – Constipação intestinal. Síndrome do intestino irritável. Colo.

REFERENCES

1. Vakil N, Stelwagon M, Shea EP, Miller S. Symptom burden and consulting behavior in patients with overlapping functional disorders in the US population. United European Gastroenterol J 2016;4:431-22.
2. Enck P, Leinert J, Smid M, Kohler T, Schwille-Kiuntke J. Somatic comorbidity in chronic constipation: more data from the GECCO study. Gastroenterol Res Pract 2016;2016:5939238.
3. Drossman DA. Functional Gastrointestinal Disorders: history, pathophysiology, clinical features and Rome IV. Gastroenterology 2016;Feb 1. pii: S0016-5085(16)00223-7.
4. Holtmann GJ, Ford AC, Talley NJ. Pathophysiology of irritable bowel syndrome. Lancet Gastroenterol Hepatol. 2016;1:133-46.
5. Jadallah KA, Kullab SM, Sanders DS. Constipation-predominant irritable bowel syndrome: a review of current and emerging drug therapies. World J Gastroenterol. 2014;20:8898-909.
6. Mearin F, Ciriza C, Minguez M, Rey E4, Mascort JJ5, Peña E, et al. Clinical practice guideline: irritable bowel syndrome with constipation and functional constipation in the adult. Rev Esp Enferm Dig. 2016;108:32-63.
7. Aboumarzouk OM, Agarwal T, Antakia R, Shariff U, Nelson RL. Cisapride for intestinal constipation. Cochrane Database Syst Rev. 2011;(1):CD007780.
8. Ryu HS, Choi SC. Recent updates on the treatment of constipation. Intest Res. 2015;13:297-305.
9. Love BL, Johnson A, Smith LS. Linaclotide: a novel agent for chronic constipation and irritable bowel syndrome. Am J Health Syst Pharm. 2014;71:1081-91.
10. Jin Y, Blikslager AT. ClC-2 regulation of intestinal barrier function: translation of basic science to therapeutic target. Tissue Barriers. 2015;3(4):e1105906.
11. Thomas RH, Luthin DR. Current and emerging treatments for irritable bowel syndrome with constipation and chronic idiopathic constipation: focus on prosecretory agents. Pharmacotherapy. 2015;35:613-30.
12. Schoenfeld P, Cook D, Hamilton F, Laine L, Morgan D, Peterson W. An evidence-based approach to gastroenterology therapy. Gastroenterology. 1998;114:1318-25.
13. Johnston JM, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Linaclotide improves abdominal pain and bowel habits in a phase IIb study of patients with irritable bowel syndrome with constipation. Gastroenterology. 2010;139:1877-86.
14. Lembo AJ, Kurtz CB, MacDougall JE, Lavins BJ, Currie MG, Fitch DA, et al. Efficacy of linaclotide for patients with chronic constipation. Gastroenterology. 2010;138:886-95.
15. Lembo AJ, Schneier HA, Shiff SJ, Kurtz CB, MacDougall JE, Jia XD, et al. Two randomized trials of linaclotide for chronic constipation. N Engl J Med. 2011;365:527-36.
16. Chey WD, Lembo AJ, Lavins BJ, Shiff SJ, Kurtz CB, Currie MG, et al. Linaclotide for irritable bowel syndrome with constipation: a 26-week, randomized, double-blind, placebo-controlled trial to evaluate efficacy and safety. Am J Gastroenterol. 2012;107:1702-12.
17. Rao SS, Lembo AJ, Shiff SJ, Lavins BJ, Currie MG, Jia XD, et al. A 12-week, randomized, controlled trial with a 4-week randomized withdrawal period to evaluate the efficacy and safety of linaclotide in irritable bowel syndrome with constipation. Am J Gastroenterol. 2012;107:1714-24.
18. Johanson JF, Morton D, Geenen J, Ueno R. Multicenter, 4-week, double-blind, randomized, placebo-controlled trial of lubiprostone, a locally-acting type-2 chloride channel activator, in patients with chronic constipation. Am J Gastroenterol. 2008;103:170-7.
19. Drossman DA, Chey WD, Johanson JF, Fass R, Scott C, Panas R, Ueno R. Clinical trial: lubiprostone in patients with constipation-associated irritable bowel syndrome—results of two randomized, placebo-controlled studies. Aliment Pharmacol Ther. 2009;29:329-41.
20. Fukudo S, Hongo M, Kaneko H, Ueno R. Efficacy and safety of oral lubiprostone in constipated patients with or without irritable bowel syndrome: a randomized, placebo-controlled and dose-finding study. Neurogastroenterol Motil. 2011;23:544-e205.
21. Ondo WG, Kenney C, Sullivan K, Davidson A, Hunter C, Jahan I, et al. Placebo-controlled trial of lubiprostone for constipation associated with Parkinson disease. Neurology. 2012;78:1650-4.
22. Cryer B, Katz S, Vallejo R, Popescu A, Ueno R. A randomized study of lubiprostone for opioid-induced constipation in patients with chronic noncancer pain. Pain Med. 2014;15:1825-34.
23. Fukudo S, Hongo M, Kaneko H, Takano M, Ueno R. Lubiprostone increases spontaneous bowel movement frequency and quality of life in patients with chronic idiopathic constipation. Clin Gastroenterol Hepatol. 2015;13:294-301.

24. Jamal MM, Adams AB, Jansen JP, Webster LR. A randomized, placebo-controlled trial of lubiprostone for opioid-induced constipation in chronic noncancer pain. Am J Gastroenterol. 2015;110:725-32.
25. Christie J, Shroff S, Shahnavaz N, Carter LA, Harrison MS, Dietz-Lindo KA, et al. A randomized, double-blind, placebo-controlled trial to examine the effectiveness of lubiprostone on constipation symptoms and colon transit time in diabetic patients. Am J Gastroenterol. 2017;112:356-64.
26. Miner PB, Koltun WD, Wiener GJ, De La Portilla M, Prieto B, Shailubhai K, et al. A randomized phase III clinical trial of plecanatide, a uroguanylin analog, in patients with chronic idiopathic constipation. Am J Gastroenterol. 2017;112:613-21.
27. Chey WD, Lembo AJ, Rosenbaum DP. Tenapanor treatment of patients with constipation-predominant irritable bowel syndrome: a phase 2, randomized, placebo-controlled efficacy and safety trial. Am J Gastroenterol. 2017;112:763-74.
28. Lee-Robichaud H, Thomas K, Morgan J, Nelson RL. Lactulose versus polyethylene glycol for chronic constipation. Cochrane Database Syst Rev 2010;7:CD007570.
29. Nelson AD, Camilleri M, Chirapongsathorn S, Vijayvargiya P, Valentin N, Shin A, et al. Comparison of efficacy of pharmacological treatments for chronic idiopathic constipation: a systematic review and network meta-analysis. Gut. 2017;66:1611-22.

ORIGINAL ARTICLE

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The role of the transdiaphragmatic pressure gradient in the pathophysiology of gastroesophageal reflux disease

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ABSTRACT – Gastroesophageal reflux disease (GERD) is the most common disease of the upper gastrointestinal tract in the Western world. GERD pathophysiology is multifactorial. Different mechanisms may contribute to GERD including an increase in the transdiaphragmatic pressure gradient (TPG). The pathophysiology of GERD linked to TPG is not entirely understood. This review shows that TPG is an important contributor to GERD even when an intact esophagogastric barrier is present in the setting of obesity and pulmonary diseases.

HEADINGS – Gastroesophageal reflux disease. Pressure. Lower esophageal sphincter. Obesity. Respiratory tract diseases.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disease in the Western world with a raising prevalence in the last decades. It is currently the most common chronic disorder of the upper digestive tract[1] and it is estimated that GERD affects 10%-20% of the population[2]. In the US, GERD symptoms are felt at least weekly by 10%-25% of the population[3,4].

GERD pathophysiology is multifactorial with different factors contributing to its genesis. A defective esophagogastric barrier is commonly found in patients with GERD, since 75% of the individuals have a hypotonic lower esophageal sphincter (LES)[5]. A quarter of the individuals; however, have normal LES pressure and length. Some studies showed that transient LES relaxation (TLESR) may be the cause for GERD in these patients[1,5,6]. Others believe on the role of esophageal body dysmotility that leads to a faulty esophageal clearance exacerbating mucosal damage and allowing reflux to reach higher levels[6] or on the defective action of the diaphragm as an extrinsic sphincter in the absence of hiatal hernia (HH)[7]. Other possible factors are still the composition of the refluxate, mucosal integrity, visceral sensitivity, esophagogastric diminished compliance, and delayed gastric emptying[1,5].

Transdiaphragmatic pressure gradient (TPG) is part of GERD pathophysiology as well. The difference in pressure between positive gastric/abdominal pressure (AP) and the negative esophageal/thoracic pressure (TP) may exceed the pressure of the esophagogastric barrier represented by the LES and the diaphragm. This gradient may account for GERD[8]. Some groups of patients – such as those with lung diseases[9] or obesity[10] – have a higher risk of developing an elevated TPG and, not surprisingly, are at higher risk to have GERD. The mechanism is a raise in AP in the case of obesity[11] and a decrease in TP in chronic pulmonary disorders[12].

This review focuses on the role of TPG on GERD pathophysiology.

Transdiaphragmatic pressure gradient quantification by esophageal manometry

AP and TP are parameters not routinely measured during esophageal manometry. At the time of conventional manometry, only few studies[13-15] tried to measure TPG in GERD patients comparing inspiratory, mean respiratory or both pressures with variable methodology and without establishing reference values for normal individuals[13-15]. This is related to several limitations faced by conventional manometry, such as: (a) catheter movement artifacts that may include LES pressure with gastric or thoracic pressures if measurements are taken close to the sphincter; (b) inability to identify altered respiratory movements such as thoracic pressurization during moments of stress; (c) different parameters for zeroing baseline if different channels are used to measure thoracic or abdominal pressure; and (d) inability to identify gastric contractions that may be included during abdominal pressure recording[16].

High resolution manometry eliminates some of these limitations and recently some studies are focused on TPG at the light of this technology[16-20]. There is not; however, a standardization of methodology yet. Our preference is to calculate TPG subtracting the thoracic pressure measured at 2 cm above the upper border of the LES considering its respiratory excursion and the abdominal pressure at 2 cm below the lower border of the LES also considering its respiratory excursion. Both pressures are calculated based on the average pressure in a 30 s period encompassing all phases of the respiration (mid-respiratory measurement)[17] (FIGURE 1). We also measure LES retention pressure as defined by LES mid-respiratory basal pressure minus TPG.

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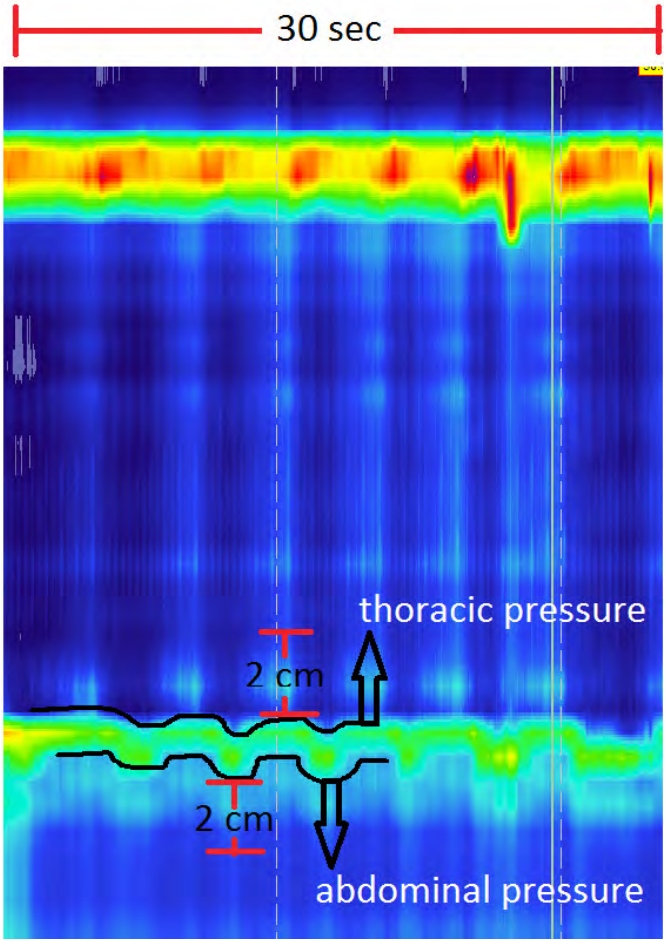

FIGURE 1. Measurement of the abdominal and thoracic pressures to calculate the transdiaphragmatic pressure gradient with the aid of the high resolution manometry.

Transdiaphragmatic pressure gradient in health

There is no reference values originated from healthy volunteers available. We use the parameters obtained from 32 healthy volunteers studied in our laboratory (n=32, mean age 33.1±8.7, 70% females). The results are expressed in TABLE 1.

Some physiologic conditions may influence TPG, such as exercise. Physical activity may alter TPG due to changes in both AP and TP[20]. Also, the number of TLESR seems to increase during exercise[21]. During the postprandial period, and increase in AP and TPG may be noticed[22].

Transdiaphragmatic pressure gradient and gastroesophageal reflux disease

The role of TPG on GERD pathophysiology is not well understood. Apart from altered AP and TP, TPG may be also influenced by compliance of the distal esophagus, changes in diaphragmatic morphology[13,23-25]. The important role of TPG must be; however, associated to TLESR, obesity, hiatal hernia and pulmonary diseases.

• Transient lower esophageal sphincter relaxation and the transdiaphragmatic pressure gradient

TLESR is a physiologic phenomenon secondary to gastric distension, defined by LES relaxation occurring in absence of swallowing, lasting more than 10 seconds, and associated with crural inhibition[26]. GERD patients have two times more episodes of reflux during TLESR as compared to normal individuals[27]. A possible explanation for an increase in the episodes of reflux is an increase in the TPG in these patients[8,18,22-23,25,27-30] that occurs shortly before TLESR[31]. This may explain GERD in the setting of a normotonic LES[5,32].

• Obesity and transdiaphragmatic pressure gradient

Obesity increases the risk for GERD[11,33]. Different studies showed that increase in weight is linked to a higher prevalence of GERD[10,11,34-36]. Moreover, obese individuals have more symptoms[35,36], increased esophageal acid exposure[37], higher incidence of Barrett´s esophagus[38], and HH[11,39] as compared to lean individuals. Although TPG is intuitively considered part of GERD pathophysiology in obese individuals, this condition has been poorly studied objectively. Increased AP (and consequent increased TPG) found in the obese favors GERD[14,39]. Increased waist circumference and body mass index are associated to a raise in TPG[14,17,40]. For each 1-point increase in body mass index, AP is expected to increase 10%[41]. Few studies however, were able to demonstrate a direct link between AP and esophageal acid exposure in the obese[14,42].

Obesity may affect not only AP[11]. Diaphragm elevation due to intraabdominal visceral obesity can lead to respiratory restriction, and consequent higher effort in the respiratory drive with a consequent decrease in the TP[43]. Moreover, sleep apnea is highly prevalent in the obese population[44] and affects TP as well[45].

TABLE 1. Transdiaphragmatic pressure gradient in healthy individuals.

Manometric parameter	Method	Average ± Standard deviation	Median (interquartile 25-75)	Range
Abdominal pressure (mmHg)	2 cm bellow lower border LES	11.6±4.5	11.4 (7.8-15.1)	2.6–19.6
Thoracic pressure (mmHg)	2 cm above upper border LES	7.4±5.4	7.4 (4.2-8.8)	-3.7–18.4
Transdiaphragmatic pressure gradient	Abdominal pressure Thoracic pressure	4.5±2.9	4.4 (2.0-7.1)	-0.2–10.6
LES retention pressure (mmHg)	LES basal pressure Transdiaphragmatic pressure gradient	16.5±12.1	13.3 (6.6-28.9)	-1–39.7

LES: lower esophageal sphincter.

• Hiatal hernia and transdiaphragmatic pressure gradient

HH is an independent risk factor for GERD[5]. HH leads to a morphologic alteration at the esophagogastric junction leading to the loss of some natural antireflux mechanisms and decreasing LES pressure[23,24,46]. TPG may also be increased due to pressurization of the herniated supra-diaphragmatic gastric pouch and a decrease of the esophageal compliance[14,47].

On the other side, an increased TPG may increase the chance of a HH. Pandolfino et al.[19] demonstrated that spatial separation of the LES and the diaphragm at the high resolution manometry is higher in overweight and obese individuals with increased TPG (due to an increased AP). Also, there is a high incidence of HH in patients with pulmonary interstitial fibrosis probably due to a decreased TP[48].

TPG may challenge the hiatal repair performed during an antireflux operation and affect HH recurrence. HH recurrence seems to be higher in the obese[11]. In the chronic pulmonary diseases population, although antireflux operations are currently performed even in end-stage transplant-list patients, late results and the real HH recurrence rate are elusive in the literature.

• Pulmonary diseases and transdiaphragmatic pressure gradient

The association of GERD and pulmonary disease is a frequent one and certainly a causality association not a spurious relation. Several recent studies showed an increased prevalence of GERD in patients with asthma, pulmonary fibrosis, chronic cough and chronic obstructive pulmonary disease (COPD)[12,17,49-52]. GERD may damage the lung due to aspiration of gastric contents but pulmonary diseases may cause GERD due to changes in the TPG. The increased respiratory effort common in certain lung disorders may alter TP. This was clearly demonstrated in patients with COPD and GERD[17]. This group of patients has a lower TP compared to patients with COPD but without GERD, even though LES pressure is similar for both[17]. Interestingly, TP is significantly increased after bronchodilators are inhaled[52]. In other lung disorders, such as interstitial fibrosis; however, an intrinsic failure of the LES is the most common finding[53,54].

Transdiaphragmatic pressure gradient – therapeutic applications

GERD has a complex pathophysiology with many factors contributing to the ascent of gastric contents to the esophagus. However, in summary, GERD occurs as a result of failure of the esophagogastric barrier, either due to an intrinsic defect of the valve apparatus or its retention capacity subdued by an altered TPG[55]. GERD control, in patients in whom TPG may play an important role, may be thus aimed towards the esophagogastric barrier or normalization of TPG.

• Non-obese, non-pulmonary patients

Laparoscopic fundoplication is very effective in controlling GERD[56,57]. This technique not only restores the competence of the esophagogastric barrier by improving LES pressure[58] but also decreases the number of TLESR[59,60]. Scheffer et al. showed that TPG is higher when an episode of reflux is associated to a TLESR and that a fundoplication decreases TPG during TLESR[8]. Moreover, a fundoplication improves esophageal body contractility[58]. This action may influence distal esophageal compliance raising TP[17].

• Obese patients

Weight loss leads to a reduction in AP. This is translated in a decrease in GERD symptoms[61] and pH monitoring parameters[62,63].

Fundoplication in the obese is a controversial topic[10]. While it does not act in the major component of GERD pathophysiology, i.e., TPG, it is a simple and efficient procedure with good outcomes even in the obese[64-66]. However, there are data showing a higher rate of complications, technical difficulty and worse results[67,68]. A recent tendency is to offer a bariatric operation to these patients[69-71].

Some bariatric procedures – such as gastric band and sleeve gastrectomy – lead to a decrease in visceral adiposity and consequent lower AP but may have controversial results in regards to intra-gastric pressure. While some believe there is a raise in intragastric pressure due to flow restriction[72], others support that gastric emptying is accelerated[73]. Studies focused on the development or amelioration of GERD after these restrictive procedures are still very controversial[10, 11, 72-78].

Roux-en-Y gastric bypass on the other hand is considered an excellent treatment for GERD in the obese[71]. Several series show improvement in symptoms[79,80], acid exposure[81] and extra-esophageal manifestations[82]. Weight loss summed to maintenance of esophageal[83] and rapid gastric emptying[84] favorably act on favor of decreasing TPG and GERD control that is added to a decrease in the population of acid-producing parietal cells and bile diversion.

• Pulmonary patients

GERD plays an important role in the pathogenesis of pulmonary diseases[85], and efforts must be made to accurately diagnose it and properly treat it[9]. A laparoscopic fundoplication does not act directly in the pulmonary mechanics to improve TPG but it controls GERD. Asthma exacerbations and medication usage are decrease after GERD treatment[86-88]. Idiopathic fibrosis is also improved by GERD control[89]. Better respiratory parameters are achieved in COPD patients after antireflux surgery that may affect TP towards normalization[90,91].

CONCLUSION

GERD has a multifactorial and complex pathophysiology. TPG may be an important contributor to GERD even with an intact esophagogastric barrier during TLESR and in the setting of obesity and pulmonary diseases. The current literature on the topic is still faulty. Clear conclusions on the influence of TPG in GERD pathophysiology are currently not possible but plausible theories may be drawn based on data extrapolation.

Authors' contribution

Del Grande LM: acquisition of data, drafting the article, analysis and interpretation of data, final approval of the version to be published. Herbella FAM: conception and design, acquisition of data, analysis and interpretation of data, drafting the article, final approval of the version to be published. Katayama RC: acquisition of data, final approval of the version to be published. Schlottmann F: review for intellectual content, final approval of the version to be published. Patti MG: conception and design, analysis and interpretation of data, review for intellectual content, final approval of the version to be published.

Del Grande LM, Herbella FAM, Katayama RC, Schlottmann F, Patti MG. O papel do gradiente pressórico transdiafragmático na fisiopatologia da doença do refluxo gastroesofágico. Arq Gastroenterol. 2018;55(Suppl 1):13-7.

RESUMO – A doença do refluxo gastroesofágico (DRGE) é a enfermidade mais comum do trato digestivo alto no mundo ocidental. A fisiopatologia da DRGE é multifatorial. Diferentes mecanismos podem contribuir para um aumento do gradiente pressórico transdiafragmático (GPT). A fisiopatologia da DRGE associada ao GPT não é totalmente compreendida. Esta revisão enfoca que o GPT é um importante contribuinte para DRGE mesmo na presença de uma barreira gastroesofágica intacta como na obesidade e doenças pulmonares crônicas.

DESCRITORES – Refluxo Gastroesofágico. Pressão. Esfíncter esofágico inferior. Doenças respiratórias.

REFERENCES

1. Herregods TV, Bredenoord AJ, Smout AJ. Pathophysiology of gastroesophageal reflux disease: new understanding in a new era. Neurogastroenterol Motil. 2015;27:1202-1213.
2. Katz P, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-328; quiz 329.
3. Hummel K, Richards W. Endoscopic treatment of gastroesophageal reflux disease. Surg Clin North Am. 2015;95:653-67.
4. Moraes-Filho JP, Chinzon D, Eisig JN, Hashimoto CL, Zaterka S. Prevalence of heartburn and gastroesophageal reflux disease in the urban Brazilian population. Arq Gastroenterol. 2005;42:122-7.
5. Herbella FA, Patti MG. Gastroesophageal reflux disease: From pathophysiology to treatment. World J Gastroenterol. 2010;16:3745-9.
6. Patti MG, Diener URS, Tamburini A, Molena D, Way LW. Role of esophageal function testes in diagnosis of gastroesophageal reflux disease. Dig Dis Sciences. 2001;4:597-602.
7. Pandolfino JE, Kim H, Ghosh SK, Clarke JO, Zhang Q, Kahrilas PJ. High-resolution manometry of the EGJ: an analysis of crural diaphragm function in GERD. Am J Gastroenterol. 2007;102:1056-63.
8. Scheffer RC, Gooszen HG, Hebbard GS, Samsom M. The role of transsphincteric pressure and proximal gastric volume in acid reflux before and after fundoplication. Gastroenterology. 2005;129:1900-9.
9. Lee AL, Goldstein RS. Gastroesophageal reflux disease in COPD: links and risks. Int J Chron Obstruct Pulmon Dis. 2015;10:1935-49.
10. Khan A, Kim A, Sanossian C, Francois F. Impact of obesity treatment on gastroesophageal reflux disease. World J Gastroenterol. 2016;22940:1627-38.
11. Nadaleto BF, Herbella FA, Patti MG. Gastroesophageal reflux disease in the obese: Pathophysiology and treatment. Surgery. 2016;159:475-86.
12. Casanova C, Baudet JS, del Valle Velasco M, Martin JM, Aguirre-Jaime A, de Torres JP, Celli BR. Increased gastro-oesophageal reflux disease in patients with severe COPD. Eur Respir J. 2004;23:841-5.
13. Ayazi S, DeMeester SR, Hsieh CC, Zehetner J, Sharma G, Grant KS, et al. Thoraco-abdominal pressure gradients during the phases of respiration contribute to gastroesophageal reflux disease. Dig Dis Sci. 2011;56:1718-22.
14. de Vries DR, van Herwaarden MA, Smout AJ, Samsom M. Gastroesophageal pressure gradients in gastroesophageal reflux disease: relations with hiatal hernia, body mass index, and esophageal acid exposure. Am J Gastroenterol. 2008;103:1349-54.
15. Fornari F, Fucilini LM, Risson C, Rossi L, Gelain A, Barros SG. Contribution of standard oesophageal manometry in sliding hiatal hernia: from the gastro-oesophageal pressure gradient to the diagnosis. Dig Liver Dis. 2009;41:886-90.
16. Herbella FA, Aprile LR, Patti MG. High-resolution manometry for the evaluation of gastric motility. Updates Surg. 2014;66:177-81.
17. Del Grande LM, Herbella FA, Bigatao AM, Abrao H, Jardim JR, Patti MG. Pathophysiology of Gastroesophageal Reflux in Patients with Chronic Pulmonary Obstructive Disease Is Linked to an Increased Transdiaphragmatic Pressure Gradient and not to a Defective Esophagogastric Barrier. J Gastrointest Surg. 2016;20:104-10.
18. Ribolsi M, Balestrieri, R. Holloway H, Emerenziani S, Cicala M. Intra-bolus pressure and esophagogastric gradient, assessed with high-resolution manometry, are associated with acid exposure and proximal migration of refluxate. Dis Esophagus. 2016;29:1020-6.
19. Pandolfino JE, El-Serag HB, Zhang Q, Shah N, Ghosh SK, Kahrilas PJ. Obesity: a challenge to esophagogastric junction integrity. Gastroenterology. 2006;130:639-49.
20. Maddison KJ, Shepherd KL, Hillman DR, Eastwood PR. Function of the lower esophageal sphincter during and after high-intensity exercise. Med Sci Sports Exerc. 2005;37:1728-33.
21. Herregods TV, van Hoeij FB, Oors JM, Bredenoord AJ, Smout AJ. Effect of Running on Gastroesophageal Reflux and Reflux Mechanisms. Am J Gastroenterol. 2016. doi: 10.1038/ajg.2016.122.
22. Frankhuisen R, Van Herwaarden MA, Scheffer RCh, Hebbard GS, Gooszen HG, Samsom M. Increased intragastric pressure gradients are involved in the occurrence of acid reflux in gastroesophageal reflux disease. Scand J Gastroenterol. 2009;44:545-50.
23. Kahrilas PJ, Shi G, Manka M, Joehl RJ. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology 2000;118:688-95.
24. Tipnis NA, Rhee PL, Mittal RK. Distension during gastroesophageal reflux: effects of acid inhibition and correlation with symptoms. Am J Physiol Gastrointest Liver Physiol. 2007;293:469-74.
25. Pandolfino J E, Shi G, Trueworthy B, Kahrilas PJ. Esophagogastric junction opening during relaxation distinguishes nonhernia reflux patients, hernia patients, and normal subjects. Gastroenterology. 2003;125:1018-24.
26. Roman S, Holloway R, Keller J, Herbella F, Zerbib F, Xiao Y, et al. Validation of criteria for the definition of transient lower esophageal sphincter relaxations using high-resolution manometry. Neurogastroenterol Motil. 2017;29(2). doi: 10.1111/nmo.
27. Hershcovici T, Mashimo H, Fass R. The lower esophageal sphincter. Neurogastroenterol Motil. 2011;23:819-30.
28. Van Herwaarden MA, Samsom M, Smout AJ. Excess gastroesophageal reflux in patients with hiatus hernia is caused by mechanisms other than transient LES relaxations. Gastroenterology. 2000;119:1439-46.
29. Bredenoord AJ, Weusten BL, Timmer R, Smout AJ. Intermittent spatial separation of diaphragm and lower esophagealsphincter favors acidic and weakly acidic reflux. Gastroenterology. 2006;130:334-40.
30. Pandolfino JE, Zhang QG, Ghosh SK, Han A, Boniquit C, Kahrilas PJ. Transient lower esophageal sphincter relaxations and reflux: mechanistic analysis using concurrent fluoroscopy and high-resolution manometry. Gastroenterology. 2006;131:1725-33.
31. Sifrim D, Tack J, Lerut T, Janssens J Transient lower esophageal sphincter relaxations and esophageal body muscular contractile response in reflux esophagitis. Dig Dis Sci. 2000;45:1293-300.
32. Benati CD, Herbella FA, Patti MG. Manometric parameters in patients with suspected Gastroesophageal reflux disease and normal pH monitoring. GED Gastroenterol Endosc Dig. 2014;33:52-7.
33. Friedenberg FK, Xanthopoulos M, Foster GD, Richter JE. The association between gastroesophageal reflux disease and obesity. Am J Gastroenterol. 2008;103:2111-22.
34. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. Gastroenterol Clin North Am. 2010;39:39-46.
35. Locke GR III, Talley NJ, Fett SL, Zinsmeister AR, Melton LJ III. Risk factors associated with symptoms of gastroesophageal reflux. Am J Med. 1999;106:642-9.
36. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. JAMA. 2003;290:66-7.
37. El-Serag HB, Ergun GA, Pandolfino J, , Fitzgerald S, Tran T, Kramer JR. Obesity increases oesophageal acid exposure. Gut. 2007;56:749–55.
38. Kindel TL, Oleynikov D. The improvement of Gastroesophageal Reflux Disease and Barrett´s after Bariatric Surgery. Obes Surg. 2016;26:718-20.
39. Wilson LJ, Ma W, Hirschowitz BI. Association of obesity with hiatal hernia and esophagitis. Am J Gastroenterol. 1999;94:2840–4.
40. Pandolfino JE. The relationship between obesity and GERD: "big or overblown". Am J Gastroenterol. 2008;103:1355-7.
41. El-Serag HB, Tran T, Richardson P, Ergun G. Anthropometric correlates of intragastric pressure. Scand J Gastroenterol. 2006;41:887-91.
42. Fornari F, Madalosso CA, Farré R, Gurski RR, Thiesen V, Callegari-Jacques SM. The role of gastro-oesophageal pressure gradient and sliding hiatal hernia on pathological gastro-oesophageal reflux in severely obese patients. Eur J Gastroenterol Hepatol. 2010;22:404-11.
43. Steier J, Lunt A, Hart N, Polkey MI, Moxham. Observational study of the effect of obesity on lung volumes. Thorax. 2014;69:752-9.

44. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. Obes Surg. 2003;13:676-83.
45. Marcus JA, Pothineni A, Marcus CZ, Bisognano JD. The role of obesity and obstructive sleep apnea in the pathogenesis and treatment of resistant hypertension. Curr Hypertens Rep. 2014;16:411.
46. Fein M, Ritter MP, DeMeester TR, Oberg S, Peters JH, Hagen JA, Bremner CG. Role of the lower esophageal sphincter and hiatal hernia in the pathogenesis of gastroesophageal reflux disease. J Gastrointest Surg. 1999;3:405-10.
47. Smith ABD, Dickerman RDD, McGuire CSD, East JW, McConathy WJ, Pearson HF. Pressure-overload-induced sliding hiatal hernia in power athletes. J Clin Gastroenterol. 1999;28:352–4.
48. Harding SM. Recent clinical investigations examining the association of asthma and gastroesophageal reflux. Am J Med. 2003;115 Suppl 3A:39S-44S.
49. Tossier C, Dupin C, Plantier L, Leger J, Flament T, Favelle O, et al. Hiatal hernia on thoracic computed tomography in pulmonary fibrosis. Eur Respir J. 2016;48:833-42.
50. Allaix ME, Fisichella PM, Noth I, Herbella FA, Borraez Segura B, Patti MG. Idiopathic pulmonary fibrosis and gastroesophageal reflux. Implications for treatment. J Gastrointest Surg. 2014;18:100-5.
51. Kahrilas PJ, Smith JA, Dicpinigaitis PV. A Causal Relationship Between Cough and Gastroesophageal Reflux Disease (GERD) has been Established: A Pro/Con Debate. Lung. 2014;192:39-46.
52. Del Grande LM, Herbella FA, Bigatao AM, Jardim JR, Patti MG. Inhaled Beta Agonist Bronchodilator Does Not Affect Transdiaphragmatic Pressure Gradient but Decreases Lower Esophageal Sphincter Retention Pressure in Patients with Chronic Obstructive Pulmonary Disease (COPD) and Gastroesophageal Reflux Disease (GERD). Am Surg. 2016;20:1679-82.
53. Kempainen RR, Savik K, Whelan TP, Dunitz JM, Herrington CS, Billings JL. High prevalence of proximal and distal gastroesophageal reflux disease in advanced COPD. Chest. 2007;131:1666-71.
54. Patti MG, Tedesco P, Golden J, Hays S, Hoopes C, Meneghetti A, Damani T, Way LW. Idiopathic pulmonary fibrosis: how often is it really idiopathic? J Gastrointest Surg. 2005;9:1053-6.
55. Tosato F, Marano S, Mattachione S, Luongo B, Paltrinieri G, Mingarelli V, Vasapollo L. Surgical treatment of gastroesophageal reflux disease. Advances in endoscopic surgery. 2011; p.259-90. Prof. Cornel Iancu (Ed.), ISBN: 978-953-307-717-8, InTech, Available from: http://www.intechopen.com/books/advances-in-endoscopic-surgery/surgical-treatment-of-gastroesophagealreflux-disease.
56. Wileman SM, McCann S, Grant AM, Krukowski ZH, Bruce J. Medical versus surgical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. 2010;17(3):CD003243.
57. Bello B, Herbella FA, Allaix ME, Patti MG. Impact of minimally invasive surgery on the treatment of benign esophageal disorders. World J Gastroenterol. 2012;18:6764-70.
58. Herbella FA, Tedesco P, Nipomnick I, Fisichella PM, Patti MG. Effect of partial and total laparoscopic fundoplication on esophageal body motility. Surg Endosc. 2007;21:285-8.
59. Ireland AC, Holloway RH, Toouli J, Dent J. Mechanisms underlying the antireflux action of fundoplication. Gut. 1993;34:303-8.
60. Scheffer RC, Tatum RP, Shi G, Akkermans LM, Joehl RJ, Kahrilas PJ. Reduced tLESR elicitation in response to gastric distension in fundoplication patients. Am J Physiol Gastrointest Liver Physiol. 2003;284:G815-20.
61. Ness-Jensen E, Lindam A, Lagergren J, Hveem K. Weight loss and reduction in gastroesophageal reflux. A prospective population-based cohort study: the HUNT study. Am J Gastroenterol. 2013;108:376-82.
62. Mathus-Vliegen LM, Tytgat GN. Twenty-four-hour pH measurements in morbid obesity: effects of massive overweight, weight loss and gastric distension. Eur J Gastroenterol Hepatol. 1996;8:635-40.
63. Mathus-Vliegen EM, van Weeren M, van Eerten PV. LOS function and obesity: the impact of untreated obesity, weight loss, and chronic gastric balloon distension. Digestion. 2003;68:161-8.
64. Telem DA, Altieri M, Gracia G, Pryor AD. Perioperative outcome of esophageal fundoplication for gastroesophageal reflux disease in obese and morbidly obese patients. Am J Surg. 2014;208:163-8.
65. Campos GM, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg. 1999;3:292-300.
66. Luketina RR, Koch OO, Köhler G, Antoniou SA, Emmanuel K, Pointner R. Obesity does not affect the outcome of laparoscopic antireflux surgery. Surg Endosc. 2015;29:1327-33.
67. Chisholm JA, Jamieson GG, Lally CJ, Devitt PG, Game PA, Watson DI. The effect of obesity on the outcome of laparoscopic antireflux surgery. J Gastrointest Surg. 2009;13:1064-70.
68. Morgenthal CB, Lin E, Shane MD, Hunter JG, Smith CD. Who will fail laparoscopic Nissen fundoplication? Preoperative prediction of long-term outcomes. Surg Endosc. 2007;21:1978-84.
69. Wang YR, Dempsey DT, Richter JE. Trends and perioperative outcomes of inpatient antireflux surgery in the United States, 1993-2006. Dis Esophagus. 2011;24:215-23.
70. Pagé MP, Kastenmeier A, Goldblatt M, Frelich M, Bosler M, Wallace J, Gould J. Medically refractory gastroesophageal reflux disease in the obese: what is the best surgical approach? Surg Endosc. 2014;28:1500-4.
71. Varela JE, Hinojosa MW, Nguyen NT. Laparoscopic fundoplication compared with laparoscopic gastric bypass in morbidly obese patients with gastroesophageal reflux disease. Surg Obes Relat Dis. 2009;5:139-43.
72. Daes J, Jimenez ME, Said N, Daza JC, Dennis R. Laparoscopic sleeve gastrectomy: symptoms of gastroesophageal reflux can be reduced by changes in surgical technique. Obes Surg. 2012;22:1874-9.
73. Melissas J, Leventi A, Klinaki I, Perisinakis K, Koukouraki S, de Bree E, Karkavitsas N. Alterations of global gastrointestinal motility after sleeve gastrectomy: a prospective study. Ann Surg. 2013;258:976-82.
74. Tolonen P, Victorzon M, Niemi R, Mäkelä J. Does gastric banding for morbid obesity reduce or increase gastroesophageal reflux? Obes Surg. 2006;16:1469-74.
75. Ovrebø KK, Hatlebakk JG, Viste A, Bassøe HH, Svanes K. Gastroesophageal reflux in morbidly obese patients treated with gastric banding or vertical banded gastroplasty. Ann Surg. 1998;228:51-8.
76. Rebecchi F, Rocchietto S, Giaccone C, Talha A, Morino M. Gastroesophageal reflux disease and esophageal motility in morbidly obese patients submitted to laparoscopic adjustable silicone gastric banding or laparoscopic vertical banded gastroplasty. Surg Endosc. 2011;25:795-803.
77. Tai CM, Huang CK, Lee YC, Chang CY, Lee CT, Lin JT. Increase in gastroesophageal reflux disease symptoms and erosive esophagitis 1 year after laparoscopic sleeve gastrectomy among obese adults. Surg Endosc. 2013;27:1260-6.
78. Sheppard CE, Sadowski DC, de Gara CJ, Karmali S, Birch DW. Rates of reflux before and after laparoscopic sleeve gastrectomy for severe obesity. Obes Surg. 2015;25:763-8.
79. Ortega J, Escudero MD, Mora F, Sala C, Flor B, Martinez-Valls J, et al. Outcome of esophageal function and 24-hour esophageal pH monitoring after vertical banded gastroplasty and Roux-en-Y gastric bypass. Obes Surg. 2004;14:1086-94.
80. Schauer PR, Ikramuddin S, Gourash W, Ramanathan R, Luketich J. Outcomes after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Ann Surg. 2000;232:515-29.
81. Madalosso CA, Gurski RR, Callegari-Jacques SM, Navarini D, Mazzini G, Pereira Mda S. The Impact of Gastric Bypass on Gastroesophageal Reflux Disease in Morbidly Obese Patients. Ann Surg. 2016;263:110-6.
82. Frezza EE, Ikramuddin S, Gourash W, Rakitt T, Kingston A, Luketich J, Schauer P. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. Surg Endosc. 2002;16:10.
83. Valezi AC, Herbella FA, Junior JM, de Almeida Menezes M. Esophageal motility after laparoscopic Roux-en-Y gastric bypass: the manometry should be preoperative examination routine? Obes Surg. 2012;22:1050-4.
84. Wang G, Agenor K, Pizot J, Kotler DP, Harel Y, Van Der Schueren BJ, et al. Accelerated gastric emptying but no carbohydrate malabsorption 1 year after gastric bypass surgery (GBP). Obes Surg. 2012;22:1263-7.
85. Allaix ME, Fisichella PM, Noth I, Mendez BM, Patti MG. The pulmonary side of reflux disease: from heartburn to lung fibrosis. J Gastrointest Surg. 2013;17:1526-35.
86. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. New Engl J Med. 2010;363:1128-38.
87. Sontag SJ, O'Connell S, Khandelwal S, Greenlee H, Schnell T, Nemchausky B, et al. Asthmatics with gastroesophageal reflux: long term results of a randomized trial of medical and surgical antireflux therapies. Am J Gastroenterol. 2003;98:987–99.
88. Perrin-Fayolle M, Gormand F, Braillon G, Lombard-Platet R, Vignal J, Azzar D, et al. Long-term results of surgical treatment for gastroesophageal reflux in asthmatic patients. Chest. 1989;96:40–5.
89. Eryuksel E, Dogan M, Olgun S, Kocak I, Celikel T. Incidence and treatment results of laryngopharyngeal reflux in chronic obstructive pulmonary disease. Eur Arch Otorhinolaryngol. 2009;266:1267-71.
90. Sweet MP, Patti MG, Hoopes C, Hays SR, Golden JA. Gastro-oesophageal reflux and aspiration in patients with advanced lung disease. Thorax. 2009;64:167-73.
91. Hartwig MG, Anderson DJ, Onaitis MW, Reddy S, Snyder LD, Lin SS, Davis RD. Fundoplication after lung transplantation prevents the allograft dysfunction associated with reflux. Ann Thorac Surg. 2011;92:462–8..

ORIGINAL ARTICLE

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Can three-dimensional anorectal ultrasonography be included as a diagnostic tool for the assessment of anal fistula before and after surgical treatment?

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ABSTRACT – **Background** – There is no a clear knowledge concerning the division of any part of the anal sphincter complex and the effect of this procedure on the function of the anal canal during the treatment of perianal fistula. **Objective** – To evaluate the usefulness of 3D anorectal ultrasound in the assessment of anal fistula, quantifying the length of the sphincter muscle to be transected, selecting patients for different approaches and identifying healing, failure or recurrence after the surgical treatment. **Methods** – A prospective study included patients with primarily cryptogenic transsphincteric anal fistula assessed by fecal Incontinence score, tri-dimensional anorectal ultrasound and anal manometry before and after surgery. Based on 3D-AUS, patients with ≥50% external sphincter or external sphincter+puborectalis muscle involvement in males and ≥40% external sphincter or external sphincter+puborectalis muscle in females were referred for the ligation of the intersphincteric tract (LIFT) or seton placement and subsequent fistulotomy; and with <50% involvement in males and <40% in females were referred to one-stage fistulotomy. After surgery, the fibrosis (muscles divided) and residual muscles were measured and compared with the pre-operative. **Results** – A total of 73 patients was included. The indication for the LIFT was significantly higher in females (47%), one-stage fistulotomy was significantly higher in the males (46%) and similar in seton placement. The minor postoperative incontinence was identified in 31% of patients underwent sphincter divided and were similar in both genders. The 3D-AUS identified seven failed cases. **Conclusion** – The 3D ultrasound was shown to be an effective method in the preoperative assessment of anal fistulas by quantifying the length of muscle to be divided, as the results were similar at the post-operative, providing a safe treatment approach according to the gender and percentage of muscle involvement. Additionally, 3D ultrasound successfully identified the healing tissue and the type of failure or recurrence.

HEADINGS – Anorectal malformations. Rectal fistula. Fecal incontinence. Ultrasonics.

INTRODUCTION

The management of anal fistulas depends on fistula anatomy and identification of all the components, such as, primary and secondary tract(s) and internal opening(s), as well as the extent of operative sphincter division and association with healing rates and functional compromise[1].

Bi or tri-dimensional ultrasound and magnetic resonance image (MRI) have proven useful in the assessment of fistula-in-ano, with concordance with operative findings in 73% to 100% of cases[2-5]. Studies have reported some degree of fecal incontinence in up to 73% of patients who underwent fistulotomy, according to the risk factors of the patient, including preoperative incontinence, recurrent disease, female gender, complex fistulas, and previous fistula surgery[6-9]. There is no a clear knowledge concerning the division of any part of the anal sphincter complex and the effect of this procedure on the function of the anal canal during the treatment of perianal fistula, nor concerning the follow-up with images after damage to the anal sphincter. Therefore, this study aimed to evaluate the usefulness of three-dimensional anorectal ultrasound (3D-AUS) in the assessment of anal fistula, quantifying the length of the sphincter muscle to be transected, selecting patients for different approaches and identifying healing, failure or recurrence after the surgical treatment.

METHODS

Between March 2009 and May 2016, consecutive patients with primarily cryptogenic transsphincteric anal fistula were assessed through the Cleveland Clinic Fecal Incontinence score (CCFIS)[10], 3D-AUS and anal manometry before surgery and within 4 months after wound healing was complete. Subsequently, patients underwent surgery at *Hospital das Clínicas* (Federal University of Ceará) or at *Hospital São Carlos*, both of which are in Fortaleza, Brazil. After surgery, the percentage of fibrosis (muscles divided) and residual muscles were measured using 3D-AUS and compared with the pre-operative findings. Anal pressures were measured before and

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after surgery. Patients with inflammatory bowel disease, human immunodeficiency virus (HIV), anal sphincter injury, fecal incontinence symptoms and a history of colorectal and proctological surgery or vaginal delivery were excluded. The clinical protocol was approved by the Research Ethics Committee of the Walter Cantídio University Hospital, and all patients gave written informed consent.

Assessments and follow-up

- **Three-dimensional anorectal ultrasonography (3D-AUS)**

A 3D ultrasound endoprobe (model 2052; 16 MHz; focal distance 3.0-3.5 cm, type Pro-Focus, BK Medical®) was used. Images up to 6.0 cm in length were automatically captured along the proximal-distal axis, with duration of up to 50 seconds, by moving two crystals on the extremity of the transducer without moving the probe. The examination involved a series of transaxial microsections up to 0.20 mm thick producing a high-resolution digitalized volumetric image. Volume was displayed as a 3D cube image and recorded and analyzed in multiple planes. Patients were examined in the left lateral position after rectal enema (completed two hours prior to scanning). After the digital rectal examination, the endoprobe was introduced as far as the upper anal canal. Two scans were performed. The second scan was performed after injection of 0.3-1.0 mL 10.0% hydrogen peroxide (H_2O_2) through the external fistulous opening, using an angiocatheter for infants. The length of the external anal sphincter (EAS), the internal anal sphincter (IAS), the total length of the compromised sphincter (distance from the distal part of each muscle to the point where it was crossed by the fistulous tract) and the percentage of sphincter muscle to be transected (length of the compromised sphincter divided by total muscle length) were measured (FIGURE 1). Based on these findings, patients with ≥50% EAS or EAS plus puborectalis (EAS-PR) muscle involvement in males and ≥40% EAS or EAS-PR in females were referred for the ligation of the intersphincteric tract (LIFT) or seton placement and subsequent fistulotomy in two or three steps to induce fibrosis. Patients with <50% EAS involvement in males and <40% EAS involvement in females were referred to one-stage fistulotomy. After surgery, the percentage of the fibrosis (muscles divided) and residual muscles were measured using 3D-AUS and compared with the pre-operative findings (FIGURES 1 and 2) (FIGURE 3). The anal pressures were measured before and after surgery.

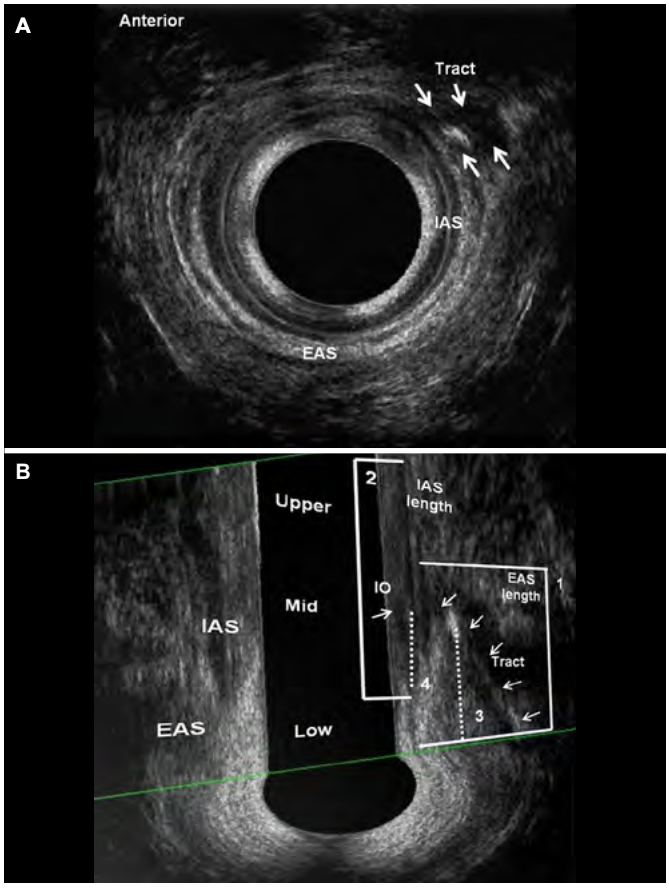

FIGURE 1. Before surgery – hydrogen peroxide-enhanced 3-DAUS image of female patient with anterior transsphincteric fistula in the 13 o'clock position. The length of the EAS (line 1), the IAS (2), the length of the EAS (3-dotted line) and the IAS (4-dotted line) compromised by the fistulous tract are indicated. The tract compromised >50% of anterior EAS. (a) Axial plane – mia anal canal. (b) Coronal and oblique plane. EAS: external anal sphincter; IAS: internal anal sphincter; IO: internal opening.

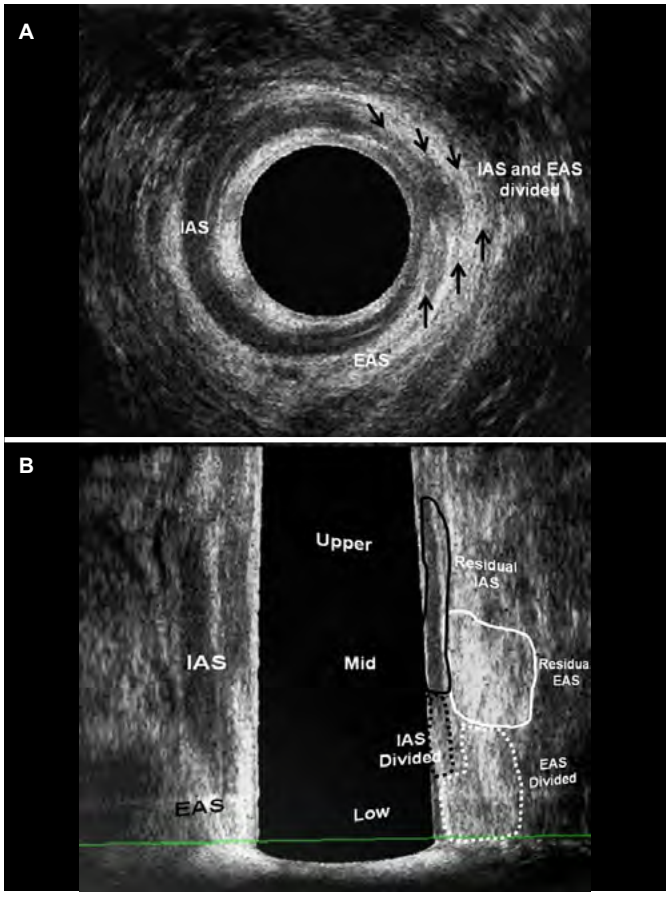

FIGURE 2. After surgery – patient (Fig. 1) underwent seton placement and subsequent fistulotomy in two. (a) Axial plane – the fibrosis that correspond the IAS and EAS divided (arrows). (b) Coronal and oblique plane – the fibrosis – EAS and IAS divided (dotted area) and residual EAS and IAS (area). EAS: external anal sphincter; IAS: internal anal sphincter; IO: internal opening.

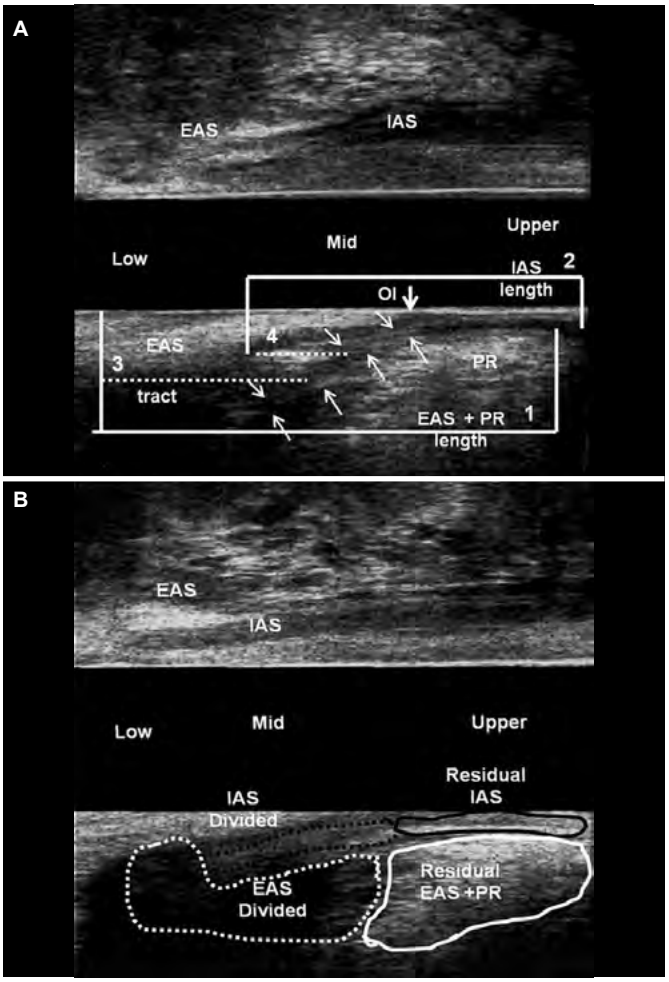

FIGURE 3. (a) Before surgery – hydrogen peroxide-enhanced 3-DAUS image of male patient with posterior transsphincteric fistula in the 6 o'clock position. The length of the EAS+PR (line 1) and the IAS (2), the length of the EAS +PR (3 dotted line) and the IAS (4 dotted line) compromised by the fistulous tract are indicated. (b) After surgery – sagittal plane – the fibrosis – EAS+PR and IAS divided (dotted area) and residual EAS+PR and IAS (area). EAS: external anal sphincter; EAS+PR: external anal sphincter+puborectal; IAS: internal anal sphincte; PR: puborectal muscle; IO: internal opening.

All patients were examined by a single colorectal surgeon (SMMR) with experience in 3D-AUS and all measurements before surgery and after (within 4 months after wound healing was completed) were blinded.

The operative technique was chosen according to the ultrasound findings and the same expert team of 3 colorectal surgeons specialized in coloproctology (Brazilian Board of Colorectal Surgery) operated all patients.

• Anorectal manometry

Anorectal manometry was performed in the all patients before surgery and within 4 months after wound healing was complete. A flexible, polyethylene, water-perfused catheter and an 8-channel manometer were used with ProctoMaster software (DynaMed, São Paulo, Brazil) to calculate anal canal pressure at rest and maximum anal squeeze pressure. All evaluations of manometric data were performed by the same examiner.

• Clinical follow-up

Clinical evaluation of wound healing was performed weekly until the wound healing was complete and incontinence was assessed by means of the CCFIS within 4 months after wound healing was complete.

Statistical analysis

Males and females were compared with regard to the percentage of EAS, EAS-PR and IAS sphincter muscle to be transected, as well as CCFIS, the percentage of sphincter muscle to be transected and anal pressures before and after surgery within 4 months after wound healing was complete). Differences between groups were assessed by means of Student's *t*-test and one-way ANOVA for continuous data. The level of statistical significance was set at $P<0.05$.

Data were analyzed using SPSS software (version 14.0 for Windows; IBM-SPSS, Chicago, IL).

RESULTS

Patient characteristics

A total of 73 patients with median age 39 years (range, 17- 66 years) were eligible (39 male and 34 female). All of them did not complain of fecal incontinence and the CCFIS was 0. Of these, in 46 (63%) patients, of both genders, the fistulous tract was positioned in the anterior quadrant. The percentage of the anterior EAS to be transected was significantly higher in the females than the males, while the percentage of anterior internal anal sphincter (IAS) was similar. The percentage of the posterior EAS-PR was similar in both genders, with the percentage of the posterior IAS being significantly higher in the males (TABLE 1).

TABLE 1. 3D-AUS data before surgical treatment for anal fistula.

Ultrasound finding	Male	Female	*P*
Before surgery	39 (53%)	34 (47%)	
Anterior / posterior tract position	21 / 18	25 / 9	0.49
Percentage of anterior EAS to be transected mean (SD)	44% (±19)	59% (±16)	0.00
Percentage of anterior IAS to be transected mean (SD)	33% (±07)	32% (±14)	0.86
Percentage of posterior EAS-PR to be transected mean (SD)	45% (±18)	47% (±14)	0.60
Percentage of posterior IAS to be transected mean (SD)	38% (±12)	22% (±08)	0.00

EAS: external anal sphincter; IAS: internal anal sphincter; EAS-PR: external anal sphincter plus puborrectalis muscles.

Operative technique

The indication for the LIFT procedure was significantly higher in females (47% – 16/34), with seton placement and subsequent fistulotomy in two or three steps (35% – 12/34) and the fistulous tract being positioned in the anterior quadrant. However, in the male patients, the position of the fistulous tract was balanced, comparing anterior with posterior (10 vs 11). Of them, 12 (31%) male patients underwent a seton placement and 9 (23%) LIFT (TABLE 2).

TABLE 2. Treatment Approach according to gender and fistula tract position.

Treatment approach (n)	Male 39 (53%)	Female 34 (47%)	*P*
Seton placement with subsequent fistulotomy (n=24)			
Anterior tract position	04	11	0.80
Posterior tract position	08	01	
LIFT (n=25)			
Anterior tract position	06	14	0.00
Posterior tract position	03	02	
Fistulotomy (n=24)			
Anterior tract position	11	00	0.01
Posterior tract position	07	06	

LIFT: ligation of the intersphincteric tract.

In total, the LIFT procedure was performed in 25 patients. Of these, 16 were female (14 in the anterior quadrant) and 9 male (6 in the anterior quadrant). The 3D-AUS identified complete healing in 20/25 (80%), visualizing fibrosis in the intersphincteric space (IS) and in the extrasphincteric position (EP) previously occupied by the external opening (FIGURES 4 and 5). Of them, in two cases the healing was delayed due to the small persistent cavity in the IS space and the previous EP (FIGURE 6), both of

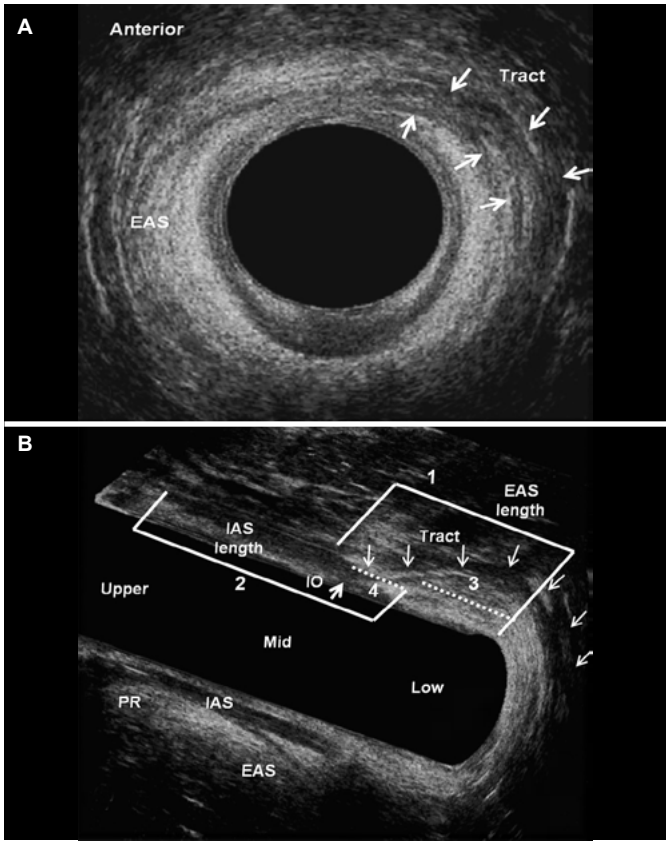

FIGURE 4. Hydrogen peroxide-enhanced 3-DAUS image of female patient with anterior transsphincteric fistula in the 1 o'clock position. The length of the EAS (line 1), the IAS (2), the length of the EAS (3-dotted line) and the IAS (4- dotted line) compromised by the fistulous tract are indicated. The tract compromised >50% of anterior EAS. (a) Axial plane – mia anal canal. (b) Sagittal and coronal plane. EAS: external anal sphincter; IAS: internal anal sphincter; PR: puborectal muscle; IO: internal opening

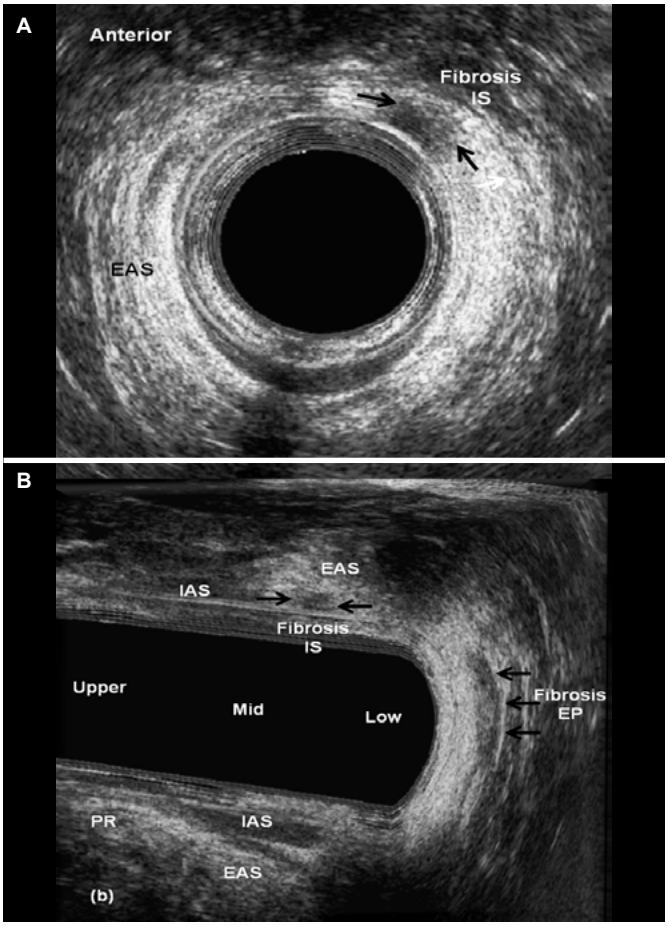

FIGURE 5. After surgery – patient (Fig. 4) underwent a LIFT procedure and identified the complete healing by visualizing fibrosis in the intersphincteric space (IS) and in the extrasphincteric position (EP) previously occupied by the external opening (arrows). (a) Axial plane – mid anal canal. (b) Sagittal and coronal plane. EAS: external anal sphincter; IAS: internal anal sphincter; PR: puborectal muscle; IO: internal opening.

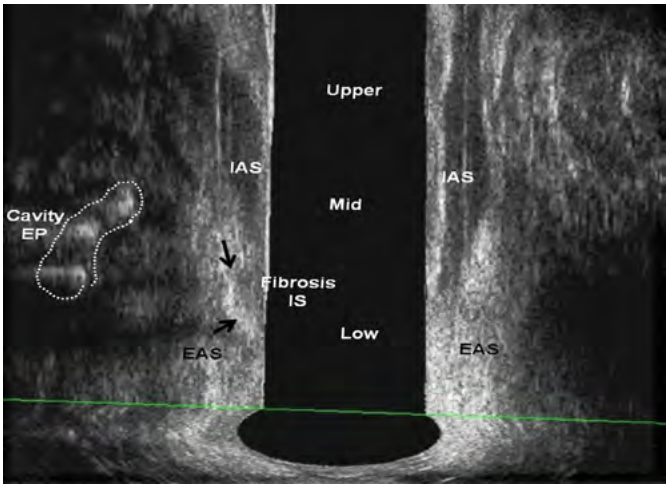

FIGURE 6. After surgery – patient underwent a LIFT procedure and identified small cavity in the extrasphincteric position (EP) (area) and the fibrosis in the intersphincteric space (IS) (arrows). EAS: external anal sphincter; IAS: internal anal sphincter.

whom were treated conservatively. The 3D-AUS identified five failed cases, one as intersphincteric fistula and four due to recurrences of transphincteric fistula. All of these patients underwent another surgical procedure. Of these, four cases of transphincteric fistula: two underwent LIFT and two seton placement with subsequent fistulotomy and one case of intersphincteric fistula were underwent one-stage fistulotomy.

The indication for one-stage fistulotomy was significantly higher in the male patients (18/39 – 46%). Of these, in 11 patients the fistulous tract was positioned in the anterior quadrant. In all the female cases (six) the fistulous tract was positioned in the posterior quadrant (TABLE 2).

Functional outcomes and follow-up

The median postoperative follow-up was 14 months (range, 6–48 months). The patients were re-assessed 3 to 4 months after complete wound healing by means of the CCFIS, the 3D-AUS examination and anorectal manometry. Overall, minor postoperative fecal incontinence symptoms were identified in 23/73 (31%) patients and were similar in both genders. Of them, 15 patients underwent seton placement and 8 underwent one-stage fistulotomy (TABLE 3). The median CCFIS was similar comparing the males (median=0 / range, 0-8) and females (median =2 / range, 0-6). The 3D-AUS findings were concordant with the surgical findings in all cases (TABLE 3). The success rate of healing was 96%, identified by 3D-AUS after 4 months in patients that underwent seton placement and one-stage fistulotomy. The percentage of the anterior EAS, anterior IAS, posterior EAS-PR and posterior IAS were similar comparing the percentage of muscles to be transected before surgery with the percentage of fibrosis after sphincter division in both genders, measured by 3D-AUS in patients that underwent of seton placement and one-stage fistulotomy (TABLE 4). There was a significant reduction in resting and squeeze anal pressures after surgery (TABLE 5). The 3D-AUS identified two failed cases, both having undergone seton placement and fistulotomy. In all cases that underwent LIFT, there were no postoperative changes in the anal pressures or reports of FI.

TABLE 3. Fecal incontinence symptoms in patients underwent sphincter divided surgical technique.

Functional results	Male 39 (53%)	Female 34 (47%)	*P*
Fecal incontinence	11 (28)	12 (35)	0.61
FIS median (range)	0 (0-8)	2 (0-6)	0.45
Fecal incontinence – Seton placement (n=24)	07	08	0.57
Anterior tract position	03	07	
Posterior tract position	04	01	
Fecal Incontinence – Fistulotomy (n=24)	04	04	1.00
Anterior tract position	04	00	
Posterior tract position	00	04	

FIS: Wexner fecal incontinence score.

TABLE 5. Anorectal manometry outcomes before versus after surgical treatment for anal fistula in patients underwent sphincter divided.

Anorectal manometry	Sex	Mean (SD)	*P*
Resting pressure (mmHg)	Male	77±12 vs 54±13	0.00
	Female	77±23 vs 56±08	0.02
Squeeze pressure (mmHg)	Male	190±49 vs 135±34	0.00
	Female	160±47 vs 100±27	0.01
Total of patients = 73 [Male 39 (53%) Female 34 (47%)]			

DISCUSSION

This study demonstrates that the use of 3D-AUS to assess anal fistula can provide preoperative mapping of the anal fistula, identify all the components, such as, the position and type of the primary and secondary tract(s), internal opening(s), as well as quantify the length of the sphincter muscle to be transected. This makes it possible to plan the best approach for each patient according to the gender, position of the tract and the percentage of sphincter muscle transected by the tract. For decisions regarding postoperative follow-up, 3D-AUS identified the cases of healing and those that had recurrence and needed a further surgical procedure. Furthermore, the 3D-AUS visualized cases with delayed healing without recurrence, for the application of conservative treatment. More importantly, the exam image avoided repeated surgical interventions in two cases, in which only persistent small cavities without tract were identified, and classified five cases of recurrence after the LIFT procedure and two cases after seton placement and fistulotomy. Patients that undergo divided muscles should be followed with images due to the increased risk of fecal incontinence if they have history of vaginal delivery or undergo a further anorectal procedure due to newly developed perianal fistula.

The 3D-AUS with automatic scanning, high frequency and multiplane images makes it possible to provide accurate measures of the length of the muscles and the tract up to the location where it is crossed by the sphincter muscles, with this study comparing the results related to the percentage of the compromised muscles before and after surgery in those patients that underwent a sphincter divided approach. This method is well tolerated and is minimally invasive, because the endoprobe is kept stationary during image acquisition.

Table 4. 3D-us outcomes before and after surgical treatment for anal fistula in patients underwent sphincter divided.

Ultrasound finding	Male 39 (53%)	Female 34 (47%)	*P*
Percentage of anterior EAS divided before vs after surgery – mean (SD)	39% ±18 vs 40% ±15	59% ±12 vs 55% ±11	>0.05
Percentage of anterior IAS divided before vs after surgery – mean (SD)	32% ±18 vs 35% ±17	32% ± 09 vs 33% ±10	>0.05
Percentage of posterior EAS-PR divided before vs after surgery – mean (SD)	36% ±14 vs 32% ±09	45% ±17 vs 46% ±14	>0.05
Percentage of posterior IAS divided before vs after surgery – mean (SD)	38% ±13 vs 39% ±11	20% ±08 vs 26% ±10	>0.05

Eas: external anal sphincter; IAS: internal anal sphincter; EAS-PR: external anal sphincter plus puborrectalis muscles.

In the present study, patients with recurrent cryptogenic fistula, inflammatory bowel disease, human immunodeficiency virus (HIV), anal sphincter injury, fecal incontinence symptoms, a history of vaginal delivery or previous injured muscles according to 3D-AUS were excluded in order to ensure homogeneity in the study population and reduce bias. The 3D-AUS examiners were also blinded before and after the surgery concerning the percentage of muscles transected.

Despite the previous definition of complex anal fistula, including transphincteric fistulas that involve greater than 30% of the external sphincter[11-13], in the present study, all patients with ≥50% EAS or EAS-PR muscle involvement in males and ≥40% EAS or EAS-PR in females were referred for sphincter preservation surgery, such as LIFT. However, one of the group of three surgeons did not have sufficient training to perform LIFT and chose seton placement and subsequent fistulotomy in two or three steps. The difference in the percentage of muscles compromised according to gender was based on the difference of the anterior length and the distribution of the muscles comparing males with females. The anterior EAS is shorter in females and the percentage of compromised muscles is high[14]. Female patients with less than 40% and males with less than 50% of striated muscles underwent one-stage fistulotomy. All the techniques presented high healing rates, as reported in the literature[15-19]. However, 23/48 (50%) of the patients that had sphincter muscles divided (15 underwent seton and 8 fistulotomy) complained of fecal incontinence, although with low CCFS, similar to the literature that reported incontinence ranging from 4% to 62%[7,20-22].

The high rate of patients that complained of FI, even with low CCFIS, may be explained by the high values of the percentage of muscle compromised by the tract and referred to sphincter divided surgery stablished in this study in both genders, which failed to select patients that would have good functional results. The results suggest that the percentage of muscles transected should be lower than used in this study, even in those cases where the tract position was in the posterior, as seen in 9/48 (20%) cases that complained of FI (five cases underwent seton and four cases fistulotomy). Furthermore, all patients of this study had no associated risk factors, such as, preoperative incontinence, recurrent disease, female gender, complex fistulas, and previous fistula surgery, which could justify the FI symptoms.

Thus, surgeries that preserve the sphincter should be the first option of anal fistula treatment, even considering that these procedures have demonstrated higher rates of recurrence compared to fistulotomy[17-19,23,24]. Studies in the literature are controversy concerning the amount of sphincter muscle that can be safely divided in anal fistula, some have reported that the division of less than 30% of the external anal sphincter carries a minimal risk of postoperative FI[11-13]. Conversely, Garcés-Albir et al.[25]. reported that the division of the lower 66% of the external anal sphincter was associated with excellent rates of continence and healing in patients who lacked risk factors before surgery.

In this study, 1/3 of the patients underwent sphincter-sparing (LIFT) procedures that results in healing in over 80% of the patients, with the sphincter function preserved in all of them, with similar results presented in the literature[17-19].

As demonstrated in this study, the high accuracy of 3D-AUS in quantifying the percentage of sphincter muscle compromised by the tract before the surgery was demonstrated by the similar results after the surgery, considering the measurements of the percentage of fibrosis that substituted the muscles cut and the percentage of residual muscles. A further study should establish the percentage of muscles that can be divided in different situations, such as, for each tract position (anterior or posterior) and for each gender, to avoid FI symptoms. Weaknesses in the study included the small number of patients in each subgroup, considering the gender, position of the tract and percentage of compromised muscles, which did not allow the parameters to be evaluated separately. In addition, further studies should compare all measurements performed by 3D-AUS imaging with MRI.

CONCLUSION

The 3D-AUS was shown to be an effective method in the preoperative assessment of anal fistulas by quantifying the length of muscle to be divided, as the results were similar at the post-operative moment, providing a safe treatment approach according to the gender and percentage of muscle involvement. Additionally, 3D-US successfully identified the healing tissue and the type of failure or recurrence.

Authors' contribution

Murad-Regadas SM: study design, ultrasonography, critical revision for intellectual content. Regadas Filho FSP and Veras LB: data acquisition, interpretation of data and drafting the article. Holanda EC and Lopes MS: data acquisition and drafting the article.

Murad-Regadas SM, Regadas Filho FSP, Holanda EC, Veras LB, Vilarinho AS, Lopes MS. O ultrassom anorretal tridimensional pode ser incluído como um método diagnóstico na avaliação da fístula anal antes e após o tratamento cirúrgico? Arq Gastroenterol. 2018;55(Suppl 1):18-24.

RESUMO – **Contexto** – Não há dados definitivos quanto a níveis diferentes na secção do complexo esfincteriano e o efeito na função do canal anal no tratamento das fístulas anais. **Objetivo** – Avaliar a aplicação do ultrassom anorretal tridimensional no diagnóstico da fístula anal, quantificando o comprimento da musculatura que será seccionada, selecionando pacientes para diferente abordagens e identificando cicatrização e recorrência após tratamento. **Métodos** – Um estudo prospectivo incluindo paciente portadores de fístula anal criptoglandular, tipo trans-esfinctérica avaliados pelo escore de incontinência fecal, ultrassom anorretal 3D e manometria anorretal antes e após a cirurgia. De acordo com os dados do ultrassom, pacientes do sexo masculino com envolvimento ≥50% do esfíncter externo anterior ou esfíncter externo+puborretal e do sexo feminino com envolvimento ≥40% foram referidos para cirurgia de ligadura do trajeto no espaço inter-esfinctérico (LIFT) ou colocação do sedenho. Aqueles com envolvimento <50% em homens e <40% mulheres foram indicados para fistulotomia em um tempo. Após a cirurgia, a musculatura secccionada (fibrose) e o músculo residual foram medidos e comparados no pós-operatório. **Resultados** – Um total de 73 pacientes foi incluído. A indicação para LIFT foi significativamente maior em mulheres (47%) e a fistulotomia em homens (46%) e o sedenho similar em ambos os sexos. Sintomas de incontinência leve foi identificado em 31% dos submetidos à cirurgia com divisão de esfíncter e similar em ambos os sexos. O ultrassom identificou sete casos que não cicatrizaram. **Conclusão** – O ultrassom anorretal tridimensional demonstrou ser um método efetivo na avaliação da fístula anal, quantificando o comprimento do esfíncter a ser dividido, como demonstrado no resultado pós-operatório, fornecendo um tratamento seguro de acordo com sexo e percentual de músculo envolvido. Adicionalmente, identifica o tecido cicatrizado, tipo de recorrência e a falha no tratamento

DESCRITORES – Malformações anorretais. Fístula retal. Incontinência fecal. Ultrassom.

REFERENCES

1. Vogel JD, Johnson EK, Morris AM, Paquette IM, Saclarides TJ, Feingold DL, Steele SR. Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. Dis Colon Rectum. 2016;59:1117-33.
2. Gustafsson UM, Kahvecioglu B, Aström G, Ahiström H, Graf W. Endoanal ultrasound or magnetic resonance imaging for preoperative assessment of anal fistula: a comparative study. Colorectal Dis. 2001;3:189-97.
3. West RL, Dwarkasing S, Felt-Bersma RJ, Schouten WR, Hop WC, Hussain SM, Kuipers EJ. Hydrogen peroxide-enhanced three dimensional endoanal ultrasonography and endoanal magnetic resonance imaging in evaluating perianal fistulas: agreement and patient preference. Eur J Gastroenterol Hepatol. 2004;16:1319-24.
4. Buchanan GN, Halligan S, Bartram CI, Williams AB, Tarroni D, Cohen CR. Clinical examination, endosonography, and MR imaging in preoperative assessment of fistula in ano: comparison with outcome-based reference standard. Radiology. 2004;233:674-81.
5. Murad-Regadas SM, Regadas FSP, Rodrigues LV, Holanda EC, Barreto RG, Oliveira L. The role of 3-Dimensional anorectal ultrasonography in the assessment of anterior transsphincteric fistula. Dis Colon Rectum. 2010;53:1035-40.
6. Garcia-Aguilar J, Belmonte C, Wong WD, Goldberg SM, Madoff RD. Anal fistula surgery: factors associated with recurrence and incontinence. Dis Colon Rectum. 1996;39:723-9.
7. van Tets WF, Kuijpers HC. Continence disorders after anal fistulotomy. Dis Colon Rectum. 1994;37:1194-7.
8. Van Koperen PJ, Wind J, Bemelman WA, Bakx R, Reitsma JB, Slors JFM. Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of criptoglandular origin. Dis Colon Rectum. 2008;51:1475-81.
9. Roing JV, Jordán J, García-Armengol J, Esclapez P, Solana A. Changes in anorectal morphologic and functional parameters after fistula-in-ano surgery. Dis Colon Rectum. 2009;52:1462-8.
10. Jorge, JMN, Wexner, SD. Etiology and management of fecal incontinence. Dis Colon Rectum. 199:36:77-97.
11. Kondylis PD, Shalabi A, Kondylis LA, Reilly JC. Male cryptoglandular fistula surgery outcomes: a retrospective analysis. AmJ Surg. 2009;197:325-30.
12. Sangwan YP, Rosen L, Riether RD, Stasik JJ, Sheets JA, Khubchandani IT. Is simple fistula-in-ano simple? Dis Colon Rectum. 1994;37:885-9.
13. Zmora O, Neufeld D, Ziv Y, Tulchinsky H, Scott D, Khaikin M, et al. Prospective, multicenter evaluation of highly concentrated fibrin glue in the treatment of complex cryptogenic perianal fistulas. Dis Colon Rectum. 2005;48:2167-72.
14. Regadas FSP, Murad-Regadas SM, Lima DMR, Silva FR, Barreto RGL, Souza MHLP, Regadas Filho FSP. Anal canal anatomy showed by three-dimensional anorectal ultrasonography. Surg Endoscopy. 2007;21:2207-11.
15. Davies M, Harris D, Lohana P, Chandra Sekaran TV, Morgan AR, Beynon J, Carr ND. The surgical management of fistula-in-ano in a specialist colorectal unit. Int J Colorectal Dis. 2008;23:833–8.
16. Ritchie RD, Sackier JM, Hodde JP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis. 2009;11:564-71.
17. Sunoda A, Sada H, Sugimoto T, Nagata H, Kano N. Anal function after ligation of the intersphincteric fistula tract. Dis Colon Rectum. 2013;56:898-902.
18. Hong KD, Kang S, Kalaskar S, Wexner SD. Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis. Tech Coloproctol. 2014;18:685-91.
19. Alasari S, Kim NK. Overview of anal fistula and systematic review of ligation of the intersphincteric fistula tract (LIFT). Tech Coloproctol. 2014;18:13-22.
20. Lunniss PJ, Kamm MA, Phillips RK. Factors affecting continence after surgery for anal fistula. Br J Surg. 1994;81:1382-5.
21. Cavanaugh M, Hyman N, Osler T. Fecal incontinence severity index after fistulotomy: a predictor of quality of life. Dis Colon Rectum. 2002;45:349-53.
22. Ritchie RD, Sackier JM, Hodde JP. Incontinence rates after cutting seton treatment for anal fistula. Colorectal Dis. 2009;11:564-71.
23. Jarrar A, Church J. Advancement flap repair: a good option for complex anorectal fistulas. Dis Colon Rectum. 2011;54:1537-41.
24. Champagne BJ, O'Connor LM, Ferguson M, Orangio GR, Schertzer ME, Armstrong DN. Efficacy of anal fistula plug in closure of cryptoglandular fistulas: long-term follow-up. DisColon Rectum. 2006;49:1817-21.
25. Garcés-Albir M, García-Botello SA, Esclapez-Valero P, Sanahuja-Santafé A, Raga-Vázquez J, Espi-Macías A, Ortega-Serrano J. Quantifying the extent of fistulotomy. How much sphincter can we safely divide? A three-dimensional endosonographic study. Int J Colorectal Dis. 2012;27:1109-16.

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Water ingestion dynamics in patients with achalasia: influence of sex and age

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ABSTRACT – **Background** – Achalasia is a disease that affects esophageal bolus transit due to the absence of esophageal peristaltic contractions and impaired or absent relaxation of the lower esophageal sphincter. **Objective** – The objective of this investigation was: a) to evaluate the dynamics of water ingestion in patients with achalasia, idiopathic or caused by Chagas' disease; b) to evaluate the influence of sex and age on water ingestion dynamics. **Methods** – The investigation was conducted with 79 patients with achalasia (27 idiopathic and 52 Chagas' disease) and 91 healthy volunteers, all evaluated by the water-drinking test. The individuals drank, in triplicate, 50 mL of water without interruption. The time and the number of swallows for this task were counted. We also measured: (a) inter-swallow interval – the time to complete the task, divided by the number of swallows during the task; (b) swallowing rate – volume drunk divided by the time; (c) volume per swallow – volume drunk divided by the number of swallows. **Results** – Patients with achalasia took longer to ingest all the volume (mean 12.2 seconds) than healthy controls (mean 5.4 seconds), had greater number of swallows, longer interval between swallows, lower swallowing rate (5.2 mL/s vs 10.9 mL/s in controls) and lower volume per swallow (9.1 mL vs 14.4 mL in controls, $P<0.01$). Among healthy volunteers, women had a shorter interval between swallows and lower volume per swallow compared with men, and in the achalasia group, women had a longer interval between swallows and lower ingestion rate. No difference in the drinking test results was found between younger and older subjects in achalasia or control group. Also, no differences were observed between patients with Chagas' disease and those with idiopathic achalasia, or between patients with increased and normal esophageal diameter. **Conclusion** – Patients with achalasia have difficulty in ingesting water, taking a longer time to complete the task, which is influenced by sex but not by age or severity of the disease.

HEADINGS – Deglutition disorders. Esophageal achalasia. Chagas' disease. Esophagus. Deglutition. Esophageal diseases. Esophagogastric junction.

INTRODUCTION

Dysphagia for liquid and solid foods and regurgitation are the most frequent symptoms of achalasia[1-7], an esophageal motility disorder caused by impairment or loss of the neurons of the esophageal myenteric plexus[1-7], with decreased or absent lower esophageal sphincter (LES) relaxation and loss of peristaltic contractions in the esophageal body[1,4,5]. Achalasia may be idiopathic[1,2,4] or associated with a known disease[8], such as Chagas' disease, a tropical parasitic disease caused by the flagellate protozoan *Trypanosoma cruzi*[6,7].

Patients with achalasia caused by Chagas' disease take longer to drink a volume of water, with slower swallowing rate and lower volume in each swallow than controls subjects[9]. Previous investigations showed, using the water-drinking test, that healthy women, compared with healthy men, have lower swallowing capacity and volume per swallow[10,11]. In addition, aging process causes a decline in the volume per swallow and in swallowing capacity[10]. However, the effect of age and sex have not been reported in achalasia. Our hypothesis was that sex and age have influence on the dynamics of water ingestion in patients with achalasia.

Our aim in this investigation was to: a) evaluate the dynamics of water ingestion in patients with achalasia and healthy volunteers; b) evaluate the effect of sex and age in water ingestion; c) evaluate the influence of the esophageal involvement by the disease on water ingestion; d) compare the results of idiopathic achalasia with achalasia caused by Chagas' disease.

METHODS

Seventy-nine patients (28 men; 35%) with achalasia, 50 caused by Chagas' disease and 29 with idiopathic achalasia, aged from 23 to 79 years (mean: 52.7 years, SD: 14.2 years) and 91 healthy volunteers (44 men; 48%) aged from 20 to 77 years (mean: 46.5, SD: 15.7 years) were included in the study.

Patients had dysphagia for liquid and solid foods, with esophageal retention of barium sulfate inside the esophageal body showed by radiologic examination. Upper digestive endoscopy was performed in all patients to rule out complications of the disease or other causes of dysphagia. The degree of esophageal involvement was assessed by anteroposterior radiograph of esophagus obtained at a fixed distance of 1.8 m at 10 seconds after the swallowing of 200 mL of liquid barium sulfate. The result was considered normal if there was no barium remaining in the esophagus; grade I esophageal disease if there was esophageal retention of barium sulfate but the distal esophageal diameter was less than 4 cm; or grade II if there was esophageal retention and the distal esophageal diameter was between 4 and 7 cm[12]. Epidemiology and serologic test for Chagas'

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disease was used to establish the diagnosis of idiopathic or Chagas' disease achalasia. Final diagnosis of achalasia was confirmed by manometric examination, performed with the method of water perfusion in all subjects with clinical and radiological suspect of achalasia. Aperistalsis in the esophageal body and impaired or absent relaxation of the lower esophageal sphincter were indicative of achalasia[1,8]. No patient had endocrine, neurologic or cardiologic diseases, and none of those with Chagas' disease had cardiac failure or cardiac arrhythmia[13].

Control group was composed of healthy volunteers from the same community as the patients, recruited by advertisement in the hospital. They did not have dysphagia, regurgitation, heartburn; or other digestive symptoms, endocrine, neurologic, cardiologic diseases or other notable systemic disease. The investigation was approved by the Human Research Committee of the University Hospital. All controls and patients gave written informed consent to participate in the study and the anonymity of each participant was preserved.

Swallowing dynamics was assessed by the water-drinking test[10,11,14-16]. In the sitting position, individuals were asked to drink in a "confortable" way without interruption 50 mL of water at room temperature from a plastic cup. A stopwatch was started when the first drop of water touched the lip, and stopped when the larynx of the volunteers came to rest after the last swallow. The drinking test was performed in triplicate, with an interval of at least 30 seconds between measurements. The mean of the three tests of each individual was used for analysis. The researchers involved in this study had previous training in timing and counting the swallows, which was defined as the number of movements of the upper larynx. The following parameters were also calculated: (a) inter-swallow interval – the time required to complete the task, in seconds, divided by the number of swallows during the task; (b) swallowing rate – volume of water (mL) divided by the time, in seconds; (c) volume in each swallow – volume drunk (mL) divided by the number of swallows.

Participants were grouped by sex (men and women), age (younger: 20-49 years, older: 50-79 years), severity of the esophageal radiological findings (Grade I or Grade II), and by etiology of the disease (idiopathic or Chagas). Mean age was 33.4 (7.7) years among younger and 61.1 (7.2) years among older subjects in the control group, and 38.3 (7.7) years and 63.1 (7.2) years among younger and older subjects, respectively, in the achalasia group.

Between-group comparisons were analyzed by covariance test (ANCOVA). Results are reported as mean and standard deviation (SD). All tests were two-tailed, and a p value of ≤0.05 was considered statistically significant.

RESULTS

Patients with achalasia had a longer time to ingest the water, a greater number of swallows, had a longer inter-swallows interval, a lower swallowing rate and a smaller volume per swallow (TABLE 1).

Women with achalasia had a longer inter-swallow interval and lower swallowing rate as compared with men with achalasia, whereas in control volunteers women had a shorter inter-swallow interval and a lower volume in each swallow than men (TABLE 2).

TABLE 1. Results of the water drinking test in patients with achalasia (n=79) and controls (n=91).

	Controls		Achalasia		*P*
	Mean (SD)	95% CI	Mean (SD)	95% CI	
Time (s)	5.4 (2.1)	5.0 – 5.9	12.2 (6.4)	10.8 – 13.7	< 0.01
Number of swallows	4.2 (1.5)	3.9 – 4.5	6.1 (2.0)	5.7 – 6.6	< 0.01
Inter-swallow interval (s)	1.4 (0.5)	1.3 – 1.5	1.9 (0.6)	1.8 – 2.1	< 0.01
Swallowing rate (mL/s)	10.9 (4.5)	10.0 – 11.9	5.2 (2.1)	4.7 – 5.6	< 0.01
Volume per swallow (mL)	14.4 (7.9)	12.7 – 16.0	9.1 (2.8)	8.4 – 9.7	< 0.01

TABLE 2. Results of the water drinking test patients with achalasia (n=79) and controls (n=91), by sex.

	Controls			Achalasia		
	Men (n=44)	Women (n=47)	*P*	Men (n=28)	Women (n=51)	*P*
Time (s)	5.4 (2.2)	5.4 (2.0)	0.79	10.3 (3.5)	13.3 (7.4)	0.07
Number of swallows	4.1 (1.6)	4.4 (1.3)	0.45	5.7 (1.4)	6.4 (2.2)	0.08
Inter-swallow interval (s)	1.5 (0.6)	1.3 (0.3)	0.05	1.7 (0.3)	2.1 (0.7)	0.04
Swallowing rate (mL/s)	11.2 (4.9)	10.7 (4.0)	0.61	5.7 (1.8)	4.9 (2.2)	0.03
Volume per swallow (mL)	16.2 (10.5)	12.7 (3.8)	0.03	9.5 (2.3)	8.8 (3.0)	0.23

Mean and (SD).

We found no effect of age on swallowing parameters in our study groups (TABLE 3). However, considering the age subgroups, healthy individuals aged 60-79 years (n=23) had a significantly lower swallowing rate (9.1 mL/s) than younger subjects (n=48, 11.8 mL/s, *P*=0.04), whereas in patients with achalasia (n=33) this difference was not observed (4.8 mL/s *vs* 5.4 mL/s, respectively, *P*>0.05). With respect of the volume per swallow these oldest group has a volume of 12.6 mL among the healthy volunteers and 9.1 mL among the achalasia patients, without differences with the younger group (controls: 15.1 mL, achalasia: 9.4 mL, *P*>0.05).

There was no difference between grade I and grade II achalasia patients, or between patients with idiopathic achalasia and those with Chagas' disease in swallowing parameters (*P*>0.30, TABLE 4).

DISCUSSION

As expected, water drinking test showed that patients with achalasia had difficulty in drinking 50 mL of water, probably due to altered esophageal motility and dysphagia.

Water ingestion in healthy individuals has shown to be different between men and women. Women have short interval between swallows, and lower number of swallows, swallowing rate and volume per swallows than men[11]. These findings were corroborated by our results, showing a shorter inter-swallows interval and a lower volume per swallows in healthy women than men. In addition, a more severe impairment of swallowing was found in women with achalasia than men, with a significant longer inter-swallow intervals and lower swallowing rate. However, the possibility that this difference may be caused by the influence of sex on swallowing behavior rather than by a more severe impairment of esophageal motility and transit than men cannot be ruled out. Also, differences in swallowing between men and women is a matter of controversy[17], and may not be clinically relevant among patients with achalasia. In healthy subjects, gender does not seem to influence esophageal motility[18].

Aging process has a clear influence on swallowing[19-23]. Swallowing capacity decreases as the individual gets older, with altered oral, pharyngeal and esophageal function[19], manifested by prolongation of oral and pharyngeal phases[23], esophageal motility abnormalities[23], and reduction in the cross-sectional area of the upper esophageal sphincter opening during swallows[19]. In patients with idiopathic achalasia without treatment, however, the frequency and severity of the symptoms are inversely correlated with age[24], which means that older subjects have less symptoms than younger ones, indicating that these functional abnormalities are not aggravated by aging. This is also seen in patients with Chagas' disease, in whom aging is not associated with aggravation of esophageal dysfunction[12].

During the aging process, there is a loss of the esophageal myenteric plexus[25,26], which explain the deterioration in esophageal motility and function in subjects with established esophageal motility disease[21]. This change, however, does not exacerbate esophageal dysfunction in achalasia, be it before or after treatment[24] or in Chagas' disease[12].

TABLE 3. Results of the water drinking test in younger (20-49 yeas) and older (50-79 years) patients with achalasia and control subjects.

	Controls			Achalasia		
	Younger (n=48)	Older (n=43)	*P*	Younger (n=30)	Older (n=49)	*P*
Time (s)	5.0 (1.9)	5.9 (2.2)	0.06	11.4 (6.0)	12.7 (6.7)	0.33
Number of swallows	4.2 (1.6)	4.3 (1.3)	0.75	5.7 (1.8)	6.4 (2.1)	0.07
Inter-swallow interval (s)	1.3 (0.5)	1.4 (0.5)	0.07	2.0 (0.6)	1.9 (0.6)	0.60
Swallowing rate (mL/s)	11.8 (4.9)	10.0 (3.8)	0.07	5.4 (2.0)	5.0 (2.1)	0.27
Volume per swallow (mL)	15.1 (9.9)	13.6 (4.9)	0.53	9.4 (2.4)	8.8 (3.0)	0.30

Mean (SD).

TABLE 4. Results of the water-drinking test in patients with grades I and II idiopathic achalasia and achalasia caused by Chagas disease.

	Idiopathic achalasia			Chagas' disease		
	Grade I (n=15)	Grade II (n=14)	Total (n=29)	Grade I (n=26)	Grade II (n=24)	Total (n=50)
Time (s)	12.9 (6.7)	14.2 (9.0)	13.5 (7.7)	11.0 (5.1)	11.8 (6.3)	11.4 (5.7)
Number of swallows	5.9 (1.7)	6.0 (2.6)	6.0 (2.1)	6.2 (1.9)	6.2 (2.1)	6.2 (2.0)
Inter-swallow interval (s)	2.2 (0.7)	2.1 (0.7)	2.1 (0.7)	1.8 (0.5)	1.9 (0.4)	1.8 (0.5)
Swallowing rate (mL/s)	4.9 (2.1)	5.4 (2.6)	5.2 (2.4)	5.5 (2.1)	5.1 (1.8)	5.3 (2.0)
Volume per swalow (mL)	9.4 (3.2)	9.6 (2.9)	9.5 (3.0)	8.9 (2.6)	9.1 (3.1)	9.0 (2.8)

Mean (SD). *P*>0.30 grade I vs grade II and Chagas' disease vs idiopathic achalasia.

Although one may expect that patients with increased esophageal diameter have a more severe esophageal dysfunction than patients with normal esophageal diameter, we did not find differences in the drinking test results between these subgroups of patients. It is possible that, for water ingestion, the most important influencing factor on bolus transit is the absence of lower esophageal sphincter relaxation, which may not be different between grades I and II. In fact, this is, at least in part, the reason for therapeutic success of achalasia by pneumatic dilation or myotomy, which promotes a reduction in the gastroesophageal junction resistance to flow and improvement of symptoms in patients grades I and II. In addition, despite known differences between achalasia caused by Chagas' disease and idiopathic[27-29], including altered pharyngeal transit[30,31], our results did not show differences in the test between patients with these conditions.

The investigation has some limitations. Drinking test results may be affected by the subjects' behavior and perception of dysphagia. However, reflects what happens to patients during the everyday water ingestion. The different results between men and women with achalasia could be consequence of a more intense esophageal impairment by the disease in women, however grade II in esophageal radiologic examination were more frequent in men (61%) than in women (43%). Evaluation of ingestion of other consistency, as a paste bolus, should added more information to the investigation.

In conclusion, patients with achalasia has difficulty in drinking water. This investigation showed a gender but not an age effect on the results of water-drinking test. The aging process do not seems to cause further deterioration of this functional test. There was no difference in swallowing parameters between patients with idiopathic achalasia and patients with Chagas' disease, or difference between patients with increased esophageal diameter and patients with normal esophageal diameter.

Authors' contribution

Dantas RO, Cassiani RA, Santos CM and Alves LMT: participated in the design of the study, in collection, analysis and interpretation of data, in the writing of the manuscript and in making the decision to submit it for publication.

Dantas RO, Cassiani RA, Santos CM, Alves LMT. Dinâmica da ingestão de água em pacientes com acalasia: influência de sexo e idade. Arq Gastroenterol. 2018;55(Suppl 1):25-9.

RESUMO – **Contexto** – Acalásia é uma doença que causa dificuldade no transporte do bolo deglutido da boca ao estômago, consequente à ausência das contrações peristálticas no esôfago e relaxamento parcial ou ausente do esfíncter inferior do esôfago. **Objetivo** – O objetivo desta investigação foi: a) avaliar a dinâmica da ingestão de água em pacientes com acalásia, idiopática ou causada pela doença de Chagas; b) avaliar a influência do sexo e da idade na dinâmica da ingestão de água. **Métodos** – A investigação foi realizada em 79 pacientes com acalásia (27 idiopática e 52 Chagas) e 91 voluntários saudáveis, todos avaliados pelo teste de ingestão de água. Os indivíduos ingeriam, em triplicata e sem pausas, 50 mL de água, a ingestão era cronometrada e o número de deglutições contadas. Também foram medidos: (a) intervalo entre deglutições – tempo para completar a tarefa, dividido pelo número de deglutições durante a tarefa; (b) fluxo de deglutição – volume ingerido dividido pelo tempo de ingestão; (c) volume de cada deglutição – volume ingerido dividido pelo número de deglutições. **Resultados** – Os pacientes com acalásia levaram mais tempo (média 12,2 segundos) para ingerir todo o volume que voluntários sadios (5,4 segundos), e apresentaram maior número de deglutições, intervalo mais longo entre as deglutições, menor fluxo de deglutição (5,2 mL/s vs 10,9 mL/s, nos controles) e menor volume em cada deglutição (9,1 mL vs 14,4 mL nos controles). Entre os voluntários saudáveis, as mulheres tiveram um intervalo entre deglutições mais curto e menor volume em cada deglutição em comparação aos homens e, na acalásia, as mulheres tiveram um intervalo mais longo entre as deglutições e menor fluxo de ingestão. Não houve diferenças significativas entre indivíduos mais jovens e mais velhos, entre os voluntários saudáveis e entre os indivíduos com acalásia. Não houve diferenças entre pacientes com doença de Chagas e pacientes com acalasia idiopática, ou entre pacientes com aumento ou não no diâmetro esofágico. **Conclusão** – Pacientes com acalásia têm dificuldade em ingerir água, levando mais tempo para completar a tarefa, que é influenciada pelo sexo dos indivíduos, mas não pela idade ou dilatação do esôfago.

DESCRITORES – Transtornos de deglutição. Acalásia esofágica. Doença de Chagas. Esôfago. Deglutição. Doenças do esôfago. Junção esofagogástrica.

REFERENCES

1. Pressman A, Behar J. Etiology and pathogenesis of idiopathic achalasia. J Clin Gastroenterol. 2017;51:195-202.
2. Ates F, Vaezi MF. The pathogenesis and management of achalasia: current status and future directions. Gut Liver. 2015;9:449-63.
3. Farrukh A, Mayberry JF. Achalasia: an epidemiologic update. Esophagus.2015;12:170-4.
4. Pandolfino JE, Gawron AJ. Achalasia: a systematic review. JAMA. 2015;313:1841-52.
5. Pandolfino JE, Kahrilas PJ. Presentation, diagnosis and management of achalasia. Clin Gastroenterol Hepatol. 2013;11:887-97.
6. Matsuda NM, Miller SM, Évora PRB. The chronic gastrointestinal manifestations of Chagas' disease. Clinics. 2009;64:1219-24.
7. Oliveira RB, Troncon LEA, Dantas RO, Meneghelli UG. Gastrointestinal manifestations of Chagas' disease. Am J Gastroenterol. 1998;93:884-9.
8. Vaezi MF, Felix VN, Penagini R, Mauro A, Moura EGH, Pu LZCT, Martinek J, Rieder E. Achalasia: from diagnosis to management. Ann N Y Acad Sci. 2016;1381:34-44.
9. Dantas RO, Alves LMT, Cassiani RA, Santos CM. Clinical measurement of swallowing and proximal esophageal contractions in Chagas' disease. Esophagus. 2009; 6:231-6.
10. Hughes TA, Wiles CM. Clinical measurement of swallowing in healthy and neurogenic dysphagia. Q J Med. 1996;89:109-16.
11. Alves LMT, Cassiani RA, Santos CM, Dantas RO. Gender effect on the clinical measurement of swallowing. Arq Gastroenterol. 2007;44:227-9.
12. Meneghelli UG, Peria FM, Darezzo FMR, Almeida FH, Rodrigues CM, Aprile LRO, et al. Clinical, radiographic, and manometric evolution of esophageal involvement by Chagas' disease. Dysphagia 2005;20:40-5.
13. Rassi A Jr, Rassi A, Marin-Neto JA. Chagas' disease. Lancet 2010; 375:1388-402.
14. Belo LR, Gomes NAC, Coriolano MGWS, Souza ES, Moura DAA, Asano AG, et al. The relationship between limit of dysphagia and average volume per swallow in patients with Parkinson's disease. Dysphagia. 2014;29:419-24.
15. Chee C, Arshad S, Singh S, Mistry S, Hamdy S. The influence of chemical gustatory stimuli on oral anaesthesia on healthy human pharyngeal swallowing. Chem Senses. 2005;30:393-400.
16. Teismann IK, Steinstraeter O, Stoeckight K, Sontrup S, Wollbrink A, Pantev C, et al. Functional oropharyngeal sensory disruption interferes with the cortical control of swallowing. BMC Neuroscience. 2007;8:62-9.
17. Molfender SM, Steele CM. Variation in temporal measures of swallowing: sex and volume effects. Dysphagia. 2013; 28:226-33.
18. Costa TV, Dantas RO. Esophageal motility in men and women evaluated by high-resolution manometry. Arq Gastroenterol. 2017;54:145-7.
19. Wirth R, Dziewas R, Beck AM, Clavé P, Handy S, Heppner HJ, et al. Oropharyngeal dysphagia in older persons – from pathophysiology to adequate intervention: a review and summary of an international expert meeting. Clin Interv Aging. 2016;11:189-208.
20. Smukalla SM, Dimitrova I, Feintuch JM, Khan A. Dysphagia in the elderly. Curr Treat Options Gastro 2017; 15:382-96.
21. Shim YK, Kim N, Park YH, Lee JC, Sung J, Choi YJ, et al. Effects of age on esophageal motility: use of high-resolution esophageal impedance manometry. J Neurogastroenterol Motil. 2017;23:229-36.
22. Alvarenga EHL, Dall'Oglio GP, Murano EZ, Abrahão M. Continuum theory: presbyphagia to dysphagia? Functional assessment of swallowing in the elderly. Eur Arch Otorhinolaryngol. 2018;275:443-9.
23. Aslam M. Vaezi MF. Dysphagia in the elderly. Gastroenterol Hepatol. 2013;9:784-95.
24. Downs DJ, Jadick G, Swaid F, Ross SB, Rosemurgy AS. Age and achalasia: how does age affect patients presentation, hospital course, and surgical outcomes? Am Surg 2017;83:952-61.
25. Köberle F. Chagas' disease and Chagas' syndromes: the pathology of American trypanosomiasis. Adv Parasitol. 1968;6:63-116.
26. Meciano Filho J, Caravalho VC, de Souza RR. Nerve cell loss in the mienteric plexus of the human esophagus in relation to age: a preliminary investigation. Gerontology. 1995;41:18-21.
27. Dantas RO, Deghaide NHS, Donadi EA. Esophageal motility of patients with Chagas' disease and idiopathic achalasia. Dig Dis Sci. 2001;46:1200-6.
28. Herbella FAM, Oliveira DRFC, Del Grande JC. Are idiopathic and chagasic achalasia two different diseases? Dig Dis Sci. 2004;49:353-60.
29. Dantas RO. Differences between idiopathic and chagasic achalasia. Mini-Invasive Surg. 2017:353-60.
30. Jones B, Donner MW, Rubesin SE, Ravich WJ, Hendrix TR. Pharyngeal findings in 21 patients with achalasia of the esophagus. Dysphagia. 1987;2:87-92.
31. Santos CM, Cassiani RA, Dantas RO. Videofluoroscopic evaluation of swallowing in Chagas' disease. Dysphagia. 2011;26:361-5.

ORIGINAL ARTICLE

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Normative values for a new water-perfused high resolution manometry system

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ABSTRACT – **Background** – Esophageal manometry is the most reliable method to evaluate esophageal motility. High resolution manometry (HRM) provides topographic contour colored plots (Clouse Plots) with simultaneous analysis from the pharynx to the stomach. Both solid state and water-perfused systems are available. **Objective** – This study aims to determinate the normative data for a new water-perfused HRM. **Methods** – HRM was made in 32 healthy volunteers after 8 hours fasting. HRM system used consisted of a 24-channel water-perfused catheter (Multiplex, Alacer Biomedica, São Paulo, Brazil). The reusable catheter is made of polyvinyl chloride (PVC) with 4.7 mm of diameter. Side holes connected to pressure transducers are spaced 2 cm for the analysis from the pharynx to the lower esophageal sphincter (LES). Holes are spaced 5 mm and 120° in a spiral disposition in the LES area. The sensors encompass 34 cm in total. Upper esophageal sphincter (UES) parameters studied were basal and relaxation pressures. Esophageal body parameters were distal contractile integral (DCI), distal latency (DL) and break. LES parameters studied were basal pressure, integrated residual pressure (IRP), total and abdominal length. Variables are expressed as mean ± standard deviation, median (interquartile range) and percentiles 5–95th. **Results** – All volunteers (17 males, aged 22-62 years) completed the study and tolerated the HRM procedure well. Percentiles 5–95th range were calculated: Upper Esophageal Sphincter (UES) basal pressure 16.7–184.37 (mmHg), DL: 6.2–9.1 (s), DCI: 82.72–3836.61 (mmHg.s.cm), break: <7.19 (cm), LES basal pressure: 4.89–37.16 (mmHg), IRP: 0.55–15.45 (mmHg). **Conclusion** – The performance and normative values obtained for this low-cost water-perfused HRM seems to be adequate for clinical use.

HEADINGS – Esophageal motility disorders. Manometry, trends. Low cost technology.

INTRODUCTION

Esophageal Manometry is the most reliable method to evaluate esophageal motility[1]. It was introduced in medical practice by the 1940ies with simple systems based on water–filled balloons that evolved to the current high resolution systems[2]. High resolution manometry (HRM) provides topographic contour colored plots (Clouse Plots) with simultaneous analysis from the pharynx to the stomach making the test faster, more comfortable, less susceptible to inter-observer variability, easier to interpret and compensation of movements' artefacts[3].

HRM is based on closely distanced and multiple sensors organized along the probe that varies in number according to different systems[4,5]. Both solid state and water-perfused systems are available. This myriad of different configurations demands the determination of reference values according to each technology as has been demonstrated by different studies[2].

This study aims to determinate the normative data for a new 24 channel water-perfused HRM.

METHODS

Subjects

We studied 32 (17 males, mean age 34 years range 21-62, mean body mass index 24 Kg/m^2 range 21–32) healthy volunteers. Individuals with upper digestive symptoms in the past 6 months; on drugs that could affect esophageal motility; systemic diseases that can modify esophageal motility; upper digestive tract surgery; or unable to understand the consent form were exclude form the study.

High resolution manometry

All individuals underwent a HRM after 8 hours fasting. The test was performed in left lateral decubitus. After a period for adaptation to the catheter, individuals were instructed to prevent swallowing for a period of 30 seconds in order to acquire resting parameters and subsequently 10 swallows of 5-mL every 30 seconds were offered to acquire dynamic parameters.

HRM system used consisted of a 24-channel water-perfused catheter (Multiplex, Alacer Biomedica, São Paulo, Brazil). The reusable catheter is made of polyvinyl chloride (PVC) with 4.7 mm of diameter. Side holes connected to pressure transducers are spaced 2 cm for the analysis from the pharynx to the lower esophageal sphincter (LES). Holes are spaced 5 mm and 120° in a spiral disposition in the LES area. The sensors encompass 34 cm in total (FIGURE 1). Perfusion is managed by an original patented controlled peristaltic pump.

Manometric parameters

Manometric parameters evaluated were those standardized by the International High Resolution Manometry Working Group in 2015, the Chicago classification 3.0[6]. Data was obtained based on automated analysis by the dedicated software (Esofagica v.1492. Alacer Biomedica, São Paulo, Brazil).

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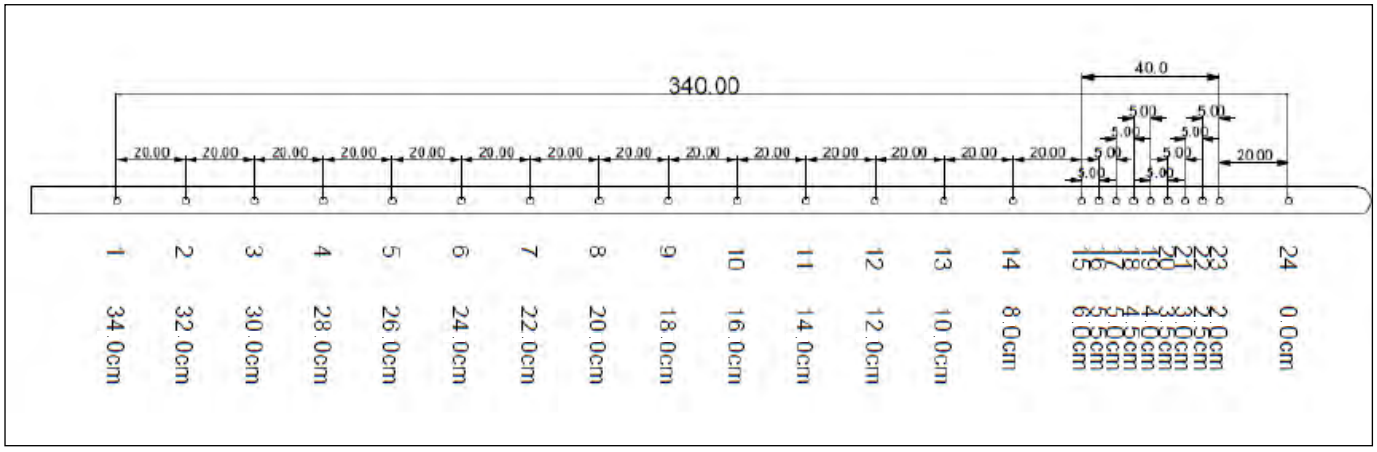

FIGURE 1. High resolution manometry water-perfused 24-sensors catheter.

Upper esophageal sphincter (UES) parameters studied were basal and relaxation pressures (FIGURE 2). Esophageal body parameters were distal contractile integral (DCI), distal latency (DL) and break (FIGURE 3). Lower esophageal sphincter (LES) parameters studied were basal pressure, integrated residual pressure (IRP), total and abdominal length (FIGURE 4).

Stastistical analysis

Variables are expressed as mean ± standard deviation, median (interquartile range) and percentiles 5–95th.

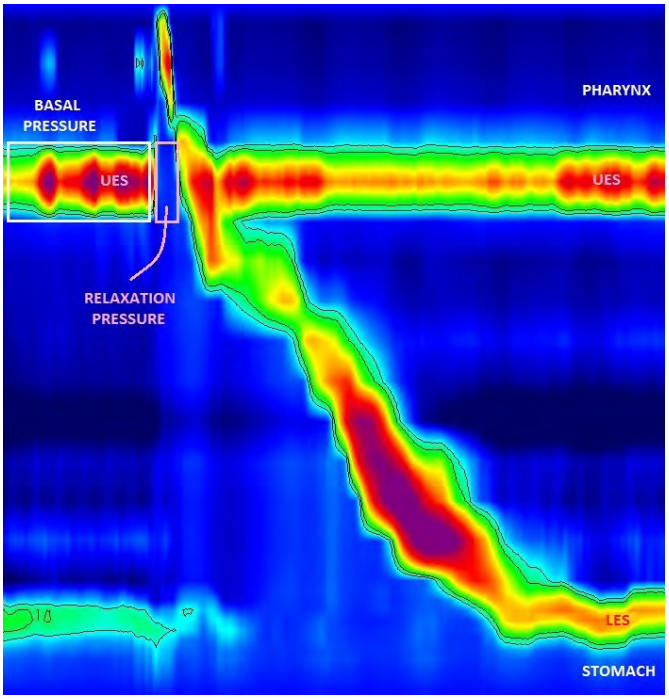

FIGURE 2. Manometric parameters for the upper esophageal sphincter (UES). UES basal pressure is determined by the higher pressure within the user determined limits of the sphincter. The measurement is obtained just in one instance in the resting status. Relaxation pressure is determined by the nadir pressure lesser pressure within the user determined limits of the sphincter during swallows. The measurements are performed for all swallows and averaged.

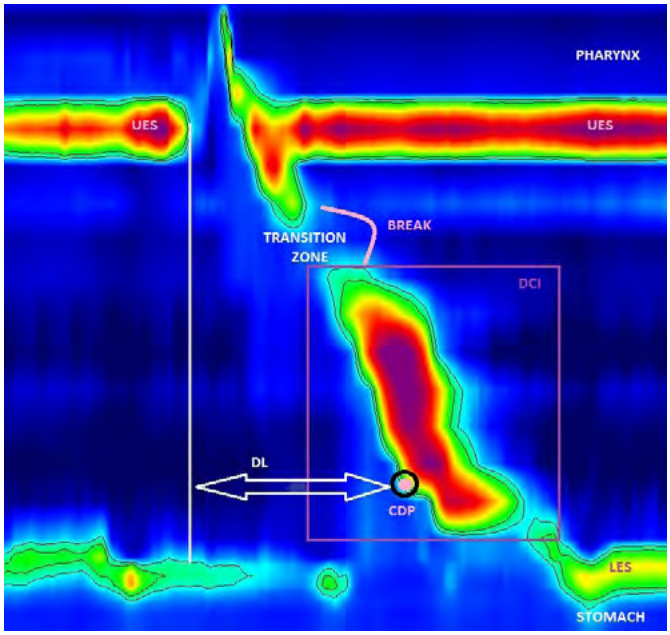

FIGURE 3. Manometric parameters for the esophageal body. Distal latency (DL) is measured the time between the beginning of swallow (upper esophageal sphincter relaxation) to the contractile desaceleration point (CDP) manually determined by the user. CDI is automatically calculated within the area of the user-determined peristaltic wave as the product of the mean amplitude of contraction in the distal esophagus (mmHg) times the duration of contraction (seconds), times the length of the distal esophageal segment (cm) exceeding 20 mmHg for the region spanning from the transition zone to the proximal aspect of the lower esophageal sphincter (LES). Break is calculated by the gap between zones of pressures >20 mmHg within the user-determined defined zone.

Ethics

The project was approved by local ethics committee and all participants signed a consent form before entering the study.

The authors are responsible for the study, no professional or ghost writer was hired.

The corresponding author is a consultant for the HRM manufacturer.

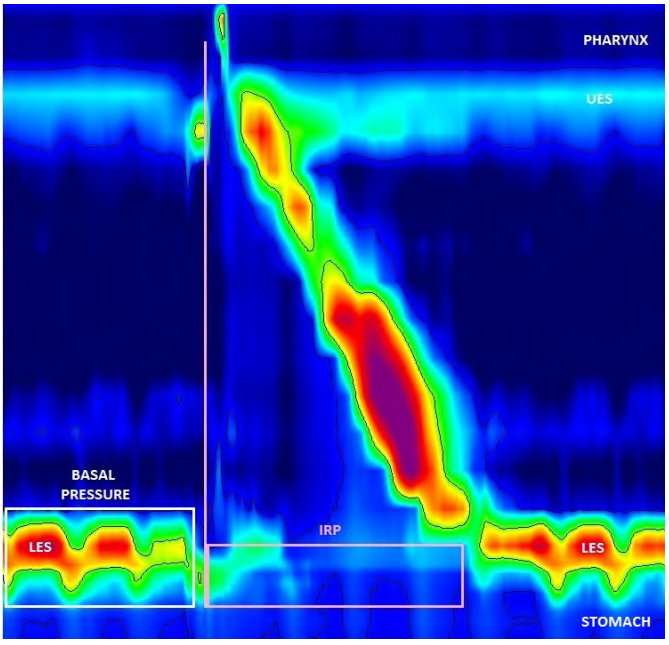

FIGURE 4. Manometric parameters for the lower esophageal sphincter (LES). LES basal pressure is determined by the higher pressure within the user determined limits of the sphincter. The measurement is obtained just in one instance in the resting status. Relaxation pressure is determined by the integrated relaxation pressure (IRP) within the user determined limits of the sphincter during swallows. The measurements are performed for all swallows and a median calculated.

RESULTS

Manometric parameters are shown in TABLE 1.

DISCUSSION

HRM has proven advantages over conventional manometry[7]. Solid state HRM systems have a faster response to changes in pressure and circumferential disposition of sensors[2] but a higher cost. These characteristics allow better evaluation of striated muscles[8] and sphincters relaxation[9]. Water-perfused HRM systems are cheaper and may be adequate for routine clinical practice[5,10-12]. It is worth remembering that most of the conventional manometry equipment used a water-perfused system[13]. The number of sensors; however, may be limited by the diameter of water-perfused catheters. Most current systems adopted a HRM sensor disposition – i.e. circumferential sensors closely spaced – limited to the LES area[2]. The asymmetry of the LES imposes a circumferential disposition in this zone forcing the use of most of the sensors available in this part of the catheter.

The system tested in this study employs a spiral disposition of the sensors. This original configuration was developed to allow a radial evaluation of the LES and save sensors to be used for the esophageal body and UES. Other studies that defined normative values employed only two different commercial systems that use 22 or 36 sensors disposed every 1 cm in the areas measuring the LES, and every 2 cm in the areas measuring the esophageal body, similar to our equipment, but with a radial distribution of distal sensors[5,10,12].

The colorful intuitive panoramic view of the esophageal motility provided by HRM stimulated the human eyes to distinguish subtle parameters unknown or uncomprehend so far[14] culminating with the Chicago Classification that defined the current parameters used for the evaluation of esophageal motility[6]. UES was neglected on the 3.0 version of the Chicago classification with a promised inclusion on the next version[6]. In our study, UES was detected and analyzed in all cases. Our system performed visually similar to solid-state equipment with a centrifuge decrease of pressure but well-defined borders. The limitation of the non-

TABLE 1. Esophageal parameters in healthy volunteers (n=32).

	Mean ± SD	Median (interquartile 25–75)	Percentile 5–95 th	Range
Upper esophageal sphincter				
Basal pressure – mmHg	77.41±63.13	62.15 (34.1–86.07)	16.7–184.37	12.2–309.3
Relaxation pressure – mmHg	- 6.11±9.63	- 5.4 (-8.25– -2.22)	-20.72– +5.95	- 42.7– +11.4
Esophageal body				
DCI – mmHg.s.cm	1868.25±1231.34	1659.35 (992.9–2598.77)	82.72–3836.61	20.8–5261.3
DL – s	7.59±0.94	7.5 (6.85–8.02)	6.2–9.1	6.1–9.2
BREAK – cm	2.58±2.41	2.1 (0.8–4.1)	0.0055–7.19	0–8.1
Lower esophageal sphincter				
Basal pressure – mmHg	18.95±9.91	17.5 (12.85–26.65)	4.89–37.16	0.6–40
IRP – mmHg	6±4.91	5.35 (2.75–7.22)	0.55–15.45	0.2–19.9
Total lenght – cm	3.82±0.95	3.75 (3.45–4.5)	2.31–5.43	1.6–5.7
Abdominal lenght – cm	2.19±0.97	2.4 (1.75–2.8)	0.65–3.19	0–5

DCI – distal contractile integral. DL – distal latency. IRP – integrated residual pressure.

circumferential analysis in this area is yet to be proven, as the UES pressures are also asymmetrical radially[15]. Detailed visualization of the structures of the pharynx was not possible as compared to solid state systems[8].

Esophageal body contractions are symmetrical radially. The lack of radial sensors in our low-cost system for the esophageal body area does not preclude a detailed analysis of this segment. Sensors are; however, 2 cm spaced, not 1 cm as usual in solid-state systems. Segmental defects of peristalsis (fragmented peristalsis) are rare in routine clinical practice and long peristaltic gap in the transition zone (break) is considered pathologic if over 5 cm[3], thus amenable to detection by the tested system. The determination of the contractile deceleration point (CDP) – necessary to define the DL – may have a ± 1 cm error, what we believe is also not clinically significant. Interestingly, all water-perfused systems have similar normal values for DL (TABLE 2) and higher than the solid-state systems[2]. This may be explained by the retarded response sensors due to the delay in pressure transmission along the water-systems as compared to solid-state transducers.

A reliable assessment of the relaxation of the LES is probably the best contribution of HRM[7,16]. The concentration of sensors provided by the technology compensates for motion artifacts avoiding erroneous interpretation of LES pseudo-relaxation[17] and allows a more sophisticated parameter to evaluate relaxation in opposition to nadir pressure only, the IRP[16]. Water-perfused systems present a variable number of sensors distally in the probe but closely space to provide this advantage of HRM. The system evaluated in the current study differs from other water-perfused equipment due to a spiral disposition of the sensors. Our results of the LES are within the range of values found for different water-perfused systems.

This study evaluated a small number of volunteers due to the difficult in recruiting healthy individuals to an uncomfortable test. Also, normative values were not validated in patients yet. A study is in progress and it will include patients with well-established achalasia and other LES disorders to demonstrate that the threshold found for IRP (a sensitive parameter to be evaluated in new systems) is clinically valuable. Despite these limitations, the performance and normative values obtained for this low-cost water-perfused HRM seems to be adequate for clinical use.

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Authors' contribution

All authors listed on the manuscript have contributed sufficiently to the project to be included as authors and approved the manuscript.

TABLE 2. Normative values for water-perfused high resolution esophageal manometry systems.

	Current study	Tseng et al.	Kessing et al.	Burgos Santamaria et al.	Capovilla et al.
Number of volunteers	32	66	50	16	20
Catheter (number of sensors)	24	22	36	22	24
DCI – mmHg.s.cm	83–3837	99-2186	142–3.674	285–2.280	557–1.726
DL – s	>6.2	>6.2	>6.2	>6.1	>7.0
LES basal pressure – mmHg	5–37	8.7–46.5	<18.8	<54	NA
IRP – mmHg	<16	<20	<29.8	<20	<8.8
break – cm	>7cm	0–13.4	NA	NA	NA

LES: lower esophageal sphincter; DCI: distal contractile integral; DL: distal latency; IRP: integrated residual pressure.

Silva RMB, Herbella FAM, Gualberto D. Valores de normalidade de um novo sistema de manometria de alta resolução por perfusão de água. Arq Gastroenterol. 2018;55(Suppl 1):30-4.

RESUMO – **Contexto** – Manometria esofágica é o exame mais confiável para avaliar motilidade esofágica. Manometria esofágica de alta resolução (MAER) apresenta um gráfico dinâmico e colorido (Clouse plots) com análise simultânea da faringe ao estomago. Dois tipos de manometria estão disponíveis: estado sólido e por perfusão de água. **Objetivo** – Determinar os valores de normalidade de um novo sistema de manometria de alta resolução. **Métodos** – MAER foi realizada em 32 voluntários saudáveis após jejum de oito horas. O sistema utilizado é de perfusão de água com 24 sensores (Multiplex, Alacer Biomedica, São Paulo, Brasil). O catéter permanente é feito de cloreto de polivinil (PVC) com 4,7 mm de diâmetro. Os orifícios laterais para conexão com os transdutores de pressão são espaçados de 2 cm para análise da faringe ao esfíncter esofagiano inferior (EEI) e são esparçados em 5mm em forma espiralada com 120° entre orifícios. Os sensores no total englobam 34 cm. Para o esfíncter esofágico superior (EES), os parâmetros estudados foram às pressões basal e de relaxamento. Os parâmetros do corpo esofágico foram: integral de contratilidade distal (DCI), latência distal (DL) e quebra. Os parâmetros do EEI inferior foram pressões basal e de relaxamento e pressão de relaxamento integrada (IRP). As variáveis foram expressas em medias ± desvio padrão, medianas (variação de interquartis) e percentis 5–95. **Resultados** – Todos os voluntários (17 homens, com idade variando entre 22-62 anos) terminaram e toleraram o exame. A variação dos percentis 5–95 foi calculada: pressão basal do esfíncter esofágico superior (EES) foi 16,7–184,37 (mmHg), DL: 6,2–9,1 (s), DCI: 82,72–3836,61 (mmHg.s.cm), quebra: <7,19 (cm), pressão basal do EEI: 4,89–37,16 (mmHg), IRP: 0,55–15,45 (mmHg). **Conclusão** – A realização dos testes e os valores de normalidade determinados por este estudo parecem ser adequadas para a prática clínica.

DESCRITORES – Transtornos da motilidade esofágica. Manometria, tendências. Tecnologia de baixo custo.

REFERENCES

1. Jobe BA, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg. 2013;217:586-97.
2. Herregods TV, Roman S, Kahrilas PJ, Smout AJ, Bredenoord AJ. Normative values in esophageal high-resolution manometry. Neurogastroenterol Motil. 2015;27:175-87.
3. Schlottmann F, Herbella FA, Patti MG. Understanding the Chicago Classification: From Tracings to Patients. J Neurogastroenterol Motil. 2017;234:487-94.
4. Smout AJ. Manometry of the gastrointestinal tract: toy or tool? Scand J Gastroenterol Suppl. 2001;234:22-8.
5. Kessing BF, Weijenborg PW, Smout AJ, Hillenius S, Bredenoord AJ. Water-perfused esophageal high-resolution manometry: normal values and validation. Am J Physiol Gastrointest Liver Physiol. 2014;306:G491-5.
6. Kahrilas PJ, Bredenoord AJ, Fox M, Gyawali CP, Roman S, Smout AJ, et al. The Chicago Classification of esophageal motility disorders, v3.0. Neurogastroenterol Motil. 2015;27:160-74.
7. Salvador R, Dubecz A, Polomsky M, Gellerson O, Jones CE, Raymond DP, et al. A New Era in Esophageal Diagnostics: The Image-Based Paradigm of High-Resolution Manometry. J Am Coll Surg. 2009;208:1035-44.
8. Silva LC, Herbella FA, Neves LR, Vicentine FP, Neto SP, Patti MG. Anatomophysiology of the Pharyngo-Upper Esophageal Area in Light of High-Resolution Manometry. J Gastrointest Surg. 2013:17:2033–8.
9. Gehwolf P, Hinder RA, DeVault KR, Edlinger M, Wykypiel HF, Klingler PJ. Significant pressure differences between solid-state and water-perfused systems in lower esophageal sphincter measurement. Surg Endosc. 2015:2912:3565-9.
10. Burgos-Santamaría D, Marinero A, Chavarría-Herbozo CM, Pérez-Fernández T, López-Salazar TR, Santander C. Normal values for waterperfused esophageal high-resolution manometry. Rev Esp Enferm Dig. 2015;107:354-8.
11. Capovilla, G, Savarino, E, Costantini, M, Nicoletti, L, Zaninotto, G, Salvador, R. Inter-rater and interdevice agreement for the diagnosis of primary esophageal motility disorders based on Chicago Classification between SolidState and Water-Perfused HRM System- A Prospective, Randomized, Double Blind, Crossover Study. Gastroenterology. 2014;146:S-681.
12. Tseng PH, Wong RKM, Wu JF, Chen CC, Tu CH, Lee YC. Normative values and factors affecting water-perfused esophageal high-resolution impedance manometry for a Chinese population. Neurogastroenterol Motil. 2018;30:e13265.
13. Sweet MP, Herbella FAM, Leard L, Hoopes C, Golden J, Hays S, et al. The prevalence of distal and proximal gastroesophageal reflux in patients awaiting lung transplantation. Ann Surg. 2006;244:491-7.
14. Herbella FA, Patti MG. Can high resolution manometry parameters for achalasia be obtained by conventional manometry?. World J Gastrointest Pathophysiol. 2015;6:58-61.
15. Meyer JP, Jones CA, Walczak CC, McCulloch TM. Three-dimensional manometry of the upper esophageal sphincter in swallowing and nonswallowing tasks. Laryngoscope. 2016;126:2539-45.
16. Lafraia FM., Herbella FAM., Kalluf JR., Patti MG. A pictorial presentation of esophageal high resolution manometry current parameters. Arq Bras Cir Dig. 2017;30:69-71.
17. Katz PO, Richter JE, Cowan R, Castell DO. Apparent Complete Lower Esophageal Sphincter Relaxation in Achalasia. Gastroenterology. 1986;90:978-83.

ORIGINAL ARTICLE

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Functional constipation and overactive bladder in women: a population-based study

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ABSTRACT – **Background** – An association between urinary disorders and functional constipation has been registered in children and adults, with functional constipation being a common complaint in individuals with overactive bladder. **Objective** – To evaluate the prevalence of functional constipation, overactive bladder and its dry/wet subtypes in women and to determine which bowel symptoms predict overactive bladder. **Methods** – A cross-sectional study of women randomly approached in public spaces. Exclusion criteria: neurological/anatomical abnormalities of the bowel or urinary tract. Constipation was defined as ≥2 positive symptoms of those listed in the Rome criteria. Urinary abnormalities (frequent urination, urgency, incontinence, nocturia) were defined by a score ≥2 in the respective item of the International Consultation on Incontinence Questionnaire – Overactive Bladder. Dry overactive bladder was defined as urgency without incontinence, while wet overactive bladder included incontinence. **Results** – A total of 516 women with a mean age of 35.8±6 years were interviewed. Rates of functional constipation, overactive bladder, dry overactive bladder and wet overactive bladder were 34.1%, 15.3%, 8.9% and 6.4%, respectively. Functional constipation was associated with overactive bladder and dry overactive bladder, with functional constipation predicting dry overactive bladder (OR=2.47). Quality of life was poorer in constipated women compared to non-constipated and even worse in constipated women with wet overactive bladder (median 22.5; 95%CI: 17.25-35.25). Manual maneuvers were significantly associated with both overactive bladder subtypes. Independent predictive factors for overactive bladder were manual maneuvers (OR=2.21) and <3 defecations/week (OR=2.18), with the latter being the only predictive factor for dry overactive bladder (OR=3.0). **Conclusion** – Functional constipation is associated with overactive bladder and its dry subtype, particularly in the younger population. In addition, this association is responsible for lower quality of life scores, especially when urinary incontinence is present. The presence of manual maneuvers and less than three defecations per week should direct us to look for overactive bladder.

HEADINGS – Constipation. Overactive urinary bladder. Women. Lower urinary tract symptoms, complications. Adult health.

INTRODUCTION

Functional constipation (CF) is a frequent complaint at medical appointments and its prevalence in the general population is approximately 16%[1]. In adults, FC is more common in women, the elderly and low-income individuals, and may have negative repercussions on quality of life due to frequent need for repeated treatments[1]. Presently, Roma IV criteria is the most commonly instrument used for clinical diagnosis of this bowel dysfunction[2].

The association between FC and urinary symptoms has been well described in the pediatric population. In a recent study, our research group showed that a constipated child is 6.8 times more likely to develop lower urinary tract dysfunction[3]. In adults, an association between urinary disorders and FC has also been registered, with FC being more common in individuals with overactive bladder (OAB) than in those without OAB[4]. FC is a predictor of the intensity of OAB and is associated with moderate to severe urinary symptoms[5].

Several questionnaires have been proposed for the evaluation of OAB. The International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB) has proved to be a useful tool for the diagnosis of OAB, particularly because it is able to measure the impact of this dysfunction on quality of life[6]. Nevertheless, to the best of our knowledge, there are no studies in the literature associating the ICIQ-OAB and its quality of life score with the Rome criteria for FC in population-based studies. Furthermore, no description has been made of which bowel symptoms listed in the Rome criteria are more closely associated with this urinary dysfunction and its wet and dry subtypes (OAB with and without urinary incontinence).

The objective of this population-based study was to assess the prevalence of FC, OAB and the dry and wet subtypes of OAB in women. In addition, the study was designed to identify which of the Rome criteria are more closely associated with urinary symptoms in ICIQ-OAB and constitute associated factors for OAB and its subtypes. This evaluation should provide further information on the association between FC and OAB and may be useful in improving management of these dysfunctions.

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METHODS

A cross-sectional study was conducted with women randomly approached in public spaces in a Northeast Brazilian city. Care was taken to choose data collection sites frequented by individuals of different socioeconomic levels between June and August 2017. The research team consisted of a colorectal surgeon, a urologist, a general practitioner, and five medical students. Before starting the survey, all interviewers were trained on issues related to bowel and urological disorders, so they could answer the doubts of the women during application of the self-administered questionnaire. After having signed an informed consent form, all participants answered a self-report questionnaire inquiring about their demographic characteristics (age, schooling and number of childbirth deliveries) and about the presence of constipation and urinary symptoms. All questionnaires answered were immediately reviewed by the research team to avoid data loss. The inclusion criteria were women ≥18 years old and over willingness to sign the informed consent form. Women who reported neurological disease or diagnosed gastrointestinal and urinary tract abnormalities which need regular medical follow-up were excluded from the study population. The research team didn't have any previous contact with the women before the interview and none gastrointestinal or urology recommendations were given to improve those dysfunctions. Women were not remunerated for having answered the questions. The institution's internal review board approved the study protocol.

Constipation was assessed using the validated Rome IV criteria, which consists of six questions about the presence or absence of: Straining during more than ¼ defecation; irregular or hard stools Form Scale 102) more than ¼ defecation; Sensation of incomplete evacuation more than ¼ defecation; sensation of anorectal blockage more than ¼ defecation; manual maneuvers to facilitate more than ¼ of defecation (e.g. digital evacuation, pelvic floor support); fewer than three spontaneous defecations/week. Constipated woman was defined as at least two positive symptoms of the following for a period of three months with symptom onset at least 6 months prior to diagnosis.

The International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB) was used to evaluate symptoms of an overactive bladder. This questionnaire had already been validated for use in Portuguese language and consists of four main questions regarding daytime and nighttime urinary frequency and the presence of urgency and incontinence. Women who reported having "sometimes" experienced urgency and incontinence in the previous month (a score of 2) were considered to have these symptoms, while women who reported waking up to urinate at least twice during the night (a score of 2) were defined as having nocturia; and those who urinated more than 9 times/day (a score of 2) were defined as having frequent daytime urination. OAB was defined as the presence of urgency in the four preceding weeks. The presence of OAB without urinary incontinence was defined as dry OAB, while the presence of urgency associated with urine loss was defined as wet OAB. The degree to which quality of life was affected for each specific question in the ICIQ-OAB was based on a score that ranged from 0 to 10 (maximum of 40 points) and is referred to as ICIQ-OAB quality of life score. Higher scores indicate a greater severity of symptoms and, consequently, reflects greater impact of individual symptoms on patient's quality of life.

Statistical analysis

The SPSS software program, version 21.0 was used for the statistical analysis. The numerical variables representing age and scores were expressed as means and standard deviations or medians and interquartile ranges (IQR). The variables included in the analysis were: age, number of childbirth deliveries, schooling, urinary symptoms (urgency, urge incontinence, urinary frequency and nocturia), Roma IV criteria (straining during defecation, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal blockage, manual maneuvers to facilitate defecation and ≤3 defecations per week) and the women' score in the overactive bladder questionnaire (ICIQ-OAB).

The calculation of sample size took into consideration an assumption that 30% of constipated individuals would have a lower urinary tract disorder[7,8]. According to the hypothesis that 50% of these individuals would have a lower urinary tract disorder and 50% would not, sample size was calculated at 291 women for a power of 80% and an alpha error of 5%.

A univariate analysis using the chi-square test to compare proportions, with significance established as $P \leq 0.05$, was conducted to test the association between the presence of constipation in women and the following variables: age, number of deliveries, schooling and urinary symptoms. In addition, the association between Rome IV criteria and overactive bladder, dry overactive bladder and wet overactive bladder was made. The Mann-Whitney non-parametric test was performed to determine whether there was an association between the ICIQ-OAB quality of life scores and constipation.

For a more in-depth evaluation into the independent association between the presence of OAB, dry/wet OAB in women and constipation, a univariate and multivariate analysis was conducted in which all independent variables (age, number of childbirth deliveries, schooling and constipation) with *P*-values <0.10 were inserted into the logistic model. The variables that were statistically significant at $P<0.05$ remained in the model during the multivariate analysis. The variables were inserted and removed manually. In the same way, to evaluate the independent association between the Rome IV criteria and OAB/dry OAB, a multivariate analysis was conducted using binary logistic regression in which the independent variables (age, number of deliveries, schooling and Roma IV criteria) were included in the logistic model when p-values were <0.10, remaining in the model if they continued to be statistically significant at $P<0.05$.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments.

RESULTS

A total of 516 women with a mean age of 35.8±6 years and a mean of 2±1 deliveries were evaluated. Constipation was found in 34.1% of the population studied. OAB was found in 15.3% of the women. Dry OAB (without incontinence) was found in 8.9% of the sample and wet OAB (with incontinence) in 6.4%. TABLE 1

TABLE 1. Characteristics of the study sample (n=516) according to the presence of constipation.

	Non-constipated			Constipated			
	n	(%)	95%CI	n	(%)	95%CI	*P*-value
OAB	39	(11.50)	8.29–15.35	40	(22.70)	16.99–29.36	0.00
Wet OAB	17	(5.0)	3.04–7.73	16	(9.10)	5.47–15.04	0.07
Dry OAB	22	(6.5)	4.20–9.48	24	(13.70)	9.14–19.32	0.01
Age (years)							0.79
20-29	52	(15.30)	11.76–19.42	29	(16.50)	11.54–22.51	
30-39	185	(54.40)	49.9–59.66	90	(51.10)	43.76–58.47	
40-49	73	(21.47)	17.35–26.08	47	(26.70)	20.56–33.61	
>50	30	(8.80)	6.14–12.20	10	(5.70)	2.92–9.89	
Schooling							0.90
Elementary or less	217	(64.20)	58.61–68.80	112	(64.70)	56.33–70.50	
High school or more	121	(35.80)	30.63–40.79	61	(35.30)	27.90–41.92	
Urinary symptoms (ICIQ-OAB)							
Frequent urination	20	(5.90)	3.73–8.78	12	(6.80)	3.75–11.30	0.68
Nocturia	66	(19.40)	15.47–23.88	54	(30.70)	24.20–37.79	0.00
Urgency	39	(11.50)	8.40–15.19	40	(22.70)	16.99–29.36	0.00
Incontinence	25	(7.40)	4.92–10.51	22	(12.60)	8.21–18.02	0.05
Total	340	(65.89)	61.82–69.89	176	(34.11)	30.11–38.28	

OAB: Overactive bladder; ICIQ-OAB: International Consultation on Incontinence Questionnaire - Overactive Bladder.

describes the characteristics of the sample according to whether or not women were constipated.

Overall, 22.7% of the constipated women were found to have OAB compared to a prevalence of 11.50% in the non-constipated group (*P*=0.00) (TABLE 1). Dry OAB was found in 13.7% of the constipated women compared to 6.5% of the non-constipated women (*P*=0.01). No association was found between constipation and wet OAB (TABLE 1) and constipation was not found to be a predictive factor for the wet subtype in univariate and multivariate analyses (TABLE 2). Nevertheless, when ICIQ-OAB scores for quality of life were analyzed, median values were found to be higher in constipated women with wet OAB, reflecting the poorer quality of life in this group (TABLE 3).

From urinary symptoms mentioned in the ICIQ-OAB questionnaire, urgency and nocturia were the most common and were significantly associated with FC (TABLE 1). The presence of urinary incontinence alone was found in a greater proportion among constipated women (12.6% versus 7.4%; *P*=0.05). On the other hand, as described above, when incontinence was associated with urgency (wet OAB), no association was found with FC. No

TABLE 2. Analysis of predictive factors for subtypes of overactive bladder.

	Dry OAB		Wet OAB	
Factors	Univariate (*P*-value)	Multivariate (*P* -value) OR (95%CI)	Univariate (*P* -value)	Multivariate (*P* -value) OR (95%CI)
Age	0.16	0.23	0.79	0.55
Number of childbirth deliveries	0.54	0.59	0.88	0.96
Schooling	0.81	0.94	0.30	0.21
Constipation	0.01	0.01 2.47 (1.27-4.81)	0.07	0.08

OAB: overactive bladder.

TABLE 3. ICIQ-OAB quality of life scores (ICIQ-QoL) for overactive bladder, dry overactive bladder and wet overactive bladder, according to the presence of constipation.

	Non-constipated	Constipated	
	n Median (IQR)*	n Median (IQR)	*P*-value
ICIQ QoL – total	340 0 (0-5)	175 3 (0-10)	0.00
ICIQ QoL – OAB	39 10 (2 - 18)	40 17 (8-27)	0.03
ICIQ QoL – dry OAB	22 5 (0-10.25)	24 10 (3.25-21)	0.00
ICIQ QoL – wet OAB	17 17 (15-25)	16 22.5 (17.25-35.25)	0.00

ICIQ-OAB: International Consultation on Incontinence Questionnaire - Overactive Bladder; IQR: interquartile range.

association was found between age or schooling and constipation (TABLE 1).

From Rome criteria, the presence of manual maneuvers to facilitate defecation was the bowel symptom for which a statistically significant association was found for both OAB subtypes (TABLE 4). In multivariate analysis, this criterion, together with presence of <3 defecations/week, were found to be independent predictors of OAB (TABLE 5). In multivariate analysis conducted to identify predictive factors of dry OAB, the presence of <3 defecations/week was the only one of Rome criteria to remain in the final model (TABLE 6).

DISCUSSION

In the present study FC, OAB and its subtypes wet and dry were identified in 34.1%, 15.3%, 6.4% and 8.9% respectively. In agreement with previous studies, FC was identified in 34% of women. Adibi et al., studying a young population (median age of 24 years, range 14-41 years) have shown a FC`s prevalence of 32.9%[9]. Howell et al. also described a FC's prevalence of 30.7%[10]. Like us, both studies have analyzed dates of a general base population based on Roma criteria. Prevalence rates in self-report measure and Roma Criteria seem to be equivalent, but Roma criteria allows more objective assessment of constipation[11].

TABLE 4. Association between Rome criteria and overactive bladder, dry overactive bladder and wet overactive bladder.

Rome criteria	Overactive bladder n (%)			Dry overactive bladder n (%)			Wet overactive bladder n (%)		
	No	Yes	*P*-value	No	Yes	*P*-value	No	Yes	*P*-value
Straining during defecation	127 (29.1)	31 (39.2)	0.71	137 (29.2)	20 (43.5)	0.05	146 (30.3)	11 (33.3)	0.71
Lumpy or hard stools	126 (28.8)	34 (43)	0.01	142 (30.3)	17 (37)	0.35	142 (29.5)	17 (51.5)	0.01
Sensation of incomplete evacuation	108 (24.7)	23 (29.1)	0.41	117 (24.9)	13 (28.3)	0.62	120 (24.9)	10 (30.3)	0.49
Sensation of blockage	48 (11)	15 (19)	0.05	55 (11.7)	7 (15.2)	0.49	54 (11.2)	8 (24.2)	0.03
Manual maneuvers	37 (8.5)	17 (21.5)	0.00	44 (9.4)	9 (19.6)	0.03	45 (9.3)	8 (24.2)	0.01
<3 defecations/week	68 (15.6)	26 (32.9)	0.00	76 (16.2)	17 (37)	0.00	84 (17.4)	9 (27.3)	0.16

TABLE 5. Multivariate analysis of the Rome criteria - overactive bladder.

	OD	95% CI	*P*
Manual maneuvers	2.214	1.125–4.357	0.021
<3 defecations/week	2.178	1.230–3.855	0.008

Multivariate analysis, Rome criteria, overactive bladder.

TABLE 6. Multivariate analysis of the Rome criteria – dry overactive bladder.

	OR	95% CI	*P*
<3 defecations/week	3.03	1.59–5.79	0.001

Multivariate analysis, Rome criteria, overactive bladder.

No association was found with age. Although age was considered a risk factor for development of both FC and OAB, this finding is variable and reflects the multifactorial characteristic of these dysfunctions[1]. Likewise, neither FC nor OAB were found to be associated with schooling or with the number of childbirth deliveries in the sample population evaluated here.

FC was significantly associated with OAB in this sample. This finding is in line with others studies that reported the same association[3,4,5]. Studies has been theorizing about the important role played by the more distal segments of the colon in the development of overactive bladder[4,5]. Findings from urodynamic studies have shown that rectal distension may alter bladder function and sensitivity in patients with lower urinary tract symptoms[12]. However, the association between constipation and lower urinary tract dysfunction does not appear to be the result only of local mechanical factors such as compression of the bladder by feces-filled bowel segment, consequently reducing bladder capacity, but predominantly of the existence of nerve connections between these organs that could result in cross-sensitization of pelvic structures. This connection would not be confined to upper lumbar and lumbosacral regions of the spinal cord, in which studies have detected the presence of convergent neurons from colon and bladder in the dorsal root ganglion that would receive afferent neural signals from these two organs[13]. This cross-talk would also involve convergent interneurons from lower bowel and bladder that exist in the spinal dorsal horn, as well as a population of neurons in pontine micturition center that would be synaptically linked to both aforementioned pelvic organs[14]. Studies using functional magnetic resonance imaging have reported alterations in the activation of certain regions of the brain such as the anterior cingulate gyrus and prefrontal cortex in both conditions[15,16].

No association was found between wet OAB and FC. We believe that it occurred because our sample was mostly formed by young women. Contrary to the present finding, a study conducted with women over 40 years of age with OAB reported that latent FC (described as presence of two or more of Rome criteria) was the only factor associated with wet OAB, with no association being found between FC and dry OAB[5]. The disparity in these results may be a consequence of a major difference in the populations studied, since the present study evaluated a random sample of relatively young women in the population (a mean age of 35.8±6 years), while the other study analyzed women over 40 years of age attending a urology outpatient department. That feature may have led to a greater occurrence of OAB associated with urinary incontinence, a urinary disorder that is normally more common in older women. This finding suggests that the mechanism responsible for the appearance of OAB and its subtypes may vary according to age, with older women being more likely to develop structural changes in the pelvic floor such as pelvic organ prolapse, which would result in a greater association of FC and wet OAB in this age group. Therefore, our finding of association between manual maneuver and all OAB including wet subtype may suggest that this maneuver could represent a more longstanding stage of bowel dysfunction with impairment of pelvic floor. A future study with women under 40 years and above, also assessing the severity of constipation, may be useful in evaluating symptoms and signs most associated with OAB and its subtypes.

We found a poor Quality of life scores especially when wet OAB was associated with constipation. Men and women with urge urinary incontinence have worse quality of life scores[17]. OAB can lead to anxiety and depression by the urge to urinate and constant fear of leakage. In the same way, FC was associated with impaired on quality of life been comparable to that seen in other chronic conditions[18]. Our finding alerts to the negative effect of FC associated with OAB on quality of life of women affected by these disorders and regarding the need for appropriate management.

Manual maneuvers and <3 defecations/week were factors found to be predictive of OAB, with these symptoms being found to increase the likelihood of this urinary dysfunction by a factor of two. This finding highlights the need for further investigation into urinary disorders in women with bowel symptoms to avoid the development of urinary complications resulting from late diagnosis. Moreover, in women with OAB but without urinary incontinence, referred to here as dry OAB, the presence of <3 defecations/week was the only predictive factor for this dysfunction, increasing the likelihood of this urinary disorder by a factor of three. This emphasizes the risk involved in underestimating the importance of this bowel symptom when it is the only symptom present, and care should be taken not to overlook bowel dysfunction when fewer than two of the Rome criteria are present.

There are some limitations to the present study that need to be mentioned. The sample consisted predominantly of young women; therefore, the results cannot be extrapolated to older populations. Furthermore, since this was a population-based survey, which prevented OAB and FC from being evaluated in greater depth, causality cannot be inferred.

CONCLUSION

FC is associated with OAB and its dry subtype, particularly in younger population. In addition, this association is responsible for lower quality of life scores, especially when urinary incontinence is present. The presence of manual maneuvers and less than three defecations per week should direct us to look for OAB.

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Authors' contribution

Abreu GE and Dourado ER contributed to data collection, data analysis, interpretation of the results and drafted the manuscript. Barroso Junior U contributed to the design of the study and critical revision. Alves DN, Araújo MQ and Mendonça NSP participated in data collection. All authors have read and approved the article for publication.

Abreu GE, Dourado ER, Alves DN, Araujo MQ, Mendonça NSP, Barroso Junior U. Constipação funcional e bexiga hiperativa em mulheres: um estudo de base populacional. Arq Gastroenterol. 2018;55(Suppl 1):35-40.

RESUMO – **Contexto** – A associação entre distúrbios urinários e constipação funcional vem sendo observada em crianças e adultos, sendo a constipação funcional uma queixa comum em indivíduos com bexiga hiperativa. **Objetivo** – Avaliar a prevalência de constipação funcional, bexiga hiperativa e seus subtipos seco/úmido em mulheres e determinar quais os sintomas intestinais estão mais associados e são preditores de bexiga hiperativa. **Métodos** – Estudo de corte transversal com mulheres abordadas aleatoriamente em locais públicos. Os critérios de exclusão foram: anormalidades neurológicas/anatômicas do intestino ou do trato urinário documentadas. A constipação foi definida como ≥2 sintomas positivos daqueles listados nos critérios de Roma. Alterações urinárias (frequência urinária aumentada, urgência, incontinência e noctúria) foram definidas por um escore ≥2 no respectivos itens do Questionário Internacional de Consulta sobre Incontinência – Bexiga Hiperativa. Foi denominada de bexiga hiperativa seca a presença de sintomas de urgência sem incontinência urinária e bexiga hiperativa úmida quando a urgência estava associada a incontinência urinária. **Resultados** – Foram entrevistadas 516 mulheres com idade média de 35,8±6 anos. As taxas de constipação funcional, bexiga hiperativa, bexiga hiperativa seca e bexiga hiperativa úmida na amostra estudada foram de 34,1%, 15,3%, 8,9% e 6,4%, respectivamente. Foi observada associação entre constipação funcional e bexiga hiperativa / bexiga hiperativa seca, sendo a constipação funcional fator preditor para esse subtipo de bexiga hiperativa (OR=2,47). O escore de qualidade de vida foi pior nas mulheres com constipação funcional em comparação com as não constipadas e ainda pior nas mulheres com constipação funcional associada a bexiga hiperativa úmida (mediana 22,5; IC 95%: 17,25-35,25). A presença de manobras manuais estava significativamente associada aos dois subtipos de bexiga hiperativa. Os fatores preditivos independentes para bexiga hiperativa foram manobras manuais (OR=2,21) e <3 defecações/semana (OR=2,18), sendo este último o único fator preditivo para bexiga hiperativa seca (OR=3,0). **Conclusão** – Em mulheres, a constipação funcional está associada a bexiga hiperativa e seu subtipo seco, particularmente na população mais jovem. Além disso, essa associação é responsável por piores escores de qualidade de vida, principalmente quando a incontinência urinária está presente. A presença de manobras manuais e menos de três defecações por semana em mulheres devem nos direcionar a procurar por bexiga hiperativa.

DESCRITORES – Constipação intestinal. Bexiga urinária hiperativa. Mulheres. Sintomas do trato urinário inferior, complicações. Saúde do adulto.

REFERENCES

1. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol. 2011;25:3-18.
2. Lacy BE, Mearin F, Chang L, Chey WD, Lembo AJ, Simren M, Spiller R. Bowel disorders. Gastroenterology. 2016;150:1393-1407.e5.
3. Sampaio C, Sousa AS, Fraga LG, Veiga ML, Bastos Netto JM, Barroso U Jr. Constipation and lower urinary tract dysfunction in children and adolescents: a population-based study. Front Pediatr. 2016;4:101.
4. Coyne KS, Cash B, Kopp Z, Gelhorn H, Milsom I, Berriman S, Vats V, Khullar V. The prevalence of chronic constipation and faecal incontinence among men and women with symptoms of overactive bladder. BJU Int. 2011;107:254-61.
5. Maeda T, Tomita M, Nakazawa A, Sakai G, Funakoshi S, Komatsuda A, Ito Y, Nagata H, Tsukada N, Nakamura S. Female functional constipation is associated with overactive bladder symptoms and urinary incontinence. Biomed Res Int. 2017;2017:2138073.
6. Abrams P, Avery K, Gardener N, Donovan J; ICIQ Advisory Board. The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. J Urol. 2006;175:1063-6.
7. Carter, D. & Beer-Gabel. Lower urinary tract symptoms in chronically constipated women M. Int Urogynecol J. 2012;23:1785-89.
8. Cameron A, Fenner DE, DeLancey JO, Morgan DM. Self-report of difficult defecation is associated with overactive bladder symptoms. Neurourol Urodyn. 2010;29:1290-4.
9. Behzad E, Pirzadeh S, Mohseni M. Bowel habit reference values and abnormalities in young Iranian healthy adults. Dig Dis Sci. 2007;52:1810-3.
10. Howell SC, Quine S, Talley NJ. Low social class is linked to upper gastrointestinal symptoms in an Australian sample of urban adults. Scand J Gastroenterol. 2006;41:65766.
11. Schmidt FM, Santos VL. Prevalence of constipation in the general adult population: an integrative review. Wound Ostomy Continence Nurs. 2014;41:70-6.
12. Panayi DC, Khullar V, Digesu GA, Spiteri M, Hendricken C, Fernando R. Rectal distension: the effect on bladder function. Neurourol Urodyn. 2011;30:344-7.
13. McMahon SB, Morrison JF. Two group of spinal interneurones that respond to stimulation of the abdominal viscera of the cat. J Physiol. 1982;322:21-34.
14. Rouzade-Dominguez ML, Miselis R, Valentino RJ. Central representation of bladder and colon revealed by dual transsynaptic tracing in the rat: substrates for pelvic visceral coordination. Eur J Neurosci. 2003;18:3311-24.
15. Mugie SM, Koppen IJN, van den Berg MM, Groot PFC, Reneman L, de Ruiter MB, Benninga MA. Brain processing of rectal sensation in adolescents with functional defecation disorders and healthy controls. Neurogastroenterol Motil. 2018;30:e13228.
16. Ketai LH, Komesu YM, Dodd AB, Rogers RG, Ling JM, Mayer AR. Urgency urinary incontinence and the interoceptive network: a functional magnetic resonance imaging study. Am J Obstet Gynecol. 2016;215:449.e1-449.e17.
17. Coyne KS, Kvasz M, Ireland AM, Milsom I, Kopp ZS, Chapple CR. Urinary incontinence and its relationship to mental health and health-related quality of life in men and women in Sweden, the United Kingdom, and the United States. Eur Urol. 2012;61:88-95.
18. Belsey J, Geraint M (2010). Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31:938-49.

ORIGINAL ARTICLE

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Water-perfused high-resolution anorectal manometry (HRAM-WP): the first Brazilian study

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ABSTRACT – **Background** – High resolution anorectal manometry (HRAM-WP) allows more simplified, objective, and uniform data acquisition and interpretation of the test results. **Objective** – To validate a HRAM under water perfusion (Alacer Biomédica) with a 24-channel probe and to compare the results of anorectal manometry with other systems. **Methods** – Individuals without critical evacuation disorders were selected. Patients with incontinence, anal surgery, dyssynergia or sphincter injury were excluded. The test was performed with an Alacer Biomédica 24 channel manometry system under water perfusion, with a probe configured with 6 levels of 4 radial channels, separated from each other by 0.8 mm. The mean pressures for the functional channel were determined, in states of rest (RMP), contention effort (CMP) and evacuation effort (EEMP). The pressure extension of the sphincter was also tabulated in cm. The results were compared with those available in recent literature. **Results** – Fifty patients were studied (20 men; 30 women). Overall, the following results were obtained: the RMP was 76.9±3.0 mmHg, the CMP was 194.2±9.4 mmHg, and EEMP was 88.2±3.7 mmHg. When classified according to the gender, for men: RMP was 72.2±3.0 mmHg, CMP was 229.5±17 mmHg, and EEMP was 91.4±7.0. For women, RMP was 79.8±4.0 mmHg, CMP was 170.7±8, and EEMP was 86.1±4.3 mmHg. The sphincter gauge extension for both genders was 3.1±0.09 cm (men 3.3±0.1; women 3.0±0.1). **Discussion** – Studying HRAM-WP has become much easier. Non-mobilization of the sensor causes less discomfort and artefacts with a lower assessment time. In this study, small differential values between both sexes during rest were observed, highlighting a greater containment force in men. No difference in sphincter extension was noted. The results of this study are consistent with that of existing reports and with those obtained using solid state probes. **Conclusion** – The perfusion system yielded results similar to that of solid state systems. Further studies to evaluate parameters with respect to pelvic dyssynergia and incontinence need to be conducted. Additionally, to determine if the vector volume can furnish new information in terms of functional and anatomical aspects.

HEADINGS – Anal canal, anatomy & histology. Manometry, trends. Infusion pumps.

INTRODUCTION

In the last three decades, anorectal manometry has been used routinely to qualify and quantify evacuation disorders. Due to the large variety of protocols, systems, and probes, a comparison between studies has been very difficult[1,2]. Since the emergence of high resolution anorectal manometry (HRAM), the equipment and probes are similar in their general configuration as well as the implementation protocols of examination and interpretation of the results. The objectives of the exam remain the same; however, their interpretation have been simplified and have become more practical[3].

There are currently two systems in practice: those that use solid-state probes and those with continuous perfusion. The first system has a high cost and its probes have an uncertain validity, as they are fragile and undergo wear due to reuse and sterilization. High resolution esophageal manometry using perfusion probes, is already routinely used in esophageal exams. Besides lower cost, good sensitivity, and durability, they also give similar results as that of solid state systems[4,5]. Conventional systems for anorectal manometry using eight infusion channels have individualized channel distribution configurations along the probe, arranged spirally, or radially with single-line orifices each with 45º covering the entire circumference. Both system have advantages and disadvantages. In the helical or spiral type, the channels are separated by 0.5 to 1 cm, but do not capture the pressures at the same time throughout the circumference. In radially-disposed probes, the circumference is well represented, but the probe must be mobilized during the examination, which may produce artefacts because it is dependent on the skill of the operator. With the routine use of high-resolution perfusion manometry for the esophagus, a 24-channel anorectal manometry probe was proposed to integrate two main data: observe the anal sphincter in total extension and at circumferential gauge measurement, with dispense of the mobilization during the examination, approaching what is performed by solid state manometry.

Thus, the objective of this study was to validate a 24-channel high resolution perfusion system produced in Brazil, using the commonly described implementation protocols and to compare results already published on similar high-resolution anorectal manometry techniques, regardless of the system used.

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METHODS

Fifty individuals of both sexes without critical evacuation disorders, who underwent HRAM-WP were retrospectively selected from a group consisting of approximately 500 patients. Individuals younger than 18 or older than 70 years, those who expressed some degree of incontinence, had pelvic dyssynergia, previous anal surgery, and patients with prior anal injuries were excluded.

The 24-channel Multiplex (Alacer Biomédica, São Paulo, Brazil) was used in this study. The main characteristics of this system are continuous capillary perfusion coupled with a piezoelectric pressure sensor. Continuous capillary perfusion was controlled by a patented original peristaltic pump (Alacer Biomedica), which maintains continuous water flow of 0.6 mL per minute. The probe is made of polyvinyl chloride (PVC) 4.7 mm in diameter with six groups of four channels arranged radially at 90º, spaced 0.8 cm apart from a central channel that communicates with a latex balloon adapted at its end (FIGURE 1).

FIGURE 1. A) Manometric probe. B) 24 channels water perfused system (Alacer Biomédica). C) Perfusion pump.

After an interview and explanation of the exam, the patient remained in the left lateral decubitus position and the system was reset to atmospheric pressure at the midline of the buttocks. Once lubricated with gel, the probe was inserted gently until the numerical margin approached the anal margin.

The examination protocol, adapted from Rao et al.[6] was used as follows: accommodation of the probe for two minutes; recording of two minutes at rest pressures; pressure extension of the anal canal characterization; anorectal reflex test; sensitivity tests and rectal capacity test; containment and evacuation effort tests and finally, containment holding time test.

The parameters defined for analysis include the mean rest pressure (RMP) of the anal canal measured at the sphincter extension for 30 seconds. We characterized the sphincter extension as having an isobaric contour with pressures greater than 10 mmHg above rectal pressure (FIGURE 2). The inhibitory anorectal reflex was assumed to be present after gradual air insufflations in increments of 10 mL in a rectal balloon corresponding to the sphincter pressure drops of at least 20% relative to rest. Sensitivity and capacity tests were performed with gradual inflations of air in the rectal balloon in 20 mL increments, taking three manifestations by the patient:

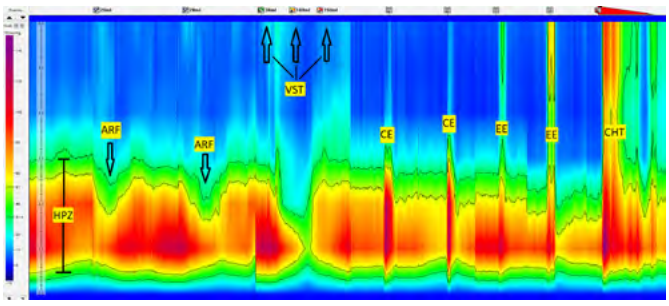

FIGURE 2. Twenty-four channels anorrectal tests graphic. HPZ: high pressure zone; AR: anorrectal reflex; VST: volume sensory test; CE: contention effort; EE: evacuation effort; CHT: containement holding time test.

volumes to trigger the first sensation, the evacuation desire and the evacuation urgency. The pressures during the contention (CMP) and evacuation efforts (EEMP) were obtained by calculating the mean pressure during three seconds of activity for three times, with an interval of 20 seconds between each test. Finally, the containment holding test was performed after the patient was asked to maintain the restraint for a period of 20 seconds while the initial resting pressure was measured, and the mean duration obtained in this time interval was compared. Possible fatigue was determined as the time after which there was a loss of force by 70% or more from the initial contraction pressure.

The mean rest pressures of the anal canal were analyzed, as well as the gauge length of the sphincter. The mean pressure and the differentials obtained in the contention and evacuation efforts were compared to those at rest. The contention holding time was tabulated for all patients. Finally, the numerical analyses obtained for the rest pressures, contention, and evacuation efforts were compared to the results of studies already published with solid state systems or under water perfusion. The sensitivity and capacity tests were also compared to those published by other authors.

The statistical analyses data of the variables are expressed as mean ± SEM. The project was approved by the local Ethics Committee under CAAE N: 89325218.5.0000.5450 and all participants signed an informed consent.

RESULTS

Altogether, 50 subjects (20 men and 30 women) were enrolled in the study. The inhibitor anorectal reflex was obtained in all patients after insufflation of air from 20-30 mL. The mean pressure ± SEM at rest of the anal canal was 76.9±3.0 mmHg. For women, the values were 79.8±4.0 mmHg and for men 72.2±3.0 mmHg. The sphincter length measured at rest was 3.15±0.09 cm overall, with 3.0±0.1 cm for women and 3.3±0.1 cm for men. In the contention state, the total pressure of the canal for both genders was 194.2±9.4 mmHg, with 170.7±8.0 mmHg for women and 229.5±17.0 mmHg for men. In the evacuation effort, the overall pressures measured were 88.2±3.7 mmHg, at 86.1±4.3 mmHg for women and 91.4±7.0 mmHg for men (TABLE 1).

The time of sustained contraction for 20 seconds were on average above 16.8 s in women and above 18.8 s for men (17.8 s overall). The results of sensitivity tests and capacity resulted in volumes of air in rectal balloon as follows: for the general group: first sensation 35.8±2.1 mL, evacuation desire 100.8±5.6 mL and urgency to evacuate 164.2±7.2 mL (TABLE 1).

TABLE 1. Values in mmHg obtained of water-perfused high-resolution anorectal manometry in total and in genders.

Present study	Total	Female	Male
n	50	30	20
Variables	Mean ± SEM	Mean ± SEM	Mean ± SEM
Mean resting pressure	76.9 ± 3.0	79.8 ± 4	72.2 ± 3
Maximum squeeze pressure	194.2 ± 9.4	170.7 ± 8	229.5 ± 17
Mean pressure in push to defecate	88.2±3.7	86.1 ± 4.3	91.4 ± 7
HPZ length (cm)	3.1 ± 0.09	3.0 ± 0.1	3.3 ± 0.1
First sensation (mL)	35.8± 2.1	31.0 ± 1.2	43.0 ± 4.8
Desire to defecate (mL)	100.8 ± 5.6	100 ± 7	102 ± 9.4
Urge to defecate (mL)	164.2 ± 7.2	162 ± 10.9	167 ± 9.8
Duration of sustained squeeze (s)	17.8	16.8	18.8

SEM: standard error of the mean; HPZ: high-pressure zone.

DISCUSSION

The MoDiNe is a tertiary center that specializes in instrumental diagnoses of alterations in digestive motility. Anorectal manometry has been performed for over 25 years in a conventional way and as of 6 months ago has aided in the development of a high-resolution perfusion system. Throughout that last 25 years, the published studies presented different results. The main cause of these variances lie in the fact that the methodology in these two decades lacked didactic publications and the protocols were adjusted according to the different centers conducting the exams. Conflicting information further increased the difficulty of understanding, performing and for referring anorectal manometry. Many of these studies contemplated the optics and personal opinions of the authors, making it difficult to reproduce the findings. This made it difficult to accept this simple and valuable diagnostic method to understand altered functional states of pelvic floor function.

With the advent of HRAM-WP, the implementation and analysis of the method was greatly facilitated[7,8]. The immobilization of the probe after placement results in reduced discomfort, less presence of artefacts and short study time. The observation of the sphincter circumferentially, including its three-dimensional and volumetric visualization, made the interpretation more intuitive. These facts have helped improve the method in contrast to the conventional system, and recent reports show that the protocols for performing the exam are uniform and the reference values are similar, regardless of the sensor used. Thus, Noelting et al., Li et al. and Carrington et al., reported similar findings in contrast to those in Lee & Barucha[9,10,11,12]. Interestingly, in the latter study, which was conducted in Korea, the general results are not consistent with that of the other authors, with lower values with respect to resting, contention, and effort pressures; although, the study reached the same conclusions with respect to the differences of the mean contention force and resting pressures between the two sexes[12]. This can be explained by the difference in the ethnicity of the participants and the subjectivity that may be related to the protocol of the exam. In a comparative study between the two systems, Rasijeff et al. demonstrated similar numbers for the resting pressure, but it shows higher values for pressures obtained by the solid state method with respect to contention effort, which they suggest maybe attributable to the probe's faster response and sensitivity. In the end, it reviews and compares several publications and recommends that the values of normality should be computed for each system[13]. Wang Al et al., when analyzing 126 volunteers, obtained results equivalent to those of the present study when the values were not classified according to the sex of the participants[14] (TABLE 2).

TABLE 2. Comparative values in mmHg of water-perfused or solid-state high-resolution manometry for both sex.

Authors	Wang[14]	Present study
Method	ARM-SS	ARM-WP
Variables	Mean ± SD	Mean ± SEM
N	126	50
Maximum resting pressure	79.3 ± 17.8	–
Mean resting pressure	71.8 ± 17.3	76.9 ± 3.0
Maximum squeeze pressure	178.7 ± 52.8	194.2 ± 9.4
HPZ length (cm)	3.4 ± 0.6	3.1 ± 0.09
First sensation (mL)	47.4 ± 10.0	35.8 ± 2.1
Desire to defecate (mL)	84.5 ± 18.2	100.8 ± 5.6
Urge to defecate (mL)	125.8 ± 28.5	164.2 ± 7.2
Duration of sustained squeeze (s)	–	18.8

ARM-SS: anorectal manometry solid state; ARM-WP: anorectal manometry water- perfused; SD: standard deviation; SEM: standard error of the mean; HPZ: high-pressure zone.

The participants enrolled in these cited studies vary with respect to the number of participants, their sex, age, and ethnicity, indicating that we should extend the studies to larger and more heterogeneous populations.

The data obtained in this study reinforce the significant discrepancies in the states of rest, containment, and the evacuation effort, considering the mean pressure of the anal canal, as shown in TABLE 1. Men presented much larger contraction pressures in contrast to women, confirming the findings of other authors and previous reports on conventional manometry[8,10,11,12,15].

The comparison with other studies aimed at demonstrating the possibility of performing the same exam in similar protocols by two different systems and to evaluate the differences and similarities in the resultant values, emphasizing that the states of contention and evacuation effort (interdependent operators and patients), may present a greater variability according to the studied population.

For the resting state, one can observe, according to TABLES 3 and 4, that the values from several authors and the present study are very similar, increasing our eagerness to establish a standard reference value that represents the normal for humans. A possible limitation of this study may be the selection of patients, as it did not involve healthy volunteers. The patients were selected through the filter of minor indications such as anal pruritus or chronic constipation. Other limitations of this study are common to other reports[10]. For example, it is not possible to check structural changes of the sphincters at the time of the procedure by ultrasound or resonance imaging. The requested effort test, both of containment and evacuation, has an important and possible role of subjectivity, since it is dependent on the willingness of the patient and the positive action of the operator, which should be considered when performing comparisons. Manometric studies of incontinence evaluation should be pre-classified by incontinence scales for a better selection and quantification of patients, is the next step in our laboratory. We speculate that in view of the current methodology, with standardization of the exam protocol, there will be greater stimulation for research and ease of comparison. Numerical results should approximate and homogenize the different populations. Clinical applicability and indications will be much more grounded and defined, and the parameters obtained in patients with pelvic dyssynergia may better guide their treatment[13,16-19]. This volumetric study (vector volume) can bring new information to the functional and anatomical aspects and prove its usefulness by iconographic representation[20].

CONCLUSION

There is a significant improvement in the conventional manometry technique to HRAM-WP. The agility and ease of implementation are the most evident highlights. Here, the parameters obtained by the system were evaluated in the states of rest and containment, as well as the manometric extension of the functional anorectal sphincter was measured. The results obtained were closely similar to that obtained using the solid state and continuous perfusion equipment from other manufacturers and the results of several previously published reports.

Authors' contribution

Viebig RG (MD): preparation of the text, analysis of the tests. Franco JT and Araujo SV: (nurses): perform the examinations, data compilation. Gualberto D (engineer): hardware and software development.

TABLE 3. Comparative values in mmHg of water-perfused or solid-state high-resolution manometry in men. Adapted from Lee & Barucha[12].

Authors	Present study	Li et al.[11]		Lee et al.[12]		Carrington et al.[10]	Cross-Adame et al.[15]		Rasijeff et al.[13]	Rasijeff et al.[13]
Method	ARM-WP	ARM-SS		ARM-SS		ARM-SS	ARM-SS		ARM-SS	ARM-WP
Variables	Mean± SEM	Mean ± SEM	95% CI	Mean	IQR	Mean± SD	Mean	95% CI	Mean (5th - 95th percentile)	Mean (5th - 95th percentile)
N	20	64	–	27	–	19	36	–	20	20
Maximum resting pressure	–	96.5±2.2	65.2-73.8	–	–	–	90	83-96	–	–
Mean resting pressure	72.2 ± 3	61.3±2.1	56.5-65.5	46	39-56	73±23	–	–	71 (49-117)	67 (340-116)
Maximum squeeze pressure	229.5 ± 17	194.8±6.9	180.9-208.6	178	140-212	290±155	266	245-287	322 (63-538)	177(36-305)
HPZ length (cm)	3.3 ± 0.1	3.6±0.1	3.4-3.8	–	–	3.9±0.8	4.3	4.1-4.5	–	–
First sensation (mL)	43.0 ± 4.8	44.2±1.8	40.6-47.8	10	10-20	–	22	20-25	–	–
Desire to defecate (mL)	102 ± 9.4	–	–	80	60-120	–	94	82-103	–	–
Urge to defecate (mL)	167 ± 9.8	102.5±4.1	94.2-110.8	130	110-178	–	163	140-167	–	–
Duration of sustained squeeze (s)	18.8	12.3±0.7	10.8-13.8	–	–	16±11	30	28-30	–	–

ARM-SS: anorectal manometry solid state; ARM-WP: anorectal manometry water- perfused; SD: standard deviation; SEM: standard error of the mean; HPZ: high-pressure zone; CI: confidence interval; IQR: interquartile range.

TABLE 4. Comparative values in mmHg of water-perfused or solid-state high-resolution manometry in women. Adapted from Lee & Barucha[12].

Authors	Present study	Noelting et al.[9]		Li et al[11]		Lee et al.[12]		Carrington et al.[10]	Cross-Adame et al.[15]		Rasijeff et al.[13]	Rasijeff et al.[13]
Method	ARM-WP	ARM-SS		ARM-SS		ARM-SS		ARM-SS	ARM-SS		ARM-SS	ARM-WP
Variables	Mean± SEM	Mean± SEM	Mean± SEM	Mean± SEM	95% CI	Mean	IQR	Mean± SD	Mean	95% CI	Mean (5th - 95th percentile)	Mean (5th - 95th percentile)
		<50anos	>50anos									
N	30	30	32	46	–	27	–	96	42	–	40	40
Maximum resting pressure	–	88±3	63±5	68.5±2.4	63.6-73.4	–	–	–	76	71-81	–	–
Mean resting pressure	79.8±4	–	–	60.2±2.2	55.8-64.6	32	24-42	65 ± 19	–	–	57 (26-94)	64 (34-101)
Maximum squeeze pressure	170.7±8	167±6	162±12	167.4±8.4	150.5-184.3	75	61-89	225±89	205	186-224	172 (35-329)	105 (27-188)
HPZ length (cm)	3.0±0.1	3.6±0.1	3.5±0.2	3.5±0.1	3.3-3.7	–	–	3.5±0.8	4	3.8-4.2	–	–
First sensation (mL)	31.0±1.2	33±2	32±2	40±1.8	36.2-43.6	10	10-20	–	24	–	–	–
Desire to defecate (mL)	100±7	56±3	59±4	–	–	60	50-70	–	88	–	–	–
Urge to defecate (mL)	162±10.9	86±5	96±5	92.6±4.4	82.2-98.6	115	98-153	–	139	–	–	–
Duration of sustained squeeze (s)	16.8	12±1	14±3	14.7 ± 0.8	13.2-16.3	–	–	11±9	28	27-30	–	–

ARM-SS: anorectal manometry solid state; ARM-WP: anorectal manometry water- perfused; SD: standard deviation; SEM: standard error of the mean; HPZ: high-pressure zone; CI: confidence interval; IQR: interquartile range.

Viebig RG, Franco JTY, Araujo SV, Gualberto D. Manometria anorretal de alta resolução sob cateter de perfusão (MARAR): primeira experiência no Brasil. Arq Gastroenterol. 2018;55(Suppl 1):41-6.

RESUMO – **Contexto** – Através da manometria anorretal de alta resolução (MARAR), a aquisição dos dados e a interpretação do exame tornaram-se mais simplificadas, objetivas e uniformes. **Objetivo** – Validar um sistema de MARAR sob perfusão de água (Alacer Biomédica), com sonda de 24 canais e comparar resultados dos exames de manometria anorretal com outros sistemas em trabalhos já publicados. **Métodos** – Selecionados indivíduos sem distúrbio evacuatório importante. Excluídos pacientes com incontinência, cirurgia orificial, dissinergia, ou lesão esfincteriana. O exame foi realizado com sistema Alacer Biomédica de manometria sob perfusão de agua de 24 canais, com sonda configurada com 6 níveis de 4 canais radiais, distanciados entre si por 0,8 mm. Estabelecidas as pressões médias para o canal funcional, nos estados de repouso (PMR), no esforço de contenção (PMC) e no esforço evacuatório (PMEE). Também foi tabulada a extensão pressórica do esfíncter em cm. Comparou-se os resultados com os disponíveis em literatura recente. **Resultados** – Foram estudados 50 pacientes (20 masc; 30 fem). No geral, foram encontrados os seguintes resultados: a PMR foi de 76,9±3,0 mmHg; PMC foi de 194,2±9,4 mmHg e; PMEE foi de 88,2±3,7 mmHg. Quando divididos por sexo: sexo masculino: PMR 72,2±3,0 mmHg; PMC: 229,5±17 mmHg e; PMEE 91,4±7,0. Sexo feminino: PMR 79,8±4,0 mmHg; PMC: 170,7±8; PMEE 86,1±4,3 mmHg. A extensão manométrica para ambos os sexos foi de 3,1±0,09 cm (masc 3,3±0,1; fem 3,0±0,1). **Discussão** – A realização do estudo da MARAR ficou muito facilitada. A não mobilização da sonda provoca menos desconforto e artefatos, com menor tempo de estudo. Em nossa série há valores diferenciais pequenos entre os sexos durante o repouso, destacando-se maior força de contenção no sexo masculino. Não houve diferença para a extensão do esfíncter. Em relação à comparação com os estudos já publicados, mesmo com sondas de solid state, há uma proximidade de valores. **Conclusão** – O sistema de perfusão utilizado permitiu reproduzir resultados similares a sistemas solid state. Resta estabelecer parâmetros em casos de dissinergia pélvica, incontinência e esclarecer se o estudo pelo vetor volume pode trazer novas informações nos aspectos funcional e anatômico.

DESCRITORES – Canal anal, anatomia & histologia. Manometria, tendências. Bombas de infusão.

REFERENCES

1. Carrington EV, Heinrich H, Knowles CH, Rao SS, Fox M, Scott SM. Methods of anorectal manometry vary widely in clinical practice: results from an international survey. Neurogastroenterol Motil. 2017;29:e13016.
2. Simpson RR, Kennedy ML, Nguyen MH, Dinning PG, Lubowski DZ. Anal manometry: a comparison of techniques. Dis Colon Rectum. 2006;49: 1033-8.
3. Dinning PG, Carrington EV, Scott SM. The use of colonic and anorectal high-resolution manometry and its place in clinical work and in research. Neurogastroenterol Motil. 2015;27:1693-708.
4. Jones PM, Post J, Crowell MD. High-resolution manometry in the evaluation of anorectal disorders: a simultaneous comparison with water-perfused manometry. Am J Gastroenterol. 2007;102:850-5.
5. Kang HR, Lee JE, Lee JS, Lee TH, Hong SJ, Kim JO, et al. Comparison of high-resolution anorectal manometry with water-perfused anorectal manometry. J Neurogastroenterol Motil. 2015;21:126-32.
6. Rao SS, Azpiroz F, Diament N, Enck P, Tougas G, Wald A. Minimum standarts of anorectal manometry. Neurogastroenterol Motil. 2002;14:553-9.
7. Vitton V, Benezech A, Bouvier M. High-resolution anorectal manometry may probably be worth every penny. Neurogastroenterol Motil. 2018;30(1). doi: 10.1111/nmo.13217.
8. Basilisco G, Bharucha AE. High-resolution anorectal manometry: An expensive hobby or worth every penny? Neurogastroenterol Motil. 2017;29(8). doi: 10.1111/nmo.13125.
9. Noelting J, Ratuapli SK, Bharucha AR, Harvey DM, Ravi K, Zinsmeister AR. Normal values for high-resolution anorectal manometry in healthy women: effects of age and significance of rectoanal gradiente. Am J Gastroenterol. 2012;107:1530-6.
10. Carrington EV1, Brokjaer A, Craven H, Zarate N, Horrocks EJ, Palit S, et al. Traditional measures of normal anal sphincter function using high-resolution anorectal manometry (HRAM) in 115 healthy volunteers. Neurogastroenterol. Motil. 2014;26:625-35.
11. Li Y, Yang X, Xu C, Zhang X. Normal values and pressure morphology for three-dimensional high-resolution anorectal manometry of asymptomatic adults: a study im 110 subjects. Int J Colorectal Dis. 2013;28:1161-8.
12. Lee TH, Bharucha AE. How to perform and interpret a high-resolution anorectal manometry test. J Neurogastroenterol Motil. 2016;22:46-59.
13. Rasijeff AMP, Withers M, Burke JM, Jackson W, Scott SM. High-resolution anorectal manometry: a comparison of solid-state and water-perfused catheters. Neurogastroenterol Motil. 2017;29(11). doi: 10.1111/nmo.13124.
14. Wang AJ, Shi YQ, Zheng XL, He XX, Zhou XJ, Li HM, et al. [Normal values for solid state high resolution anorectal manometry in healthy adult volunteers]. [Article in Chinese]. Zhonghua Nei Ke Za Zhi. 2017;56:572-6.
15. Cross-Adame E, Rao SS, Valestin J, Ali-Azamar A, Remes-Troche JM. Accuracy and reproducibility of high-resolution anorectal manometry ans pressure topography analyses in healthy subjects. Clin Gastroenterol Hepatol. 2015;13:1143-50.
16. Mion F, Garros A, Brochard C, Vitton V, Ropert A, Bouvier M, et al. 3D High-definition anorectal manometry: Values obtained in asymptomatic volunteers, fecal incontinence and chronic constipation. Results of a prospective multicenter study (NOMAD). Neurogastroenterol Motil. 2017;29(8). doi: 10.1111/nmo.13049.
17. Knowles CH, Rao SS, Fox M, Scott SM; International Anorectal Physiology Working Party Group (IAPWG). Methods of anorectal manometry vary widely in clinical practice: Results from an international survey. Neurogastroenterol Motil. 2017;29(8). doi: 10.1111/nmo.13016.
18. Ding S. [Value of anorectal manometry in defecation disorders and its clinical interpretation]. [Article in Chinese]. Zhonghua Wei Chang Wai Ke Za Zhi. 2016;19:1342-4.
19. Grossi U, Carrington EV, Barucha AE, Horrocks EJ, Scott MS, Knowles CH. Diagnostic accuracy study of anorectal manometry for diagnosis of dyssynergic defaecation. Gut. 2016:65:447-55.
20. Mion F, Garros A, Subtil F, Damon H, Roman S. Anal sphincter function as assessed by 3D high definition anorectal manometry. Clin Res Hepatol Gastroenterol. 2018. doi: 10.1016/j.clinre.2017.12.004.

ORIGINAL ARTICLE

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Functional and anatomical analysis of the anorectum of female scleroderma patients at a center for pelvic floor disorders

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ABSTRACT – **Background** – Scleroderma or progressive systemic sclerosis is characterized by a chronic inflammatory process with proliferation of fibrous connective tissue and excessive deposition of collagen and extracellular matrix in the skin, smooth muscle, and viscera. The smooth muscle most involved in scleroderma is that of the esophagus, and dysphagia is the most commonly reported symptom. However, the internal anal sphincter may also be impaired by degeneration and fibrosis, leading to concomitant anal incontinence in scleroderma patients. These patients may neglect to complain about it, except when actively questioned. **Objective** – To assess anorectal function and anatomy of female scleroderma patients with symptoms of anal incontinence through Cleveland Clinic Florida Fecal Incontinence Score (CCFIS), anorectal manometry and endoanal ultrasound at the outpatient clinic of colorectal and anal physiology, Clinics Hospital, University of São Paulo Medical School (HC-FMUSP). **Methods** – Female scleroderma patients were prospectively assessed and questioned as to symptoms of anal incontinence. The anorectal manometry and endoanal ultrasound results were correlated with clinical data and symptoms. **Results** – In total, 13 women were evaluated. Their mean age was 55.77 years (±16.14; 27-72 years) and their mean disease duration was 10.23 years (±6.23; 2-23 years). All had symptoms of fecal incontinence ranging from 1 to 15. Seven (53.8%) patients had fecal incontinence score no higher than 7; three (23.1%) between 8 and 13; and three (23.1%) 14 or higher, corresponding to mild, moderate, and severe incontinence, respectively. Ten (76.92%) patients had hypotonia of the internal anal sphincter. Three-dimensional endoanal ultrasound showed tapering associated with muscle atrophy of the internal sphincter in six cases and previous muscle defects in three cases. **Conclusion** – A functional and anatomical impairment of the sphincter is an important factor to assess in patients with progressive systemic sclerosis and it should not be underestimated.

HEADINGS – Systemic scleroderma. Fecal incontinence. Manometry. Ultrasonography.

INTRODUCTION

Anal incontinence is defined as the involuntary and recurrent passage of stool or flatus through the anal canal[1-3]. Its etiology is multifactorial; the disorder has a significant impact on the quality of life due to physical and psychological impairments[4-6]. It is the second leading cause of hospitalization among the elderly in the United States[7,8]. The estimated incidence rate lies between 2% and 7%[3], but it may go up as high as 13.6% among those over 65 years of age[9]. However, it should be emphasized that these rates are fairly underestimated[10] since 50% to 70% of the patients with fecal incontinence do not discuss the disorder with their doctors[11,12]. Therefore, research on this dysfunction is imperative, especially with respect to patients with associated risk factors.

Deterioration of the mechanisms of anal continence is known to occur mainly in the elderly population. These mechanisms include muscle atrophy and denervation processes, which lead to reduction in intra-anal pressures, impairment of the functional reservoir mechanism of the rectum (reduced capacity and compliancy), and diminished rectal sensitivity. Furthermore, the onset of systemic diseases, chiefly endocrine, neurological, and gastrointestinal disorders, is capable of triggering or aggravating incontinence symptoms in the elderly[13].

Scleroderma or progressive systemic sclerosis is characterized by a chronic inflammatory process with proliferation of fibrous connective tissue and excessive deposition of collagen and extracellular matrix in the skin, smooth muscle, and viscera[14,15]. The smooth muscle most involved in scleroderma is that of the esophagus, and dysphagia is the most commonly reported symptom. However, the internal anal sphincter may also be compromised by degeneration and fibrosis, leading to concomitant anal incontinence in scleroderma patients. These patients may neglect to complain about it, except when actively questioned[16].

The esophageal disorder in scleroderma has been the focus several studies, which point to impairment of the organ in 50% to 80% of the patients[17]. Nevertheless, analysis of the anorectal sphincter complex involvement is much less developed, as evidenced by the restricted number of studies.

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Filling the gap, Lock et al.[14] consecutively analyzed a group of 26 scleroderma patients, four of whom were male. The mean age of the group was 56 years (17-77 years). The authors found that only three (11.5%) of the patients had complained about anorectal dysfunction with anal incontinence and they were all female. On the other hand, Rose et al.[18] emphasized that anorectal involvement in scleroderma occurs in approximately 50% of the cases. Likewise, Trezza et al.[19] reported that 38% of the scleroderma patients complained of fecal incontinence to some degree.

This study aimed to assess the anorectal function and anatomy of female scleroderma patients with symptoms of fecal incontinence through Cleveland Clinic Florida Fecal Incontinence Score (CCFIS), anorectal manometry and endoanal ultrasound at the outpatient clinic of colorectal and anal physiology, University of São Paulo School of Medicine (HC-FMUSP).

METHODS

Thirteen female scleroderma patients were prospectively assessed and questioned as to symptoms of anal incontinence. All patients underwent anorectal manometry and endoanal ultrasound.

The questionnaire on anal incontinence symptoms from the Cleveland Clinic Florida (CCF)[20] was administered and the patients' comorbidities (e.g., diabetes and obesity), parity, and history of anorectal surgery were analyzed.

To prepare for the tests, the patients underwent a rectal bowel enema with a 12% glycerin solution (250-500 mL) performed at least three hours before the procedures.

For the anorectal manometry test, a device from Alacer Biomédica® (São Paulo, SP, Brazil) and an 8-channel radial catheter were employed. Prior to the introduction of the catheter, every patient underwent a proctologic examination. It consisted of an inspection and a rectal digital examination with the right index finger for a subjective assessment of the anal sphincters and confirmation that the rectal ampulla was empty of fecal content.

Subsequently, a gel-lubricated catheter was introduced as far as six centimeters from the anal verge and then, employing the station pull through technique, the device was withdrawn at one-centimeter increments with each station held for about 30 seconds. This is a technique routinely performed at our clinic and at most national and international centers. The resting and squeeze pressures, rectoanal inhibitory reflex, rectoanal sensation, and rectal capacity were measured.

The endoanal ultrasound was performed with a three-dimensional BK Medical® Ultraview 800 machine (Mileparken 34, DK-2730 Herlev, Denmark) and a 2050 transducer with the patient in left lateral decubitus with flexed limbs. Scanning was performed in the craniocaudal direction for identification of the puborectalis muscles and internal and external anal sphincter muscles and for measurement of the length of the perineal body from the examiner's index finger in the vaginal introitus. The normal values and ranges for the thickness of the internal and external anal sphincters were within 1.8 mm and 3.2 mm and within 6.0 mm and 12 mm, respectively. Values above or below these ranges were either considered hypertrophy or atrophy.

The anorectal manometry test results were compared to the standard values obtained from the international literature[20-23]. The measurements of the internal and external anal sphincters were contrasted with those within the normal limits for three-dimensional endoanal ultrasound according to Murad-Regadas et al.[24].

RESULTS

Of the 386 scleroderma patients being followed up at the rheumatology outpatient clinic of the Clinics Hospital, University of São Paulo School of Medicine in 2016, 36 exhibited intestinal change, and 13 of these were evaluated. The mean age was 55.77 years (±16.14; 27-72 years) and the mean duration of disease was 10.23 years (±6.23; 2-23 years). The symptoms of anal incontinence were in the 1 to 15 range according to the fecal incontinence CCFIS (0-20)[20]. TABLE 1 displays a summary of the scleroderma patients' clinical data.

TABLE 1. Clinical parameters of the patients with scleroderma.

Parameter	Result
Number of patients	13
Mean age	55.77±16.14 years (27-82 years)
Mean duration of scleroderma	10.23±6.23 years (2-23 years)
Mean duration of anal incontinence	4.58±8.72 years (1-15 years)
Clinical manifestations of the disease	
	CREST – 9
	Pulmonary hypertension/Fibrosis – 8
	Reynaud – 7
	Esophageal – 11
	A combination of 2 or more – 10
Obstetric history	
	Vaginal deliveries – 6
	Mean of vaginal deliveries – 2.2
	Cesarean deliveries – 3
	Nulligravida – 4

CREST: Calcinosis, Reynaud, Esophageal involvement, Sclerodactyly, Teleangectasia.

Seven (53.8%) patients had a fecal incontinence score no higher than 7, three (23.1%) between 8 and 13, and three (23.1%) 14 or higher, corresponding to mild, moderate, and severe anal incontinence, respectively.

None of the patients had diabetes mellitus, two (16.7%) were obese, and 11 (84.61%) were symptomatic and had esophageal involvement. Four (30.77%) patients were nulliparous. One patient had previously undergone colorectal surgery but she had no history of anorectal surgery. Digital rectal examination revealed low resting pressure in seven (53.85%) patients.

The anorectal manometry data (TABLE 2) showed a mean resting pressure of 32.49 mm Hg (±18.1; 7.2-62.7 mm Hg) and hypotonia in the internal anal sphincter in 10 (76.92%) patients. Of these, four had severe hypotonia with pressures no higher than 20 mm Hg, two had moderate hypotonia with pressures between 20 and 30 mm Hg, and four had mild hypotonia with pressures between 30 and 40 mm Hg. The functional anal canal was 2.2 cm long on average, and it was absent in the four patients whose resting pressures were lower than or equal to 20 mm Hg. The mean squeeze pressure was 70.88 mm Hg (20.0-126.4 mm Hg), and three (23.04%) patients had hypotonia of the external anal sphincter. The mean total squeeze sphincter pressure was 110.46 mm Hg (±17.84; 90.5-140). Mean rectal sensitivity was 71.33 (±60.71; 14-155) and

TABLE 2. Mean values of anorectal manometry and comparison with normal limits.

	Mean values	Alterations
Resting pressures	32.49±18.1 mm Hg (7.2-62.7 mm Hg)	Hypotonia in 76.92% of the cases
Total squeeze pressures	110.46±17.84 mm Hg (90.5-140 mm Hg)	Hypotonia in 23.04% of the cases
Rectal sensitivity	71.33±60.71 mL (14-155 mL)	Reduction in 53.85% of the cases
Rectal capacity	154.17±49.01 mL (87-270 mL)	Reduction in 7.69% of the cases

it was reduced in seven (53.85%) cases. On the other hand, mean rectal capacity was 154.17 mL (±49.01; 87-270) and it was reduced in only one (7.69%) patient.

The three-dimensional endoanal ultrasound results showed tapering associated with the muscle atrophy of the internal sphincter in 6 cases and with a previous muscle defect in three (69.23%) cases. Analysis of the acoustic characteristics of the external anal sphincter revealed defects in the sphincter in three cases, co-occurring with the defects of the internal anal sphincter. There was only one case of degenerative diffuse muscular atrophy.

TABLE 3 exhibits the functional and anatomical correlation between anorectal manometry and endoanal ultrasound. Only one of the three patients with normal internal sphincter pressure showed no ultrasound alterations; the mean incontinence score of these patients was 6.67. Of the three patients with mild hypotonia, one alone displayed changes in the internal sphincter on the ultrasound; the mean incontinence score of this group was 8.33. Only one of the three patients with moderate hypotonia of the internal sphincter had no anatomical alterations; the mean incontinence score of this trio was also 8.33. The four patients with severe hypotonia of the internal sphincter exhibited anatomical changes in the sphincter, and their mean incontinence score was 9.25.

TABLE 3. Anatomical and functional correlation between internal sphincter pressures, anatomical changes, and incontinence scores.

Patient	Hypotonia of the internal sphincter (no/mild/ moderate/severe)	Ultrasound changes	CCF incontinence score
Patient 4	No	Yes	14
Patient 11	No	No	5
Patient 13	No	Yes	1
Patient 1	Mild	No	7
Patient 2	Mild	Yes	8
Patient 3	Mild	No	10
Patient 6	Moderate	Yes	14
Patient 7	Moderate	Yes	8
Patient 9	Moderate	No	3
Patient 5	Severe	Yes	15
Patient 8	Severe	Yes	7
Patient 10	Severe	Yes	5
Patient 12	Severe	Yes	10

CCF: Cleveland Clinic Florida.

DISCUSSION

Although the incidence of anorectal function impairment in scleroderma patients is not insignificant, it is usually not reported by them[25] – except when they are questioned by the physician assistant – despite the steep decline in the quality of life caused by fecal leakage[15,19]. The anorectal region is estimated to be affected in 50% to 70% of scleroderma patients. Of these, 20% to 39% will experience some degree of anal incontinence[26-28], which will unfavorably impact their lives[29].

The pathogenesis of gastrointestinal dysfunctions in scleroderma is rooted in myogenic and neural abnormalities with atrophy of the muscle layer – brought on by vascular ischemia – and neural plexus disorders resulting from variable degrees of lamina propria fibrosis[15]. The anorectal sphincter complex exhibits fibrosis and dysfunction primarily of the internal anal sphincter, which consists of smooth muscle. Nonetheless, the correlations involving pathology, manometric findings, and clinical symptoms reported by patients are still unclear.

Trezza et al.[19] reported that approximately 40% of the scleroderma patients suffered from anal incontinence, which was further compounded by diarrhea and accelerated colonic transit. Fynne et al.[25], in a recent study involving 20 scleroderma patients, found that 70% had diarrhea and eight (40%) had fecal incontinence with a CCFIS over 9. Additionally, the study reported that the anal resting pressure in patients with anal incontinence was significantly lower than that of controls (P<0.001) and scleroderma patients without anal incontinence (P<0.05).

Herrick et al. analyzed anorectal manometric characteristics in 16 scleroderma patients; of these, seven had no colorectal functional symptoms, six had constipation, and three had complaints about diarrhea and/or anal incontinence. The authors reported that the mean resting pressure of patients with no anorectal symptoms was 39.8 mm Hg and that of patients with complaints about fecal incontinence was 31.7 mm Hg. Conversely, the mean squeeze pressure of patients with no anorectal symptoms was 70.1 mm Hg as compared to 103.8 mm H in patients with fecal incontinence.

Thoua et al.[27] studied 44 scleroderma patients, four (9.1%) of whom were male. Twenty-four (54.5%) told of symptoms of anal incontinence. When the patients with and without symptoms of anal incontinence were compared, a reduction in resting pressures was found. However, the decrease was not statistically significant.

Finally, in a multicentric study, Richard et al.[30] evaluated 298 scleroderma patients, 87.9% of whom were female with a mean age of 59.4 years and with symptoms lasting on average for 10.9 years. These data are similar to those in the present study, in which the mean age of the patients was 55.66 years and the mean symptom duration was 10.23 years. Besides, the authors observed that among the factors for anal incontinence in scleroderma patients, age (P=0.01), disease duration (P=0.01), female gender (P=0.056), and transvaginal delivery (P<0.001) should be emphasized when comparing scleroderma patients with and without symptoms of anal incontinence. Furthermore, urinary incontinence was found significantly associated with symptoms of fecal leakage or flatus (P<0.001) and with intestinal constipation (P<0.001).

In the present study, the anorectal manometric data of scleroderma patients with previously known symptoms of anal incontinence revealed hypotonia of the anal sphincter muscle in 76.92% of the cases with a dysfunction of voluntary contraction pressures, corresponding to 23.04% of the patients. Still, in the cases

of moderate or severe anal incontinence the mean resting pressure was 25.3 mm Hg, whereas in the women with symptoms of mild anal incontinence, it was 38.7 mm Hg.

Three-dimensional ultrasound showed a correlation between anatomical and functional changes in 9 cases (69.23%), as well as evidence of flaws, atrophies, or irregularities primarily related to the internal anal sphincter. Moreover, it showed a correlation between anatomical alterations and manometric results (low resting pressures), along with a higher incontinence score in the patients with more severe hypotonia in the internal sphincter.

A limiting factor in this study is the small sample size, attributed to the characteristics of the colorectal-anal physiology clinic which is a referral center. Nevertheless, the symptom duration of the disease and the use of a parameter validated in the anal incontinence research enhance the study.

CONCLUSION

The functional and anatomical evaluation of women with scleroderma and symptoms of anal incontinence confirmed hypotonia of the internal anal sphincter and anatomical disorders in most cases. It also showed a correlation between manometric dysfunctions and severity of anal incontinence. A functional and anatomical impairment of the sphincter is an important factor to assess in patients with progressive systemic sclerosis and it should not be underestimated.

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Authors' contribution

Pinto RA: patient recruitment, data collection, examined all patients, paper write. Corrêa Neto IJF: helped in patient recruitment, data review, review of statistical analysis and literature review. Nahas SC: supervision of patient recruitment, exams, supervision of literature review and paper review. Bustamante Lopez LA: referred patients, tables confection and review, paper review. Sobrado Junior CW: data review and support of statistical analysis, tables review. Cecconello I: senior author, supervised all work during the whole process and paper final review.

Pinto RA, Corrêa Neto IJF, Nahas SC, Bustamante Lopes LA, Sobrado Junior CW, Cecconello I. Análise funcional e anatômica anorretal de pacientes femininas portadoras de esclerodermia em um centro universitário de referência em desordens do assoalho pélvico. Arq Gastroenterol. 2018;55(Suppl 1):47-51.

RESUMO – **Contexto** – Esclerodermia ou esclerose sistêmica progressiva caracteriza-se por um processo inflamatório crônico com proliferação e fibrose do tecido conjuntivo e uma deposição excessiva de colágeno e matriz extracelular na pele, musculatura lisa e vísceras. A musculatura lisa mais envolvida é a esofágica e a disfagia é o sintoma mais comumente relatado. Entretanto, o esfíncter anal interno também pode ser acometido por essa degeneração e fibrose ocasionando incontinência anal nos pacientes portadores de esclerodermia. Isso pode ser omitido pelo paciente, exceto quando questionado de forma direta. **Objetivo** – Analisar a função e anatomia anorretal através do escore de incontinência anal de *Cleveland Clinic Florida*, manometria anorretal e ultrassom endoanal em pacientes do sexo feminino portadoras de esclerodermia e sintomas de incontinência anal atendidas no ambulatório de Fisiologia Colorretoanal no Hospital das Clínicas da Universidade de São Paulo (HC-FMUSP). **Resultados** – Treze pacientes do sexo feminino foram avaliadas com média de idade de 55,77 anos (±16,14; 27-72 anos) e duração média da doença de 10,23 anos (±6,23; 2-23 anos). O índice de incontinência anal teve variação de 1-15, sendo que sete (53,8%) pacientes apresentavam índice inferior a 7; três (23,1%) entre 8 e 13; e três (23,1%) superior a 14, correspondendo à incontinência anal leve, moderada e grave, respectivamente. Dez (76,92%) pacientes apresentavam hipotonia do esfíncter anal interno. O estudo da ultrassonografia endoanal de três dimensões demonstrou afilamento com atrofia do esfíncter anal interno em seis casos e defeito muscular em três pacientes. **Conclusão** – O prejuízo funcional e anatômico do complexo esfincteriano anorretal é um importante fator a ser analisado em pacientes portadores de esclerose sistêmica progressiva e isso não pode ser subestimado.

DESCRITORES – Escleroderma sistêmico. Incontinência fecal. Manometria. Ultrassonografia.

REFERENCES

1. Bharucha AE, Zinsmeister AR, Locke GR, Seide BM, McKeon K, Schleck CD, Melton LJ. Prevalence and burden of fecal incontinence: a population-based study in women. Gastroenterology. 2005;129:42-9.
2. Navarro JM, Arroyo Sebastián A, Pérez Vicente F, Sánchez Romero AM, Pérez Legaz J, Serrano Paz P, et al. [Sacral root neuromodulation as treatment for fecal incontinence. Preliminary results]. [Article in Spanish]. Rev. Esp Enferm Dig. 2007;99:636-42.
3. Oliveira L, Jorge JMN, Yusuf S, Habr-Gama A, Kiss D, Cecconelo I. [New treatment modality of anal incontinence: trans-sphincteric silicone injection improved quality of life in 35 incontinent patients]. [Article in Portuguese]. Rev. Bras. Coloproct. 2007;27:167-73.
4. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum. 2000;3:9-17.
5. Yusuf SAI. Avaliação da qualidade de vida na incontinência anal: validação do questionário "fecal incontinence quality of life" (FIQL). [Dissertation]. Faculdade de Medicina da Universidade de São Paulo; 2001.
6. Melenhorst J, Koch SM, van Gemert WG, Baeten CG. The artificial bowel sphincter for faecal incontinence: a single centre study. Int J Colorectal Dis. 2008;23:107-11.
7. Gordon PH, Nivatvongs. Principles and Practice of Surgery for the Colon, Rectum and Anus, 3th ed. New York; 2007. Informa Healthcare: 293-332.
8. Lahr C. Evaluation and treatment of incontinence. Pract Gastroenterol. 1998;102:895-901.
9. Aspiroz F. Guía práctica sobre incontinencia anal. Rev Esp Enferm Dig. 2003;95:722-6.
10. Dorcaratto D, Martínez-Vilalta M, Parés D. [Current indications, surgical technique and results of anterior sphincter repair as a treatment of faecal incontinence]. [Article in Spanish]. Cirugía Española. Cir Esp. 2010;87:273-81.
11. Johanson JF, Lafferty J. Epidemiology of fecal incontinence: the silent affliction. Am J Gastroenterol. 1996;91:33-6.
12. Galandiuk S, Roth LA, Greene QJ. Anal incontinence-sphincter ani repair: indications, techniques, outcome. Langenbecks Arch Surg. 2009;394:425-33.
13. Galandiuk S, Roth LA, Greene QJ. Anal Incontinence-sphincter ani repair: indications, techniques, outcome. Langenbecks Arch Surg. 2009;394:425-33.

14. Lock G, Zeuner M, Lang B, Hein R, Scholmerich J, Holstege A. Anorectal function in Systemic Sclerosis-correlation with esophageal dysfunction? Dis Colon Rectum. 1997;40:1328-35.
15. Souza NM, Williams AD, Wilson HJ, Gilderdale DJ, Coutts GA, Black CM. Fecal incontinence in Scieroderma: assessment of the anal sphincter with Thin-Section Endoanal MR imaging. Radiology. 1998;208:529-35.
16. Zaninotto G, Peserico A, Costantini M, Salvador L, Rondinone R, Roveran A, et al. Oesophageal motility and lower oesophageal sphincter competence in progressive systemic sclerosis and localized scleroderma. Scand J Gastroenterol. 1989;24:95-102.
17. Heyt GJ, Oh MK, Alemzadeh N, Rivera S, Jimenez SA, Rattan S, Cohen S, Dimarino AJ. Impaired rectoanal inhibitory response in scleroderma (systemic sclerosis):an association with fecal incontinence. Dig Dis Sci. 2004;49:1040-5.
18. Rose S, Young MA, Reynolds JC: Gastrointestinal manifestations of scleroderma. Gastroenterol Clin North Am. 1998; 27:563-94.
19. Trezza M, Krogh K, Egekvist H, Bjerring P, Laurberg S: Bowel problems in patients with systemic sclerosis. Scand J Gastroenterol. 1999;34:409-13.
20. Jorge JMN, Wexner SD. Etiology and management of anal incontinence. Dis colon rectum. 1993;36:77-97.
21. Gundling F, Seidl H, Scalercio N, Schmidt T. Schepp W, Pehl C. Influence of Gender and Age on Anorectal Function: Normal Values from Anorectal Manometry in a Large Caucasian Population. Digestion. 2010;81:207-13.
22. Denoya P, Sands DR. Anorectal physiologic evaluation of constipation. Clin Colon Rectal Surg. 2008;21:114-21.
23. Rios CC, Juan RLS, Garcia MDR, Moros ET, Durán FG, Yagüe TM, et al. Differences in the pressures of canal anal and rectal sensitivity in patients with fecal incontinence, chronic constipation and healthy subjects. Rev Esp Enfer Dig. 2010;102:683-90.
24. Regadas SMM, Regadas FSP, Rodrigues LV, Chaves RW, Lima CMM, Lopes LA. Limitações e Detalhes Técnicos do Ultra-Som Endo-Anal no Diagnóstico de Afecções Benignas e Malignas no Canal Anal. Rev bras Coloproct. 2004;24:230-9.
25. Fynne L, Worsoe J, Laurberg S, Krogh K. Faecal incontinence in patients with systemic sclerosis: is an impaired internal anal sphincter the only cause? Scand J Rheumatol. 2011;40:462-6.
26. Herrick AL, Barlow JD, Bowden A, Williams N, Hobson AR, Irving M, Jayson MIV. Investigation of anal function in patients with systemic sclerosis. Annals of the Rheumatic Diseases. 1996,55:370-4.
27. Thoua NM, Schizas A, Forbes A, Denton CP, Emmanuel AV. Internal anal sphincter atrophy in patients with systemic sclerosis. Rheumatology. 2011;50:1596-602.
28. Mawdsley AH. Patient perception of UK scleroderma services–results of an anonymous questionnaire. Rheumatology. 2006;45:1573.
29. Franck-Larsson K, Graf W, Ronnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. Eur J Gastroenterol Hepatol. 2009;21:176-82.
30. Richard N, Hudson M, Gyger G, Baron M, Sutton E, Khalidi N, et al. Clinical correlates of faecal incontinence in systemic sclerosis: identifying therapeutic avenues. Rheumatology (Oxford). 2017;56:581-8.

ORIGINAL ARTICLE

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Short-term results of minimally invasive treatment of gastroesophageal reflux disease by radiofrequency (Stretta): first Brazilian series of cases

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ABSTRACT – **Background** – New endoscopic treatments for gastroesophageal reflux (GERD) are developed every year and are indicated in cases that are refractory to conventional therapies as well as after surgical treatment failure. **Objective** – To present the first cases of endoscopic therapy for GERD performed in Brazil. **Methods** – Use of radiofrequency with the Stretta procedure in symptomatic volunteers diagnosed with GERD. **Results**: The technique was performed in three patients after they were included in the study protocol. No patient had complications, and all patients were discharged on the same day, either without medication or taking it sporadically for symptom control. **Conclusion** – Endoscopic treatment for GERD using radiofrequency was effective in the cases presented herein with no technical complications.

HEADINGS – Endoscopy. Gastroesophageal reflux. Radio waves, therapeutic use.

INTRODUCTION

Gastroesophageal reflux disease (GERD) has a worldwide prevalence ranging between 8% and 33% and affects all age groups and genders. In the United States alone, the annual spending on diagnosing and treating the disease exceeds 9 billion dollars[1].

According to the Montreal Conference consensus, GERD is defined as a disease that develops when the reflux of gastric acid causes unpleasant symptoms and/or complications. It may be attributable to anatomical or physiological defects of the gastroesophageal junction (GEJ) or to altered esophageal peristalsis, and it causes typical or atypical symptoms that negatively affect the quality of life of the individual[1-3].

The diagnosis of GERD is primarily clinical, and empirical treatment is endorsed by several associations. Diagnostic tests are used in cases of treatment failure or uncertain diagnoses[1]. The most widespread initial approach is the use of proton pump inhibitors (PPIs), alone or in combination with prokinetics, with concomitant changes in eating habits and lifestyle. However, even with adequate treatment, 20% to 40% of cases are refractory to treatment with medications, and the effect of drugs is reduced in patients with atypical symptoms[3].

Minimally invasive procedures have emerged as a "bridge" between therapy with medications and surgical treatment, which is considered the gold standard in cases involving an anatomical defect. The Stretta procedure involves the delivery of radiofrequency (RF) energy to the GEJ with the aim of improving the tonicity of the lower esophageal sphincter (LES) and reducing the number of episodes of transient relaxation.

Although there is a wide range of patients who may benefit from the method the use of radiofrequency does not have the capacity to treat anatomical defects and is not indicated in patients with complicated GERD such as active ulcers and stenoses. Complications related to this endoscopic method are rare, however, perforation is the most feared complication. No deaths were reported with this technique. The objective of the present study was to report the initial experience (first three cases) of the Stretta procedure in Brazil in terms of the results and applicability of the technique.

METHODS

The study describes the first three cases of endoscopic treatment of reflux by Stretta RF performed at the State Hospital of the School of Medicine of the ABC, in Santo André, Brazil, in September 2017. The study was approved by the ethics committee (under number 2.334.962), and all patients gave their written informed consent before being included in the study.

Three patients were selected who had a history of GERD and complaints of heartburn and regurgitation for more than six months and were using a full dose of a PPI, but whose clinical condition had not improved or had improved only partially.

All patients underwent initial 24-hour dual-channel pH monitoring and conventional esophageal manometry. The manometry results showed hypotonia of the LES but no changes in esophageal

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body motility or upper esophageal sphincter relaxation. The DeMeester score on pH monitoring was greater than 14.7 in all patients, with one patient exhibiting pathological proximal acid reflux.

TECHNIQUE

The procedures were performed in a surgical center under general anesthesia with orotracheal intubation. First, endoscopy is performed to locate and measure the gastroesophageal transition zone, and then a guidewire is passed into the stomach. At the end of the catheter, there is an inflatable balloon with four retractable titanium-coated needle electrodes that deliver the RF (FIGURE 1). The catheter is coupled to an RF generator that tightly controls the temperature of the electrodes, dissipating heat when necessary to avoid thermal injury (FIGURE 2). The system also has suction and irrigation lines for cooling during the procedure. Double-distilled water is used in the process. After adequate measurement of the gastroesophageal transition zone, the data on its position are stored in the generator, which then controls all the steps of the process.

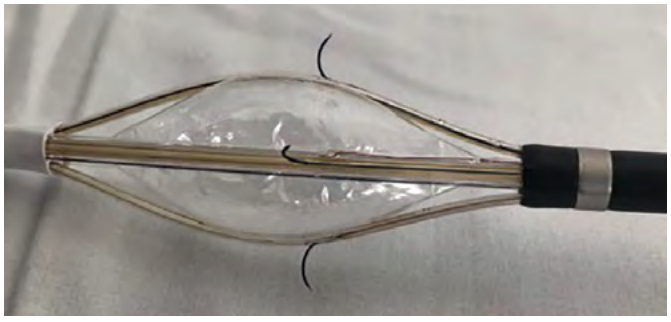

FIGURE 1. Stretta catheter.

FIGURE 2. Generator of rediofrequency.

The balloon is positioned 1 cm above the Z line and is inflated to 25 mL, the needles are deployed within the tissue, and the first command is given by depressing a foot pedal. Each RF treatment lasts approximately 60-90 seconds. After RF is delivered at each level, the needles are withdrawn, and the balloon is deflated. The catheter is then rotated 45 degrees clockwise at the same level and the process is repeated to complete the first cycle of treatment. This procedure is repeated systematically every 0.5 cm in the direction of the Z line and at its level. After completion of the esophageal treatment, the catheter is advanced into the stomach and the balloon is inflated to 25 mL and pulled against the cardia for additional cycles of RF, now with two more 30-degree rotations. These steps are repeated by inflating the balloon to 20 mL. Upon completion of this procedure, an additional upper endoscopy is performed to exclude complications and assess the created lesions (FIGURES 3 and 4). In the three cases presented below, postoperative control exams were not performed due to the short follow-up time.

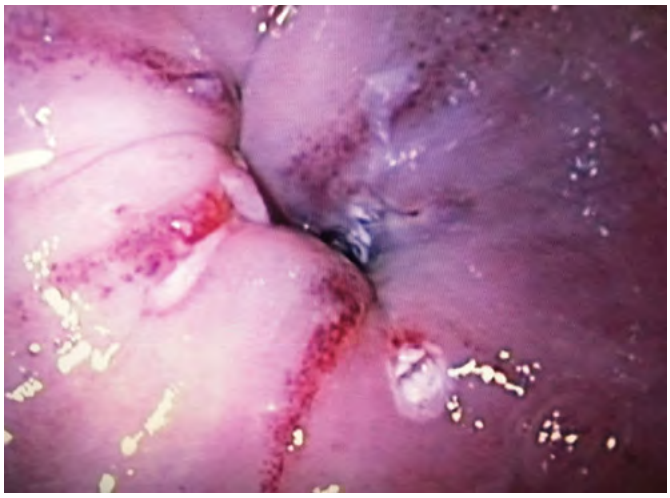

FIGURE 3. Endoscopic view of esophagus post procedure.

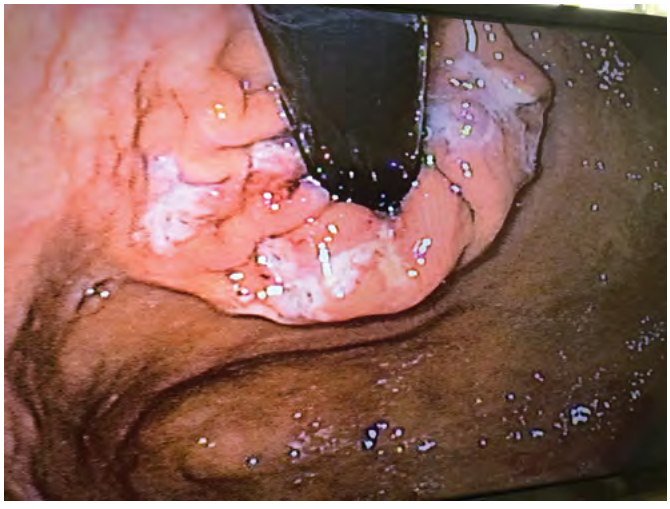

FIGURE 4. Retroflex vision of gastric junction post procedure.

RESULTS

Case 1: A 46-year-old man with a diagnosis of GERD made six years previously who was undergoing treatment with full-dose PPI with only partial improvement of symptoms. After endoscopic treatment, which was performed without complications, he was on a soft diet for 15 days and on full-dose PPI for 90 days. He progressed to mild dysphagia in the first week, after which the symptoms subsequently decreased. He stopped using PPI after the first three months and remained asymptomatic thereafter.

Case 2: A 34-year-old man with typical symptoms of GERD for two years without improvement after the use of PPI, even at a full dose. After undergoing Stretta RF, he progressed without pain and with mild discomfort for five days. He took full-dose PPI for three months, and although drug discontinuation was attempted, the reflux symptoms persisted (which he reported to be milder than before the discontinuation of PPI). He remained asymptomatic with a 20-mg dose of esomeprazole and currently takes the medication sporadically.

Case 3: A 63-year-old man with atypical symptoms of reflux (chronic cough) and a diagnosis of GERD by pH monitoring; respiratory disease was excluded as the cause of the symptoms. He exhibited symptom improvement with the use of PPI (40 mg of esomeprazole every 12 hours) but wished to reduce or discontinue the use of daily medication. After endoscopic treatment, he progressed without complaints; after three months of using PPI daily, the dose was reduced until it was discontinued. He currently takes the medication sporadically when ingesting certain liquids.

DISCUSSION

Although this study shows just a small number of patients and in a short term of follow-up, we presented the firsts cases of GERD treatment performed using radiofrequency in Brazil. Currently, around 200 procedures have already been carried out in our country.

The treatment for GERD includes a wide range of management strategies, from lifestyle changes to pharmacological, endoscopic, and surgical interventions[4,5,6]. When patients with GERD have persistent symptoms that are not controlled with drugs or when they are responders who do not wish to keep taking medication on a daily basis, the Stretta procedure is an alternative to surgery and implants. Since it is a non-surgical procedure that is performed in an outpatient setting, patients can return to their normal activities a few days after the procedure[7].

Treatment failure has become one of the most common presentations of GERD encountered by gastroenterologists[2], with up to 20% of patients unable to achieve total control of the symptoms despite the use of PPIs.

Nissen fundoplication is considered the gold standard invasive treatment for GERD, as it restores the antireflux barrier and improves the quality of life. It is indicated for non-responders to PPIs, atypical symptoms, large hiatal hernias, and complications such as stenosis and Barrett's esophagus; however, patients may develop other complications from the surgical treatment.

The use of RF in the treatment of GERD was approved by the FDA in 2000. The procedure involves the delivery of RF energy to several sites along the GEJ, inducing hypertrophy and thereby increasing the tone of the LES[3,8].

Two mechanisms may explain the results obtained with the use of the Stretta procedure: improvement of GEJ tone through the retraction and deposition of collagen at the lesion sites and the neurolysis of fibers afferent to the GEJ that are responsible for the transient relaxation of the LES, which may reduce the episodes of transient sphincter relaxation and affect the fibers responsible for heartburn complaints[9-13].

Previous studies have shown that the Stretta procedure improves reflux symptoms and quality of life, reduces or eliminates the use of medications, and reduces exposure to acid. In addition, more than 40 clinical studies have shown that the Stretta procedure is safe and effective, with long-lasting results[9].

Noar et al.[9] prospectively evaluated 18 patients refractory to previous fundoplication and 81 patients with GERD refractory to the standard treatment. They all underwent therapy with the Stretta procedure during the 10-year follow-up period. Endoscopic treatment resulted in sustained improvement, with results similar to those obtained with the standard nonsurgical treatment. Moreover, patients refractory to surgery have the possibility to undergo a different treatment via endoscopy that is safe and effective, with fewer complications compared to undergoing another surgical procedure. In a systematic review with meta-analysis, FASS et al. demonstrated that RF treatment reduced the incidence of erosive esophagitis by 24% (P<0.001); however, there was a non-statistically significant increase in LES basal pressure[10].

CONCLUSION

The pilot procedures of the first protocol of studies conducted in Brazil produced satisfactory results, similar to those reported in the literature, with discontinuation or reduction in the daily use of medications and improvement of the typical and atypical symptoms of GERD.

Authors' contribution

Souza TF, Grecco E: data collect, revision of the manuscript. Quadros LG: manuscript writing, final approval. Albuquerque YD: revision of the manuscript. Azôr FO: manuscript writing. Galvão Neto M: orientation, revision of the manuscript, final approval.

Souza TF, Grecco E, Quadros LG, Albuquerque YD, Azôr FO, Galvão Neto M. Tratamento endoscópico da doença do refluxo gastroesofágico com uso de radiofrequência (Stretta): resultados a curto prazo da primeira série de casos brasileira. Arq Gastroenterol. 2018;55(Suppl 1):52-5.

RESUMO – **Contexto** – Novos tratamentos endoscópicos para refluxo gastroesofágico são desenvolvidos a cada ano, sendo indicados em casos refratários às terapias convencionais, bem como após a falha do tratamento cirúrgico. **Objetivo** – Apresentar os primeiros casos de terapia endoscópica para tratamento do refluxo gastroesofágico realizado no Brasil. **Métodos** – Uso de radiofrequência com o procedimento de Stretta em voluntários sintomáticos e diagnosticados com DRGE. **Resultados** – A técnica foi realizada em três pacientes depois de terem sido incluídos no protocolo de estudo. Nenhum paciente teve complicações, e todos receberam alta hospitalar no mesmo dia, mantendo-se sem medicação ou fazendo uso esporádico para o controle de sintomas. **Conclusão** – Tratamento endoscópico para doença do refluxo gastroesofágico com uso de radiofrequência foi eficaz nos casos aqui apresentados e sem complicações técnicas.

DESCRITORES – Endoscopia. Refluxo gastroesofágico. Ondas de rádio, uso terapêutico.

REFERENCES

1. Gyawali, C Prakash, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018;67:1351-62.
2. Triadafilopoulos G. Stretta: a valuable endoscopic treatment modality for gastroesophageal reflux disease. World J Gastroenterol. 2014;20:7730-8.
3. Nicolau AE, Lobonţiu A, Constantinoiu S. New Minimally Invasive Endoscopic and Surgical Therapies for Gastroesophageal Reflux Disease (GERD). Chirurgia (Bucur). 2018;113:70-82.
4. Noar M, Squires P, Khan S. Radiofrequency energy delivery to the lower esophageal sphincter improves gastroesophageal reflux patient-reported outcomes in failed laparoscopic Nissen fundoplication cohort. Surg Endosc. 2017;31:2854-62.
5. Liu HF, Zhang JG, Li J, Chen XG, Wang WA. Improvement of clinical parameters in patients with gastroesophageal reflux disease after radiofrequency energy delivery. World J Gastroenterol. 2011;17:4429-33.
6. Kethman W, Hawn M. New Approaches to Gastroesophageal Reflux Disease. J Gastrointest Surg. 2017;21:1544-52.
7. Maradey-Romero C, Fass R. New and future drug development for gastroesophageal reflux disease. J Neurogastroenterol Motil. 2014;20:6-16.
8. Perry KA, Banerjee A, and Melvin WS. Radiofrequency energy delivery to the lower esophageal sphincter reduces esophageal acid exposure and improves GERD symptoms: a systematic review and meta-analysis," Surg Laparosc Endosc Percutan Tech. 2012;22:283-8.
9. Fass R, Cahn F, Scotti DJ, Gregory DA. Systematic review and meta-analysis of controlled and prospective cohort efficacy studies of endoscopic radiofrequency for treatment of gastroesophageal reflux disease. Surg Endosc. 2017;31: 4865-82.
10. van Pinxteren B, Sigterman KE, Bonis P, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database Syst Rev. 2010;(11):CD002095
11. Noar M, Squires P, Khan S. Radiofrequency energy delivery to the lower esophageal sphincter improves gastroesophageal reflux patient-reported outcomes in failed laparoscopic Nissen fundoplication cohort. Surg Endosc. 2017;31: 2854-62.
12. Utley DS. The Stretta procedure: device, technique, and preclinical study data. Gastrointest Endosc Clin N Am. 2003;13:135-45.
13. Herman, DRM, Wojtysiak, R. Jansuz, et al. Interstitial Cells of Cajal (ICC) and Smooth Muscle Actin (SMA) activity after non-ablative radiofrequency energy application to the Internal Anal Sphincter (IAS). In Poster Presentation at Digestive Disease Week Conference, 2013.

REVIEW

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Proposals to approximate the pediatric Rome constipation criteria to everyday practice

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ABSTRACT – **Background** – Acceptance of the prevailing pediatric Rome constipation criteria, by primary care physician, is still low. Even for research purposes they have not been universally adopted. Thus, it has been indicated that some re-evaluation of these criteria would be welcome. **Objective** – The authors aimed to look at the timing of diagnosis and the dietary treatment recommendations in the criteria, to make proposals trying to approximate them to everyday practice. **Methods** – The literature cited in the Rome criteria was reviewed and the publications pertinent to the subject, searched by Medline up to January 2018, were included. **Results** – An early diagnosis is fundamental to avoid evolution to bothersome complications and possibly to 'intractable' constipation, but the inclusion of two items of the criteria might hamper it. Thus, one constipation sign/symptom should suffice, usually the easily observable 'painful or hard bowel movements'. Details about dietary fiber recommendations are missing in the criteria, although its increase is usually the first approach in primary care, and overall the data about dietary fiber supplements point to beneficial effects. **Conclusion** – For diagnosis and treatment of pediatric constipation in primary care, one constipation sign/symptom should suffice. The recommended daily dietary fiber intake, according to the American Health Foundation, should be detailed as a treatment measure, and also for prevention, from weaning on.

HEADINGS – Constipation. Practice guideline. Infant. Child. Adolescent.

INTRODUCTION

Chronic childhood functional constipation (FC) can be considered a public health problem, since it is highly prevalent worldwide, the cure rate is only around 50% to 60%, recurrence rates are high, and behavior problems are often associated, leading to an important impact on quality of life and to a great economical burden[1-4]. Prevalence rates vary a lot, however, and this can be attributed, at least in part, to different definitions used for its diagnosis[4,5]. The Rome III criteria for FC, recently substituted by the Rome IV criteria, tried to uniform the diagnostic and treatment criteria[6-9], but its acceptance is still low[10-13]; up to 79.5% of the primary care physician rely on personal experience for diagnosis[12]. Reasons for the low acceptance could be the multiple and often changing criteria, the fact that they are based mainly on 'expert opinion', the grade of evidence mostly being low or very low, and/or that they do not fulfill the physician's experience and needs[11,14]. In fact, in every day clinical practice often infants present only with straining/pain at defecation of hard and/or scybalous/pebble-like stools, daily or every second day, but the Rome III/IV definition might hamper an early diagnosis at that point[15]. In addition, usually the first approach by the primary care physician is to implement a dietary fiber dense diet (DFdd) for these patients[12,16-18], but details about DF recommendations are missing in the criteria. Even for research purposes, the Rome criteria are not universally adopted[19]. Thus, it has recently been indicated that some re-evaluation of the Rome criteria would be welcome[4,10].

Diagnostic and treatment criteria should be able to let constipation be detected at its earliest signs, and to avoid that children evolve to 'intractable' constipation; this condition might end up in surgery or electric stimulation[20], and, of course, all efforts should be made to avoid that an originally functional disorder evolves to such invasive and/or expensive interventions. The question remains, however, whether the evolution to 'intractable' constipation could have been interrupted by early diagnosis, and adequate treatment and follow-up. It has been reported that early therapeutic intervention in infants (<3 months of symptoms or <2 months of treatment before referral) contributes to the resolution of constipation, that onset of constipation before age 1 year is a poor prognostic sign, and that in constipated children younger than 4 years of age, prognosis is better when the child is treated before age 2 years[1,2,6,7]. Furthermore, in children with severe constipation, evidenced by the need for rectal biopsy, a better outcome was associated with an earlier diagnosis[21].

Taking the above cited factors into account, we aimed to look at the timing of diagnosis and the dietary treatment recommendations in the prevailing pediatric Rome constipation criteria[6-9], and to make proposals trying to approximate the criteria to everyday practice.

METHODS

The references cited in the pediatric Rome constipation criteria II, III, IV [6-9,22] were reviewed. The literature cited in a recent book chapter[23] was updated for Jan 2013-Jan 2018. MEDLINE (PubMed) was searched using the headlines 'constipation children', 'constipation diet'.

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RESULTS AND DISCUSSION

Timing of diagnosis

Up to 40% of FC begins in infancy, often after weaning[6,16,17,24,25]. In Brazilian community studies, 21% to 22% of infants already present constipation[17,26]. Also, 1/3 to 2/3 of mothers of children attended with constipation refer its onset in the first year of life[16,27-30], and these data are trustable, since in a similar population it has been shown that recalled data were similar to recorded data[31]. Van Tilburg et al.[10] also showed this similarity, but agreement between daily dairies and the Rome III questionnaire was poor. However, a recent review, which tried to change childhood constipation paradigm from diagnosis and treatment to prevention, did neither mention weaning as a risk factor nor diagnosis at an early age[4].

In addition, many complications, which often also begin early in life, ensue along time (FIGURE 1)[16]. Median age at onset of constipation symptoms was 3 month, but 53 month at first visit, with a median interval of 38 month[16]. A similar mean interval of 31 month from median age at onset 27 month to first visit (57% ≥48 month) has been reported[32]. Had appropriate treatment begun at the early onset age, possibly much suffering could have been avoided, since complications disappeared after successful constipation treatment[16].

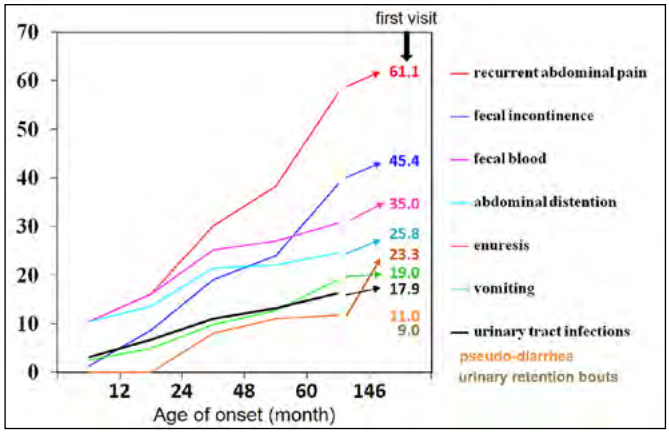

FIGURE 1. Constipation complications: cumulative percentage according to age of onset, in 163 children at the first visit (median age 53 month) to a pediatric gastroenterology outpatient unit. Only data at the first visit are available for pseudo-diarrhea and urinary retention bouts.

Thus, considering that FC frequently begins in infancy, many complications ensue along time, that diagnosis depends on definition, and that early diagnosis is desirable, definition should be able to make an early diagnosis. However, it is difficult to diagnose FC by the Rome III/IV criteria at the very beginning, because two items are needed for diagnosis, in both age ranges[6-9].

Looking at the six items for neonate/toddler in details[6,8]:

– '2 or fewer weekly defecations' is infrequent in weaned constipated infants[13]; it occurred in 13% of ≤2 years old at presentation in a general pediatric clinic[18], and it seems to occur later in the follow-up, as can be suspected from the compilation of Brazilian studies: in tertiary services 43.1%-65.8% of the children with constipation presented <3 weekly defecations, whereas this occurred only in 17.3%-27.0% in primary care units/community studies and in 4.0%-5.8% of constipated infants;

– 'impression of excessive fecal retention' may be difficult to value[6,7];

– 'large rectal fecal mass' precludes community surveys; also, a proportion of parents are unwilling to accept a rectal exam, and in fact, it is often omitted in primary care, even when only one additional Rome III criterion is present[33];

– 'fecal incontinence' and 'large diameter stools (that may obstruct the toilet)' are considered irrelevant in infants, since they could be observed only in toilet trained infants[6,8] (except large diameter, a difficult to value item);

– 'painful or hard bowel movements' is easy to observe and can, therefore, be considered the most important item for an early diagnosis in infants/early age. The Bristol Stool Chart[34] is useful in recognizing the stool characteristics.

Various studies indicate that one item, instead of two, should suffice for an early diagnosis: – in a cohort study from birth up to 4 years, scybalous stools, hard stools and/or difficult evacuation were by far the most frequent constipation signs, whereas <3 stools/week occurred in only 2.5% and 5.5% at 24 and 48 months respectively, and only 0.7% of 4 years old children off diapers presented 'feces in clothing'[35]; – by the Boston criteria[36], which consider only one item for diagnosis, 22.2% of 303 infants in three community Health Centers presented FC, whereas this would have been diagnosed in only 2.6% of them by the Rome III criteria[37]; – Malowitz et al.[32] used Rome III as the inclusion criteria, but in the discussion they stated '*there is a need for programs for primary care clinicians to educate them on recognizing and treating functional constipation according to published guidelines*', to say, delay or difficulty in defecation for ≥2 weeks sufficient to cause significant distress in the patient[38]; – only 12.8% of children seen as outpatients in a secondary-level hospital, with fecal impaction at the rectal exam, presented one additional Rome III criterion[33]; – in a recent core outcome set for clinical trials in childhood FC, defecation frequency was less often mentioned as the most important treatment outcome by parents and patients than by healthcare professionals, and 'impression of fecal retention' and 'stools that obstruct the toilet' were almost not mentioned[39].

The Rome III and IV certainly diagnose FC, but besides the diagnostic delay, one must be cautious that - in clinical studies – control children are not the reverse of children with constipation. Exemplifying: an infant with five painful, hard and scibalous defecations recorded along 2 weeks in a diary (2.5 weekly defecations), no other symptoms, would not be considered constipated by the Rome criteria, and could be wrongly included in the control group.

Treatment

The multi factorial aspect of FC treatment has to be emphasized; outcome can be unsatisfactory, for instance, if only dietary treatment is approached without disimpaction procedures. Thus, the Rome III/IV recommendations about the initial treatment steps – education, and disimpaction whenever fecal retention/fecaloma is present –, followed by a decreasing laxative schedule are to be endorsed. However, dietary treatment was ignored by Rome III for both age groups, and Rome IV does not mention diet (nor disimpaction) for neonate/toddler[6-8]. For >4 years old children/adolescents, Rome IV recommends 'normal' fiber and fluid intake, based on the joint ESPGHAN/NASPGHAN recommendations, which considered evidences "very low" to indicate DF supplements, not mentioning any specific age group[9,14].

The question is: what is a 'normal' DF intake? According to the initial pediatric Rome II constipation criteria it should be age (years)+5 g/day[22]. But, following the proposal of the American Health Foundation, this was the minimum DF intake recommended for healthy ≥3 years old children, the considered safe range being age (years)+5-10 g/day. A similar range after weaning, increasing from 4-6 months onwards, was proposed in the same Conference[40,41]. According to the US Dietary Reference Intakes the recommended amount for ≥1 year olds is even higher, to say, 14g/1.000 kcal, functional fiber being included in the latter amount[42]. All recommendations still need to be validated, however. Also the adequate soluble/insoluble DF ratio has to be considered[23]. The amount of DF which would be considered adequate for constipated children is unknown, but certainly it should not be lower than for healthy children (perhaps somewhat higher, instead), taking into account that most studies depicted a lower DF intake in constipated than in control children and, therefore, low DF intake is considered a risk factor for FC[4,23,42]. It was also shown that adherence to a 'Health Conscious' dietary pattern was associated with a lower prevalence of constipation at 24 months of age[43], that there could be a bidirectional association between fussy eating and functional constipation in preschool children[44] and that picky eating was associated with a lower DF intake and hard stools[45].

Thus, in our opinion, the recommendation about DF intake in the pediatric Rome constipation criteria needs a more detailed approach, since dietary intervention, including an increase in DF, is almost universal among pediatricians as the first treatment step[12]. It is easy to prescribe, not invasive, and has the additional advantage to decrease the risk of obesity, diabetes mellitus, cardiovascular disease, the metabolic syndrome, and several cancers, at the long term[46-48]. Considering that almost all population surveys depicted a DF intake below the minimum recommended, for the majority of the children/adolescents[23], it has the additional advantage to be educative for the dietary component of a healthy life style. Impressed leaflets, as presented in FIGURE 2, are helpful.

To help prevent and treat constipation, obesity, diabetis, cardiovascular disease, some sorts of cancer, the family's diet should always contain much dietary fiber

DIETARY FIBER DENSE FOODS

CEREALS: 6 portions/day, half full-corn: breads (wheat/rye), popcorn, pasta, breakfast cereals, rice, kibbe wheat. Add wheat bran if necessary

VEGETABLES: 3–5 portions/day. Don't throw away what can be eaten

FRUITS: 2-4 portions/day (with bagasse/seeds)

"fresh" unpeeled (not sieved for juice)

dried: coconut, raisins, apricot, etc

OIL SEEDS: 1-2 portions/day: olives, all sorts of nuts and seeds

PULSES: 1 portion/day: beans and other legumes

REMINDERS

HEALTHY SNACKS: dried fruits and nuts, separate or together, olives

SWEETS: add fresh/dried fruits, berries with condensed milk, pumpkin, etc.

DRINK WATER WITH DIETARY FIBER DENSE FOODS

Almost NO DIETARY FIBER in watermelon, melon, peeled cucumber

DECREASE excess of protein (milk, eggs, meat, etc.), and of junk food

(_____-_____-__) whenever necessary.

FIGURE 2. Example of impressed leaflets for a dietary fiber rich diet.

Part of the resistance to recommend a DFdd could be the fear of a lower nutrient biodisponibility due to DF. But, adverse effects of overconsumption appear unlikely, except at extremes of intake[49]. In line with this, respectively 27.6% and 17.1% of healthy community 2-5 years old children had an age (years)+5-10g/day and >age+10g/day DF intake [somewhat lower proportions after 10 years (26.4% and 13.4%) and also in older children/adolescents][50]. Also Kranz et al.[51] presented a proportion of 2-5 years old children above the considered upper limit. In our experience, the bowel habit recovery of children with constipation was significantly associated with DF intake >age+10 g/day; this amount was ingested at 57.5% of their follow-up visits along up to 2 years, without adverse effect on the growth curves[52].

There is a belief that it is difficult to achieve children's and their family's adherence to a DFdd, and several interventions to increase acceptance have been tested[23]: goal setting, stimulate patient's responsibility, point rating, and physician's *versus* physician's plus dietitian's diet advice. In the latter study, although physician's plus dietitian's advice was somewhat better, detailed physician's dietary advice alone did also significantly increase DF intake[53], and this is also the authors experience[52].

Treatment with polyethylene glycol (PEG) and lactulose were detailed in the 'evidence–based recommendations', but DF intake was not, although the level of evidence for a 'normal' fiber intake (instead of additional fiber), for disimpaction with PEG, as well as for PEG and lactulose for maintenance therapy, were equally graded "very low"[14]. It was stated that there are no data to support a DFdd or DF supplements for treating childhood constipation, but there are also no data to refute the claim that they are helpful. In fact, a recent review stated that 'limited evidence suggests that administration of a fiber supplement is more effective than placebo for the treatment of childhood constipation'[54]. Reported studies about the outcome of constipation treatment, so far, have included children whose diets contained their usual foods or supplementation with mainly soluble (SDF) or insoluble fibers (IDF). In theory, IDF is better for laxation than SDF, and wheat bran, a predominantly IDF with a high pentose content, seems better than cocoa husk, whose main component is cellulose[52,55,56]. Data about the outcome of constipated children receiving DF supplementation were recently compiled. It calls attention that in 6/7 studies with IDF supplements, wheat bran was employed[23,42]. Overall, notwithstanding methodological aspects in these studies, they should be valued, since all point in the same direction of beneficial effects. In addition, a recent publication showed that green banana biomass can be safely used to reduce laxative doses[57]. Thus, supplementation should not be condemned 'a priori', but could be recommended when a DFdd is not sufficiently accepted, or not effective, and for economically deprived populations, who cannot afford full corn products, usually more expensive than the refined ones. It seems much more reasonably to use a food component, like wheat bran (if available), to supplement refined cereals, than to use laxatives over years, and in fact, it is very helpful in our everyday practice. In Brazil – and possibly in many other countries – wheat bran is cheap and tested by governmental entities for food security, since it is included in horse and cattle food[52]. Also, no negative influence on biochemical or anthropometric data was shown in the studies in which the supplementation was used[23].

Besides normal fiber diet, normal fluid intake is recommended in childhood FC[9,14]. A classical publication by Loening-Baucke and some guidelines recommended higher water intake as part of

constipation treatment[38,58-60]. Although results of clinical assays about this topic are controversial, there is some epidemiological evidence that higher intake of water is associated with lower risk of constipation[61]. Nevertheless, when DF intake is increased, a greater amount of water intake is necessary, since DF water adsorption underlies its physiological mechanism of action.

PROPOSALS

Taking the above considerations into account, the proposals to approximate the pediatric Rome constipation criteria to everyday practice are:

Include prevention, starting at weaning[6,17,43]. Besides an adequate formula (whenever economically possible), complementary food containing DF according to Agostoni et al.[41] should be recommended. Had weaning already occurred between age 2-6 month, relactation could be tried as a first step, and, if not successful, poorly sensitizing complementary food containing DF should be anticipated, along with the formula[23]. Had weaning occurred before age 2 month, the infant has to be closely observed, to introduce lactulose at the first constipation signs/symptoms.

Diagnosis and treatment should not be postponed: avoid delay in diagnosis, recognizing the initial symptoms and using the Bristol Stool Chart[34]; one constipation sign/symptom should suffice to begin dietary treatment.

Treatment should be as vigorous as possible, with disimpaction (whenever fecal retention/fecaloma and/or complications are present), and at least age (years)+5-10g/day DF. DF supplements, mainly of IDF, should be recommended whenever a DFdd is not sufficiently accepted, or not effective, and for economically deprived populations.

CONCLUSION

Prevention and early diagnosis of FC are important and should be contemplated in the criteria. In addition, although many studies with emphasis on a DFdd and/or DF supplements fail methodological aspects, DF treatment of constipation should not be neglected, since overall the studies point in the same direction of beneficial effects.

Authors' contribution

Maffei HVL: wrote the text and approved the final version of the article. Morais MB: critically revised the manuscript and approved the final version of the article to be published.

Maffei HVL, Morais MB. Propostas para aproximar os critérios de Roma para constipação intestinal em pediatria à prática diária. Arq Gastroenterol. 2018;55(Suppl 1):56-60.

RESUMO – **Contexto** – O emprego dos prevalecentes critérios de Roma para constipação em pediatria, no atendimento primário de saúde, ainda é baixo. Mesmo com finalidade de pesquisa, estes critérios não têm sido adotados universalmente. Assim, tem sido indicado que seria bem-vinda alguma revisão de tais critérios. **Objetivo** – Avaliar criticamente o 'timing' do diagnóstico e as recomendações dietéticas dos critérios, a fim de apresentar propostas que os aproximem da prática clínica diária. **Métodos** – Foi revisada a literatura citada nos critérios de Roma e foram incluídas as publicações pertinentes ao assunto pesquisadas pela Medline até janeiro 2018. **Resultados** Diagnóstico precoce é fundamental, a fim de evitar evolução para complicações indesejáveis e possivelmente para constipação dita intratável, mas a necessidade de inclusão de dois itens – segundo os critérios – pode inviabilizá-lo. Assim, um sinal/sintoma seria suficiente, em geral a presença de 'evacuações dolorosas e/ou duras', facilmente observáveis. Ademais, nos critérios faltam detalhes quanto à recomendação sobre fibra alimentar, embora o seu incremento seja usualmente a primeira abordagem no atendimento primário, e no geral os dados sobre suplementos de fibra alimentar apontem para efeitos benéficos. **Conclusão** – Para diagnóstico de constipação em pediatria no atendimento primário, um sinal/sintoma de constipação deve ser suficiente. A ingestão diária de fibra alimentar, conforme a *American Health Foundation*, deve ser detalhada para o tratamento da constipação e também como medida preventiva desde o desmame.

DESCRITORES – Constipação intestinal. Guia de prática clínica. Lactente. Criança. Adolescente.

REFERENCES

1. van Ginkel R, Reitsma JB, Buller HA, van Wijk MP, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond puberty. Gastroenterology. 2003;125:357-63.
2. van den Berg MM, Van Rossum CH, de Lorijn F, Reitsma JB, Di Lorenzo C, Benninga MA. Functional constipation in infants: a follow-up study. J Pediatr. 2005;147:700-4.
3. Pijpers MAM, Bongers MEJ, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr. 2010;50:256-68.
4. Rajindrajith S, Devanarayana NM, Crispus Perera BJ, Benninga MA. Childhood constipation as an emerging public health problem. World J Gastroenterol. 2016;22:6864-75.
5. Morais MB, Maffei HVL. Constipation. J Pediatr (Rio J). 2000;76(Suppl 2):S147-56.
6. Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate / toddler. Gastroenterology. 2006;130:1519-26.
7. Rasquin A, DiLorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130:1527-37.
8. Benninga MA, Nurko S, Faure C, Hyman PE, St James-Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology 2016;150:1443-55.e2.
9. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150:1456-68.
10. van Tilburg MA, Squires M, Blois-Martin N, Leiby A, Langseder A. Test of the child/adolescent Rome III criteria: agreement with physician diagnosis and daily symptoms. Neurogastroenterol Motil. 2013;25:302-7. e246.
11. Sood MR. Evidence-based diagnosis and treatment of functional constipation: 'are we there yet?' J Pediatr Gastroenterol Nutr. 2015;60:288-9.
12. Scarpato E, Quitadamo P, Roman E, Jojkic-Pavkov D, Kolacek S, Papadopoulou A, et al. Functional gastrointestinal disorders in children: a survey on clinical approach in the Mediterranean area. J Pediatr Gastroenterol Nutr. 2017;64:e142-6.
13. Koppen IJN, Vriesman MH, Tabbers MM, Di Lorenzo C, Benninga MA. Awareness and implementation of the 2014 ESPGHAN/NASPGHAN guideline for childhood functional constipation. J Pediatr Gastroenterol Nutr. 2018;66:732-7.
14. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58:258-74.
15. Levy EI, Lemmens R, Vandenplas Y, Devreker T. Functional constipation in children: challenges and solutions. Pediatric Health Med Ther. 2017;8:19-27.

16. Maffei HVL, Moreira FL, Kissimoto M, Chaves SM, Faro SE, Aleixo AM. Clinical and alimentary history of children attending a pediatric gastroenterology outpatient clinic with functional chronic constipation and its possible complications. J Pediatr (Rio J). 1994;70:280-6.
17. Aguirre ANC, Vitolo MR, Puccini RF, Morais MB. Constipation in infants: influence of type of feeding and dietary fiber intake. J Pediatr (Rio J). 2002;78:202-8.
18. Loening-Baucke V. Prevalence, symptoms and outcome of constipation in infants and toddlers. J Pediatr. 2005;146:359-63.
19. Kuizenga-Wessel S, Benninga MA, Tabbers MM. Reporting outcome measures of functional constipation in children from 0 to 4 years of age. J Pediatr Gastroenterol Nutr. 2015;60:446-56.
20. Hutson JM, Dughetti L, Stathopoulos L, Southwell BR. Transabdominal electrical stimulation (TES) for the treatment of slow-transit constipation (STC). Pediatr Surg Int. 2015;31:445-51.
21. Tran K, Staller K, Macklin E, Goldstein A, Belkind-Gerson J, Kuo B. Need for rectal biopsy for childhood constipation predicts severity of illness and need for laxatives. J Pediatr Gastroenterol Nutr. 2016;62:834-9.
22. Rasquin-Weber A, Hyman P, Cucchiara S, Fleisher D, Hyams J, Milla P, et al. Childhood functional gastrointestinal disorders. Gut. 1999;45 Suppl 2:II60–8.
23. Maffei HVL. Dietary fiber and wheat bran in childhood constipation and health. In: Watson RR, Preedy VR, Zibadi S. Wheat and rice in disease prevention and health. San Diego: Elsevier (AP), 2014:227-39.
24. Turco R, Miele E, Russo M, Mastroianni R, Lavorgna A, Paludetto R, et al. Early-life factors associated with pediatric functional constipation. J Pediatr Gastroenterol Nutr. 2014;58:307–12.
25. Vandenplas Y, Abkari A, Bellaiche M, Benninga M, Chouraqui JP, Cokuðraþ F, et al. Prevalence and health outcomes of functional gastro-intestinal symptoms in infants from birth to 12 months of age. J Pediatr Gastroenterol Nutr. 2015;61:531-7.
26. Motta MEFA, Silva GAP. Chronic functional constipation in children: diagnosis and prevalence in a low-income community. J Pediatr (Rio J). 1998;74:451-4.
27. Morais MB, Vítolo MR, Aguirre NA, Fagundes-Neto U. Measurement of low dietary fiber intake as a risk factor for chronic constipation in children. J Pediatr Gastroenterol Nutr. 1999;29:132-5.
28. Del Ciampo IRL, Galvão LC, Del Ciampo LA, Fernandes MIM. Prevalence of chronic constipation in children at a primary health care unit. J Pediatr (Rio J). 2002;78:497-502.
29. Inaba MK, Peret-Filho LA, Val AC, Penna FJ. Prevalence and clinical characteristics of chronic constipation in children at a gastroenterology care unit. Pediatria (São Paulo). 2003;25:157-63.
30. Medeiros LCS, Morais MB, Tahan S, Fukushima E, Motta MEFA, Fagundes-Neto U. Clinical characteristics of pediatric patients with chronic constipation according to age group. Arq Gastroenterol. 2007;44:340-4.
31. Borgo HC, Maffei HVL. Recalled and recorded bowel habits confirm early onset and high frequency of constipation in day–care nursery children. Arq Gastroenterol. 2009;46:144-50.
32. Malowitz S, Green M, Karpinski A, Rosenberg A, Hyman PE. Age of onset of functional constipation. J Pediatr Gastroenterol Nutr. 2016;62:600-2.
33. Modin L, Walsted AM, Jakobsen MS. Identifying faecal impaction is important for ensuring the timely diagnosis of childhood functional constipation. Acta Paediatr. 2015;104:838-42.
34. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-4.
35. Mota DM, Barros AJD, Santos I, Matijasevich A. Characteristics of intestinal habits in children younger than 4 years: detecting constipation. J Pediatr Gastroenterol Nutr. 2012;55:451-6.
36. Hyams J, Colletti R, Faure C, Gabriel-Martinez E, Maffei HVL, Morais MB, et al. Functional gastrointestinal disorders: Working group report of the First World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2002;35(Suppl 2):S110-7.
37. Souza DS, Tahan S, Morais MB. [Constipation and dietary fiber intake in infants: relation with type of feeding, nutritional status and indicators of body iron] [abstract]. [Article in Portuguese]. Rev Med Minas Gerais. 2012;22 Suppl 3:S35.
38. Constipation Guideline Committee of the American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2006;43:e1-13.
39. Kuizenga-Wessel S, Steutel NF, Benninga MA, Devreker T, Scarpato E, Staiano A, et al. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. BMJ Paediatrics Open. 2017;1:e000017.
40. Williams CL, Bollella M, Wynder EL. A new recommendation for dietary fiber in childhood. Pediatrics. 1995;96:985-8.
41. Agostoni C, Riva E, Giovannini M. Dietary fiber in weaning foods of young children. Pediatrics. 1995;96:1002–5.
42. Stewart ML, Schroeder NM. Dietary treatments for childhood constipation: efficacy of dietary fiber and whole grains. Nutr Reviews. 2013;71:98-109.
43. Kiefte-de Jong JC, de Vries JH, Escher JC, Jaddoe VW, Hofman A, Raat H, et al. Role of dietary patterns, sedentary behaviour and overweight on the longitudinal development of childhood constipation: the Generation R study. Matern Child Nutr. 2013;9:511-23.
44. Tharner A, Jansen PW, Kiefte-de Jong JC, Moll HA, Hofman A, Jaddoe VWV, et al. Bidirectional associations between fussy eating and functional constipation in preschool children. J Pediatr. 2015:166;91-6.
45. Taylor CM, Northstone K, Wernimont SM, Emmett PM. Picky eating in preschool children: Associations with dietary fibre intakes and stool hardness. Appetite. 2016:1;100:263-71.
46. Carlson JJ, Eisenmann JC, Norman GJ, Ortiz KA, Young PC. Dietary fiber and nutrient density are inversely associated with the metabolic syndrome in US adolescents. J Am Diet Assoc. 2011;111:1688-95.
47. World Cancer Research Fund / American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011:1-43. Available from: https://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf.
48. Kranz S, Brauchla M, Slavin JL, Miller KB. What do we know about dietary fiber intake in children and health? The effects of fiber intake on constipation, obesity, and diabetes in children. Adv Nutr. 2012;3:47-53.
49. Aggett PJ, Agostoni C, Axelsson I, Edwards CA, Goulet O, Hernell O, et al. Nondigestible carbohydrates in the diets of infants and young children: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2003;36:329-37.
50. Saldanha LG. Fiber in the diet of US children: results of national surveys. Pediatrics. 1995;96:994-7.
51. Kranz S, Mitchell DC, Siega-Riz AM, Smiciklas-Wright H. Dietary fiber intake by American preschoolers is associated with more nutrient-dense diets. J Am Diet Assoc. 2005;105:221-5.
52. Maffei HVL, Vicentini AP. Prospective evaluation of dietary treatment in childhood constipation: high dietary fiber and wheat bran intake are associated with constipation amelioration. J Pediatr Gastroenterol Nutr. 2011;52:55-9.
53. Karagiozoglou-Lampoudi T, Daskalou E, Agakidis C, Savvidou A, Apostolou A, Vlahavas G. Personalized diet management can optimize compliance to a high-fiber, high-water diet in children with refractory functional constipation. J Acad Nutr Diet. 2012;112:725-9.
54. Horvath A, Szajewska H. Probiotics, prebiotics, and dietary fiber in the management of functional gastrointestinal disorders. World Rev Nutr Diet. 2013;108:40-8.
55. Cummings JH. The effect of dietary fiber on fecal weight and composition. In: Spiller GA. Handbook of dietary fiber in human nutrition. Boca Raton: CRC Press. 2001:183-252.
56. Maffei HVL. Chronic functional constipation: which supplementary fiber to choose? J Pediatr (Rio J). 2004;80:167-8.
57. Cassettari VMG, Machado NC, Lourenção PLTA, Carvalho MA, Ortolan EVP. Combinations of laxatives and green banana biomass on the treatment of functional constipation in children and adolescents: a randomized study. J Pediatr (Rio J). 2018. pii: S0021-7557(17)30638-1. [Epub ahead of print].
58. Loening-Baucke V. Chronic constipation in children. Gastroenterology. 1993;105:1557-64.
59. National Collaborating Centre for Women's and Children's Health (UK). Constipation in children and young people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. London: RCOG Press. 2010:91-149.
60. Lindberg G, Hamid SS, Malfertheiner P, Thomsen OO, Fernandez LB, Garisch J, et al. World Gastroenterology Organisation global guideline: Constipation–a global perspective. J Clin Gastroenterol. 2011;45:483-7.
61. Boilesen SN, Tahan S, Dias FC, Melli LCFL, Morais MB. Water and fluid intake in the prevention and treatment of functional constipation in children and adolescents: is there evidence? J Pediatr (Rio J). 2017;93:320-7.

REVIEW

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Neural control of swallowing

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ABSTRACT – **Background** – Swallowing is a motor process with several discordances and a very difficult neurophysiological study. Maybe that is the reason for the scarcity of papers about it. **Objective** – It is to describe the chewing neural control and oral bolus qualification. A review the cranial nerves involved with swallowing and their relationship with the brainstem, cerebellum, base nuclei and cortex was made. **Methods** – From the reviewed literature including personal researches and new observations, a consistent and necessary revision of concepts was made, not rarely conflicting. **Results and Conclusion** – Five different possibilities of the swallowing oral phase are described: nutritional voluntary, primary cortical, semiautomatic, subsequent gulps, and spontaneous. In relation to the neural control of the swallowing pharyngeal phase, the stimulus that triggers the pharyngeal phase is not the pharyngeal contact produced by the bolus passage, but the pharyngeal pressure distension, with or without contents. In nutritional swallowing, food and pressure are transferred, but in the primary cortical oral phase, only pressure is transferred, and the pharyngeal response is similar. The pharyngeal phase incorporates, as its functional part, the oral phase dynamics already in course. The pharyngeal phase starts by action of the pharyngeal plexus, composed of the glossopharyngeal (IX), vagus (X) and accessory (XI) nerves, with involvement of the trigeminal (V), facial (VII), glossopharyngeal (IX) and the hypoglossal (XII) nerves. The cervical plexus (C1, C2) and the hypoglossal nerve on each side form the *ansa cervicalis*, from where a pathway of cervical origin goes to the geniohyoid muscle, which acts in the elevation of the hyoid-laryngeal complex. We also appraise the neural control of the swallowing esophageal phase. Besides other hypotheses, we consider that it is possible that the longitudinal and circular muscular layers of the esophagus display, respectively, long-pitch and short-pitch spiral fibers. This morphology, associated with the concept of energy preservation, allows us to admit that the contraction of the longitudinal layer, by having a long-pitch spiral arrangement, would be able to widen the esophagus, diminishing the resistance to the flow, probably also by opening of the gastroesophageal transition. In this way, the circular layer, with its short-pitch spiral fibers, would propel the food downwards by sequential contraction.

HEADINGS – Deglutition. Cranial nerves. Brain stem. Basal ganglia. Cerebral cortex. Neural pathways.

INTRODUCTION

To understand how the nervous system controls any biological process, we must know what are the necessary afferent and efferent impulses, where they came from, what is their destination and which functions integrate this process[1]. Swallowing is a motor process with a very difficult neurophysiological study, and subject of several discordances[2]. These observations and the literature review show that great part of the accepted mechanisms for the neural control of swallowing could not be considered trustworthy hypotheses. In this way, the neural control of swallowing remains as a research field, open to new considerations.

The swallowing process is formed by the oral, pharyngeal and esophageal phases[2,3], with much controversy involving their mechanisms. Great evolution has been obtained with observations of neurological lesions and many are the methods available for confirmation of the hypotheses that, in the end, remain as just hypotheses. Nevertheless, there is an expressive quantity of new morphological and functional conceptions that, even being only hypotheses, at least are more structured than the empirical others used until now to explain the swallowing mechanisms.

It had been believed that the swallowing control center was located exclusively in the brainstem, and that the entire swallowing mechanism, automatic and semiautomatic movements of chewing and swallowing, were involuntary by genesis and regulation. From observations of patients with cortical dysphagia, the role of the cerebral cortex in the swallowing control mechanism has been recognized and extensively studied[4].

Based on the nervous system embryology a rhombencephalic center, formed by association of the third primitive vesicle (hindbrain) with the second one (mesencephalon or midbrain), origin of the brainstem and cerebellum was described. The rhombencephalic center would receive stimuli produced by the food bolus passage over existing receptors at the base of the tongue, on the palatoglossal and palatopharyngeal pillars, on the palate, and pharyngeal walls, especially in the posterior one, starting an involuntary and coordinated process that would characterize the pharyngeal phase of swallowing. The assumption was that this phase would be controlled, in physiological circumstances, by a framework continuously modified by peripheral afferent stimuli that would especially influence the muscular function, adjusting strength and time of contraction to the size of bolus swallowed. The bolus entrance in the oropharynx would produce soft palate elevation and reflex contraction of the upper pharynx constrictor. In addition, to protect the airways, the bolus entrance would initiate a peristaltic wave that would propagate to the other muscles, narrowing the pharynx, except at the level of the cricopharyngeal muscle, which would relax, allowing the passage of the pharyngeal content to the esophagus[5].

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A center involving sensory and motor nuclei integrated by a network of interneurons located in the brainstem complements the described coordination[6,7,8].

A new approach considers the oropharynx functional activity as composed by the oral and pharyngeal phases of swallowing[2,9,10]. This functional activity would be produced by muscular contraction, and coordinated by a control center in the brainstem, designated as the Central Pattern Generator (CPG) for Swallowing[9,11-15].

This pattern-generating center would consist of two hemicenters, one on each side of the brainstem, which, under physiological conditions, would synchronize and organize the bilateral contraction of the oral and pharyngeal muscles. Their nerve fibers would cross the midline of the brainstem, interconnecting the two halves of the involved generating centers with swallowing-linked neurons in the dorsal and ventral regions of the brainstem[16,17].

It has been admitted that in this pattern-generating center the solitary tract nucleus would receive information that would converge to it both from peripheral impulses triggered by the swallowing stimulus and from the cerebral cortex[9,18]. This convergence of stimuli to the solitary tract nucleus would be primarily important for the induction of voluntary swallowing[15]. It's been considered that the first event observed in the "swallowing reflex" would occur in the oropharyngeal cavity (oral and pharyngeal cavities), where the bolus would produce a sensory afferent stimulus that would inform the brainstem and cortex[19-21].

In nutritive swallowing, the first cortical command would be sent to the solitary tract nucleus. Thus, eating and drinking sequentially could be voluntarily initiated or facilitated by the cerebral cortex through the neural network (CPG) of the brainstem[2,20,22,23]. It was also considered that, in voluntary deglutition, regions of the cortex and subcortical areas related to swallowing would serve mainly to trigger and control the onset of the swallowing motor sequence, especially the oral phase[20].

In disagreement with the bilateral integration of the brainstem, admitted in the pattern-generating center conception[9,11-15], it has already been described that both the dorsal (sensory) and ventral (motor) regions represented on both sides of the brainstem would be able to independently coordinate the pharyngeal and esophageal phases of swallowing on each side[24].

Although the oral and pharyngeal cavities are morphologically contiguous and have sequential function, the oral and pharyngeal swallowing phases are distinct from each other in structures, innervation and neural control. The oral phase is voluntary and the pharyngeal one is reflex. Designating the oral and pharyngeal phases as oropharyngeal or buccopharyngeal[2,9,10,12,25,26] is inadequate, although not rare. Anatomically, the oropharynx is the intermediate segment that communicates the oral and pharyngeal cavities, receiving the contents transferred during swallowing, which in no way defines the functional role of the oral and pharyngeal phases of swallowing.

High dysphagia has been often defined as oropharyngeal dysphagia. High dysphagia may occur with impairment of both phases, but the possibility of exclusively oral or pharyngeal injury cannot be ignored. The fact that the injury of one neighboring phase interferes with the dynamics of the other emphasizes commitment of the sequence, and not of both phases. The oropharyngeal designation for this kind of dysphagia diverts the clinical and therapeutic focuses, which should be directed to the actually compromised phase**,** with doubtful therapeutic adequacy. The designation of oropharyngeal dysphagia led us to misclassify the dysphagia that affects the oral and pharyngeal phases as transference dysphagia, and the esophageal dysphagia, as a conduction one. Transference is proper to the oral phase, and conduction, to the pharyngeal and esophageal phases. Transference is a voluntary process and occurs in the voluntary oral phase, and conduction occurs in the pharyngeal and esophageal phases, both reflex[27].

It is a fact that we have learned very much by observing neurological dysphagia. In addition, today there are many methods available for study of swallowing and its disorders, which, while enabling us to better understand the swallowing physiology, highlight the significant number of conflicting concepts still in force.

The aim of this work is to offer new conceptual alternatives, based on the literature and personal research, to give a more solid basis to the hypotheses used to explain the swallowing mechanisms and, consequently, the neural control of swallowing.

CHEWING

Mastication, basically voluntary, integrates the activation of the chewing muscles, innervated by the trigeminal pair (V), the tongue muscles, innervated by the hypoglossal pair (XII), and with less evident participation, of the expression muscles, in special the orbicular of the lips and buccinators, which, like other skin-inserted muscles, are innervated by the facial pair (VII). Trigeminal afferent fibers reach the dorsal region of the brainstem (the main sensory nucleus of the V) and, still in an afferent pathway through the trigeminal lemniscus, reach the thalamus, from where axons go to the postcentral gyrus (somatosensory cortex) in the parietal region of the cerebral cortex[1]. The postcentral gyrus transfers information to the precentral gyrus (somatomotor cortex) in the frontal region, generating a motor efferent response by the nuclear cortical route (pyramidal-voluntary), which reaches the ventral region of the brainstem, where on each side the trigeminal motor nucleus is located. From this nucleus, the motor route of the trigeminal nerve activates the chewing muscles[1,28-31].

By activation from the cortex-nuclear pathway, the hypoglossal motor nucleus in the brainstem gives dynamics to the tongue in its participation in the chewing process. Afferent and efferent facial nerve pathways, in functional association, participate in the accommodation of the bolus and in the oral cavity pressure by adjusting the tension of the cavity walls, especially dependent on the orbicularis of the lips and buccinators.

The afferent trigeminal fibers also reach its mesencephalic nucleus, which connects its sensory route with its motor root in absence of cortical relation. This direct, sensory-motor relationship allows the chewing action, which is voluntary, to have a reflex component[1], which, by proprioceptive perception during the preparation of the bolus, modulates the variation of the chewing intensity produced by the continuous modification of the resistance of the bolus under preparation.

ORAL QUALIFICATION

The oral cavity is able to identify several characteristics of the inner bolus. It presents at least four distinct types of perception, thermal, painful, mechanical and chemical[32,33].

The thermal-reception can perceive hot or cold in various levels. When pleasing and adequate with the type of food, they can be incorporated to the pleasure of the diet. When extreme and damaging, they produce rejection.

The pain-reception is usually due to mechanical, thermal or chemical hyper-stimuli produced on sensitive afferent pathways, warning and preventing injury. However, there is a painful submodality produced by capsaicin, present in a large number of peppers, probably using the same pain way, whose perception is often perceived as dietary pleasure.

The mechanical-reception allows noticing the contact of the bolus against the intraoral structures. The tongue that presses the bolus, gathering information defined as tactile. This information allows perceiving the physical characteristics of the bolus, detecting if there is impropriety in its contents. Mechanical-reception is also responsible for the characterization of oral bolus volume and viscosity, to define how much motor units must be depolarized for the necessary generation of oral pressure to transfer the contents from the oral cavity to the pharynx.

The chemical-reception identifies the tastes by different mechanisms. Sweet appears to be identified by coupling of a primary messenger (taste protein) with a secondary messenger (cAMP – cyclic adenosine monophosphate), whose concentration increase closes the potassium channels in the gustatory receptors, with membrane depolarization. It is considered that the intracellular metabolic pathways responsible for natural sweeteners would be distinct from those activated by artificial sweeteners, whose secondary messenger would be the IP3 (inositol triphosphate), which would act on the calcium channels, provoking calcium input into the cells, with depolarization. The identification of the bitter taste is given by coupling of the same primary messenger (taste protein), resulting in calcium increase due to action of the IP3 secondary messenger, releasing a neurotransmitter without membrane depolarization. The salty perception is generated by direct passage of sodium through the membrane channels that depolarize. The hydrogen from sour or acid penetrates the cellular membrane by blocking the potassium channels, which supports the membrane depolarization[32,33].

Although sweet, salty, sour and bitter are the tastes considered basic, others like metallic, astringent and more recently, umami (monosodium glutamate) have been suggested as primary. Nevertheless, the first four were the ones that resisted as basic over time. It is not very clear whether and how the association of basic tastes (sweet, salty, sour and bitter) can appropriately produce the palate, i.e. the gustatory perception as a whole. The palate, which can distinct for each of us, is an association of the social level and learning, basic tastes, tactile and thermal perceptions, and certainly the impressions permitted by the vision and smell senses[33,34].

The perception of tastes in the oral cavity has been prioritized on the tongue. Classic description points to sequential areas on each side of the anterior 2/3 of the tongue as having selective capacity for the basic tastes, the anterior tip to sweet, the sides, in sequence to salty and sour, and the posterior central area, to bitter[31,34-39]. This concept, already contested, shows that the tongue is able to perceive all the basic tastes in all its regions, with expressive predominance of the bitter one[40-42].

The tongue's filiform, fungiform, foliate and circumvallate papillae are anatomical elements involved with the chemical senses (taste). These papillae display incrusted gustatory buttons. In the filiform papillae, gustatory buttons are rare or absent. In the fungiform ones there are few, but in the foliate papillae and especially in circumvallate ones, there are many gustatory buttons[41,42].

Buttons considered as gustatory can be identified, in addition to the tongue papillae, on the palate and vallecula. Buttons with similar morphology to those defined as gustatory have been found on the pharynx regions, where, at first, no taste is perceived. In the vallecula, even with the oral cavity anesthetized, the bitter taste transferred to the pharynx can be perceived by vagus nerve conduction[41].

As far as we know, in the oral cavity there have not been described or observed any other morphological kind of receptors than that admitted as gustatory. However, the oral cavity holds several other perceptions. Specific receptors to be stimulated are supposedly necessary. Nevertheless, there is no evidence indicating that any receptor is responsible for detecting only one type of stimulus[43].

It is possible that receptors deemed gustative are also able to receive other oral stimuli. This hypothesis is reinforced by the presence of receptors morphologically similar to the gustatory receptor, where tastes are not perceived as palate, in the pharynx (except the in vallecula) and larynx[34]. There are also gustatory perception descriptions by thermal stimulation of the tongue[44], such as sweet perception by heating the anterior edge of the tongue from a cool state, and evocation of acid or salty perception with cooling intensification[45].

CRANIAL NERVES

The cranial nerves associated with the swallowing process are the trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X), accessory (XI) – usually not considered – and hypoglossal (XII). It should be emphasized that the structures involved in the swallowing process are pairs, both anatomically and/or functionally, due to the dual-side innervation. Anatomically unique, the tongue, palate, pharynx and larynx are functional pairs, each side having independent innervation[1,7,29,30].

From receptors on each side of the oral cavity, the trigeminal (V), facial (VII) and glossopharyngeal (IX) nerves conduct information to the brainstem. These mixed nerves lead sensitivity (afferent pathway) and motor command (efferent pathway). The afferent pathways of the anterior two thirds of the tongue are supplied by the lingual nerve, which associates the trigeminal (general sensibility) with the facial nerve (taste). In the posterior third of the tongue, both the general sensibility and taste are conducted by the glossopharyngeal nerve[33,39,41-46].

In its afferent pathways toward the brainstem, the trigeminal, facial and glossopharyngeal nerves of both sides will make ganglionar synapses similar to the posterior roots of the spinal cord. The afferent pathway of the trigeminal nerve makes synapses in the trigeminal ganglion (Gasser), the facial nerve, in the geniculate ganglion, and the glossopharyngeal, in the rostral ganglion (upper one)[1,30,39].

The trigeminal nerve (V) has three branches; upper (ophthalmic), middle (maxillary) and lower (mandibular). The upper and medium are exclusively sensitive, and the inferior, mixed. The sensitive fibers of the three branches innervate the face in transverse bands of representation. Regarding the oral cavity, the middle branch (maxillary) has sensitive responsibility for the upper arcade teeth, upper lip, cheeks, hard palate (mouth mucosa) and mucosa of the rhinopharynx. The sensitive portion of the lower branch (mandibular) is responsible for the sensitivity of the lower arcade teeth and lower mucosa of the mouth, as well as by the general sensitivity of the anterior 2/3 of the tongue[1,29,30].

From the trigeminal ganglion to the brainstem, all the sensory pathways will end in the posterior portion of the brainstem, over the trigeminal sensitive nucleus that occupies the medulla oblongata

(spinal tract nucleus of the cranial nerve V), the pons (main sensory nucleus of the cranial nerve V) and the midbrain (midbrain nucleus of the cranial nerve V). Centrally the sensitive fibers divide into short, ascending branches that end in the main sensorial nucleus, to attend to tactile sensibility, and into long, descending branches that serve to tact, temperature and pain, also providing collateral pathways to the spinal nucleus of the cranial nerve V[29].

It is believed that proprioceptive fibers from the midbrain nucleus of the trigeminal neve, in synapse with its motor nucleus located in the upper portion of the pons[47], would be able to integrate important chewing reflex arcs[1,29]. Unless expressly desired, these arcs allow reflex modulation of chewing intensity based on bolus consistency variations, even during the voluntary bolus chewing preparation.

The motor root of the trigeminal nerve emerges from the ventral portion of the pons and runs through the mandibular root to innervate the chewing muscles, the mylohyoid, the anterior belly of the digastric and the tensor muscle of the palate[1,29,30].

The facial nerve (VII) is a mixed one, considering its motor root in association with the sensitive root given by the intermediate (Wrisberg) nerve[1]. The taste of the anterior two thirds of the tongue on each side are its responsibility. From the tongue, this afferent, pre-ganglionic route follows through the lingual nerve (association of nerves V and VII), and afterwards through the tympanic cord nerve (facial branch), to make synapses on the geniculate ganglion. Through the intermediate nerve, the postganglionic fibers (afferent visceral special – gustative route) synapse in the solitary tract nucleus of the medulla oblongata, associated with the general afferent visceral fibers, providing sensitive innervation to the mucosa of the nasal cavities and soft palate[1].

The parasympathetic efferent fibers of the facial nerve, originating from the upper salivary nucleus located on each side of the upper portion of the medulla oblongata, run through the intermediate nerve and afterwards through the tympanic cord nerve to make synapses in the submandibular ganglion. Thence, through postganglionic fibers, they stimulate salivary secretion of the submandibular and sublingual glands[1].

The motor portion of the facial nerve has its nucleus on the ventral portion of the pons. Its fibers stimulate the skin-inserted muscles in the face, neck and scalp, as well as the posterior belly of digastric and stylohyoid muscles[1,8,29,39].

The glossopharyngeal (IX) nerve comes out of the skull together with the vagus (X) and accessory (XI) nerves. The visceral general afferent and the visceral special afferent fibers of the glossopharyngeal nerve are associated. The visceral general afferent fibers are responsible for the general sensitivity of the oropharynx mucosa and the posterior third of the tongue, and the special visceral afferent fibers, for the taste of the posterior third of the tongue. These preganglionic fibers make synapses with the upper ganglion. The postganglionic fibers will end at the solitary tract nucleus[1,8,29].

The glossopharyngeal nerve's efferent pathways come from two distinct nuclei of the medulla oblongata, the salivary inferior (parasympathetic) nucleus and ambiguous motor (special visceral efferent) nucleus. The parasympathetic fibers stimulate the salivary secretion after synapses with the optic ganglion, from which postganglionic fibers emerge to innervate the parotid gland[1,29,31].

The glossopharyngeal nerve's only motor role is with the stylopharyngeus muscle. Nevertheless, it has already been considered as motor to the superior pharyngeal constrictor muscle, whose activity had been previously attributed to the vagus nerve, responsible for the motor innervation of all pharyngeal constrictors muscles[1,29].

The vagus (X) nerve has relationships extending from the cervical region to the abdomen (transverse colon). Its sensory afference (sensory pathway) connects with the solitary tract nucleus located in the medulla oblongata. The visceral special efference (motor pathway) comes from the ambiguous nucleus in the ventral region of the medulla oblongata, and the parasympathetic fibers (visceral general efference), from the dorsal motor nucleus of the vagus[1,29-31].

The visceral special afferent (taste) and visceral general afferent (sensibility) pathways of the vagus nerve, after synapses in a peripheral ganglion (lower or caudal), have their postganglionic fibers end at the solitary tract nucleus, similar to that observed in the intermediate portion of the facial nerve and in the glossopharyngeal one. The visceral general afferent fibers conduct impulses related to the sensitivity of the pharynx, larynx, trachea and esophagus, and the visceral special afferent route lead taste stimuli from receptors on the vallecula and from a small posterior area of the tongue next to the vallecula[1].

The visceral general efferent (parasympathetic) fibers of the vagus nerve originate in the vagus dorsal motor nucleus, and from it, on each side, they gather in a single-trunk, descending pathway, emitting branches in the cervical, thoracic and abdominal region, where they end. These preganglionic fibers will establish synapses in peripheral ganglia of the parasympathetic vegetative or autonomous nervous system, close to, or even inside, the viscera walls[1,29-31].

The visceral special efferent (motor) fibers of the vagus originate in the ambiguous nucleus, and are responsible for innervation of the striated muscles of the pharynx, larynx and esophagus[1].

The accessory (XI) nerve, not always considered among those related to swallowing control, presents special visceral efferent fibers coming from the ambiguous nucleus (motor to striated muscles of branchial origin) that would join this type of special visceral efferent fibers of the vagus. Thus, in addition to the vagus (X) nerve, the accessory (XI) one would also be responsible for the motor innervation of the striated portions of the pharynx, larynx and esophagus. A possible second association between the vagus and accessory nerves would be the presence of parasympathetic fibers (general visceral efferent) in the accessory nerve, with origin in the dorsal nucleus of the vagus, which would accompany the vagus nerve fibers[1,29,47].

The Hypoglossal (XII) nerve, a motor one, has an individualized nucleus on the ventral-medial portion on each side of the medulla oblongata. It is responsible for the tongue extrinsic and intrinsic muscles. In addition, fibers from the cervical plexus in association with the hypoglossal nerve form the *ansa cervicalis*, from which a branch from the cervical plexus, usually C1, will innervate the geniohyoid muscle, one of the responsible for the hyoid-laryngeal displacement[1,8,29].

The pharyngeal plexus (glossopharyngeal, vagus and accessory though vagus) is considered responsible for the pharyngeal reflex phase, where afferent information from the pharynx reach the brainstem, generating efferent stimuli to the pharyngeal structures involved in this phase of the swallowing process.

The pressure transfer from the oral cavity to the pharynx by distention would produce afferent stimuli that would reach the brainstem, in special the sensitive (solitary tract) nucleus. From the sensitive nucleus, through interneurons of the reticular formation, the ventral motor (ambiguous) nucleus of the brainstem generates efferent motor stimuli to the pharyngeal structures. Several structural movements initiated during the voluntary oral phase,

remain in progress until the end of the pharyngeal phase, such as hyoid-laryngeal elevation, swallowing apnea and tongue posterior projection, to pharynx, started during the oral ejection, without considering the palate tension produced by the trigeminal nerve. In this way, several elements of the oral phase incorporated by the pharyngeal reflex phase allow us to consider the pharyngeal phase as dependent on the cranial nerves V, VII, IX, X, XI and XII of both sides.

BRAINSTEM, CEREBELLUM, BASE NUCLEI AND CORTEX

The brainstem is formed by the medulla oblongata, the pons and the midbrain. It contains the cranial nerves' nuclei related to swallowing. The sensory nuclei are posteriorly located on both sides, and the motor ones, anteriorly. Interneurons and pathways of the reticular formation interconnect the sensory and motor nuclei in the brainstem. These are also connected with peripheral receptors, cerebellum, and sensory and motor areas of the cerebral cortex through base nuclei, and with peripheral effectors like muscles and salivary glands[1,8,28-30,39].

The brainstem receives and emits pathways with stimuli information to be integrated and distributed. From peripheral receptors, the brainstem sensitive nuclei will receive peripheral sensitivity information by general afferent pathways (V, VII, IX), and taste, by special afferent ones (VII, IX, X). During the oral phase, all the bolus characteristics are identified and analyzed by the cortex, which informs the brainstem the pattern to be employed by the oral effectors. The brainstem, through the motor hypoglossal (XII) nerve, will stimulate intrinsic and extrinsic tongue muscles. The other swallowing muscles, as well as those involved in the pharyngeal phase, will be stimulated by motor fibers of visceral special efferent nerves (V, VII, IX, X and XI). The brainstem also depolarizes visceral general efferent parasympathetic pathways to salivary glands (nerves VII and IX)[8,29,30]. The vagus (X), and maybe the accessory (XI), send preganglionic parasympathetic fibers to the autonomic digestive system, through fibers from the vagus dorsal nucleus[1,29,47].

In the brainstem, swallowing cranial nerves' pathways make functional connections with the cerebellum. The swallowing cranial nerves go in and out of the cerebellum through the inferior, middle and superior cerebellar peduncles. The inferior one receives mainly afferent signals, the medium, only afferent signals, and the superior, mostly efferent signals. Specific longitudinal pathways interconnect brainstem and cerebellum nuclei with base nuclei and cerebral cortex. In this way, the cerebellum and cerebral cortex can interfere with the mechanics to be effected by the cranial nerves' pathways in the swallowing process[1,8,29].

In addition to balance and muscle tone, the cerebellum acts by determining the temporal sequence of the synergistic contraction of the different skeletal striated muscles, which can generate delay of the motor signals by fractions of a second. It also acts by sequencing the motor activities from one movement to another, and can control the relation of agonist and antagonist muscles. When necessary, the cerebellum also can make adjustments in the motor activities produced by other parts of the brain[1,8,29].

Ascending and descending cerebellar pathways connect the cortex and the cerebellum. Originated in large parts of the premotor and motor cortex, the so-called cortex-pons-cerebellar pathway follows to nuclei in the pons and thence to the contralateral hemisphere of the cerebellum. The signs that enter the cerebellum connect with its nuclei and go out to send signals that are distributed to other parts of the brain. The cerebellar pathway, whose role is to help coordinate the motor activity sequences initiated by the cerebral cortex, originates in the cerebellar cortex and, after connection with one of its main nuclei (dentate), goes to the thalamus and will end in the cerebral cortex[8]. Swallowing has its motor control bilaterally represented in the cerebral cortex[48-51]. This bilateral representation means that peripheral stimuli reach both cerebral hemispheres, with admitted dominance of one of them. This dominance assumes that, in physiological conditions, the dominant hemisphere inhibits the function of the contralateral one. In dysphagia due to involvement of the dominant hemisphere, it has been observed that the contralateral hemisphere can increase its representation, with apparent functional recovery[52-54].

The oral phase, being voluntary, allows us to decide whether to swallow the oral content. The cortical area with the oral control capacity has been identified in the lower portion of the precentral gyrus (frontal cortex) and postcentral gyrus (parietal cortex), where sensitivity (somatosensory cortex) and motor control (somatomotor cortex) are separated by the central sulcus[55,56]. (FIGURE 1).

The intraoral qualification, linked to sensory pathways of the

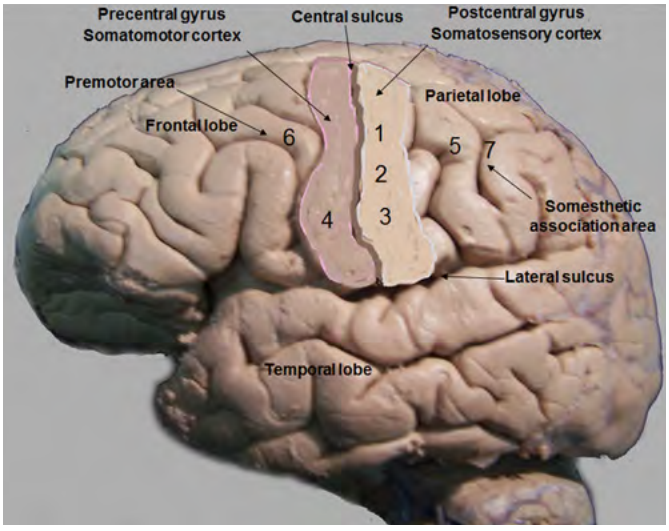


FIGURE 1. Lateral view of an anatomical specimen (brain), highlighting the sensory, postcentral and the motor, precentral gyrus, separated by the central sulcus. The main anatomical elements are described over the figure. 1, 2 and 3: areas of somatosensory cortex; 5 and 7: sensitive association areas; 4: motor cortex; and 6: premotor area.

cranial pairs V, VII and IX, with nuclei in the brainstem, will have visceral afferent general and special stimuli conducted thought base nuclei up to the cerebral cortex. From the cortex, efferent direct or indirect commands (involving the base nuclei) reach the motor nuclei of the brainstem, under cerebellar mediation, from where the motor pathways of these nerve pairs coordinate the dynamics of the peripheral effectors[1,8,29,30].

Afferent pathways of nerves V, VII and IX go to the cerebral cortex. From the trigeminal (V) sensory nucleus, tactile sensitivity pathways pass to the thalamus and cortex trough secondary dorsal tracts. From the spinal nucleus of the cranial pair V, tactile, pain and temperature pathways go to thalamus and cortex via the secondary ventral tract. The facial (VII) and glossopharyngeal (IX) nerves connect with the cerebral cortex through sensitive fibers coming from the solitary tract nucleus through medial lemniscus and

thalamus. The efferent pathways from the cortex to the brainstem motor nuclei of these three pairs of cranial nerves, modulated by the cerebellum, occur with bilateral (mainly cross) connections of the cortex-nuclear tract (voluntary). These voluntary pathways will end in the brainstem in connection with the motor nucleus of the nerves V and VII, as well as with motor neurons of the pair IX in the ambiguous nucleus[28,29].

ORAL PHASE OF SWALLOWING

The oral phase can be classified into five subtypes: 1) Nutritional voluntary oral phase; 2) Primary cortical voluntary oral phase; 3) Semi-automatic oral phase; 4) Subsequent gulps oral phase; and 5) Spontaneous oral phase. These five oral phase possibilities occur in association with pharyngeal and esophageal reflex phases.

Nutritional voluntary oral phase

The nutritive swallowing following chewing, with the bolus prepared and qualified, will put it usually over the tongue (organize) and transfer it (eject) to the pharynx[57]. The voluntary oral phase of swallowing leads information to the cortex by the afferent pathways of the nerves V, VII and IX (mixed pairs) that allow the cortex to activate the motor portions of these mixed nerves in association with the hypoglossal (XII – motor pair). Originating in peripheral receptors, afferent pathways reach the brainstem. From the sensory nuclei of the cranial pair V, through the secondary ventral and dorsal tracts, they reach the thalamus and cortex with tactile (also volume and viscosity), thermal and possibly nociceptive sensations. Afferent general (sensitivity) and special (taste) pathways led by the cranial nerves VII and IX reach the solitary tract nucleus in the dorsal region of the medulla oblongata. From this, afferent pathways connect with the base nuclei, including thalamus, and then with the cerebral cortex on the postcentral gyrus of both hemispheres, transferring the received afferent signals to the precentral gyrus, from where efferent pathways go to the brainstem motors nuclei (V, VII, IX, XII).

Based on the hemisphere dominance, one can conclude that both afferent general (sensitive) and special (taste), and efferent special (motors) and general (parasympathetic) pathways interconnecting both sides of cortex and brainstem arrive and leave as direct and cross paths. This organization gives to each cerebral hemisphere the total information collected in the oral cavity, enabling effective commands from each hemisphere to reach both sides of the brainstem, integrating the cranial nerves that act in the oral phase[58].

After activating the sensorial cortex on both sides from the base nuclei, the peripheral information passes to the motor cortex, where the necessary intensity is modulated and re-transmitted to the base nuclei and brainstem. In the latter, the efferent pathways of the trigeminal, facial and hypoglossal nerves would produce an oral dynamic that would end by ejecting its contents into the pharynx.

Although one of the hemispheres is dominant, both are fully informed, allowing them to exercise full functions[48-51]. There is evidence that the dysphagia generated by injury to the dominant hemisphere allows increase in the representation of the non-dominant (non-injured) hemisphere, associated with apparent function recovery[52-54]. There are pathways crossing from one side to the other through the corpus callosum, integrating the hemispheres. Thus, in healthy individuals, the dominant cortex can exert inhibitory action on the contralateral one by a connection that passes through the corpus callosum. It is also possible to consider the existence of excitatory pathways from the dominant motor cortex to the base nuclei of the contralateral hemisphere. This organization would explain not only the already evidenced function recovery when there is lesion of the dominant hemisphere[52-54], but also the integrated bilateral stimulus that is observed, despite the inhibition of the sensorial and motor cortex of the non-dominant hemisphere. It is also possible to assume that these excitatory pathways exist in both directions.

Between the brainstem and the cortex, there are also interconnected pathways arriving at, and leaving from, the cerebellum, considered able to modulate muscular contraction intensity and sequence. In this way, cerebellar pathways connect with efferent voluntary (cortex-nuclear) pathways that will make synapses with the motor nuclei of the cranial nerves V, VII, IX and XII. From these nuclei, the efferent stimuli follow to the oral effectors, providing them with signaling of adequate contraction intensity and sequence, coordinated by the cortex and modulated by the cerebellum.

The bolus volume and viscosity will interfere with the muscular contraction intensity, defined by the cortex according to the oral qualification, to generate the necessary oral ejection. Nevertheless, the contraction activation sequence of the effectors will be common to all sequences involving the oral phase, suggesting that the neural organization has a predefined sequence. Taste and temperature do not exert influence on the oral muscular contraction intensity defined by the cortex. This observation means that, within limits of acceptability, chemical-reception, thermo-reception and certainly pain-reception do not interfere with the oral activity, which is governed by the mechanical reception, in particular volume and viscosity, which will affect the amount of motor units to be depolarized for an effective oral phase. The generation of the necessary and adequate muscular contraction intensity will be responsible for the information to be passed and maintained during the reflex phase of swallowing. The pressure intensity transferred by the oral phase will be the stimulus to be answered to by the neural control of the reflex pharyngeal phase. The esophageal phase, also reflex, should be influenced at least partly by the oral phase[57,58].

One can describe the basic dynamics of the swallowing oral phase as follows: The Dental arcades touch one another by chewing muscle contraction (pair V). This dental arcades position allows skin-inserted muscles, in special buccinators and *orbicularis oris* (pair VII), to generate intraoral pressure resistance to prevent pressure escape out of the oral cavity during the bolus transference to the pharynx. The pressurized and resistant oral cavity will enable ejection of the bolus by the tongue (pair XII), which will transfer pressure and bolus to the pharynx. Still as part of the oral phase actions, the *tensor veli palatini* muscle (pair V) will provide resistance to the soft palate, which will be superiorly and posteriorly projected by the *levator veli palatini* muscle against the first fascicle of the pharynx superior constrictor muscle (pterygopharyngeus fascicle) at the beginning of the pharyngeal phase. The suprahyoid muscles elevate the hyoid and larynx, opening the pharyngeal-esophageal transition because it undoes the tweezers action between the vertebral body and larynx. The elevation of the hyoid and larynx that acts by undoing of the tweezers action, produced by the apposition of the larynx against the spine is coordinated mainly by the cranial nerves V and VII and also by C1 through the *ansa cervicalis*. The hyoid elevation starts at the end of the oral phase, and stays active till the end of pharyngeal phase. Contraction of the longitudinal stylopharyngeus muscle (IX) will reduce the pharyngeal distal resistance. Finally, in the end of oral

phase, by possible involvement of the respiratory center on the floor of the fourth ventricle in the brainstem, swallowing apnea (preventive apnea) takes place. In sequence, but with an independent mechanism of apnea, beginning the pharyngeal phase, vocal folds adduction will occur. All the oral events remain active during the entire pharyngeal phase by assimilation of the reflex pharyngeal phase coordination[42,59-63]. (FIGURE 2).

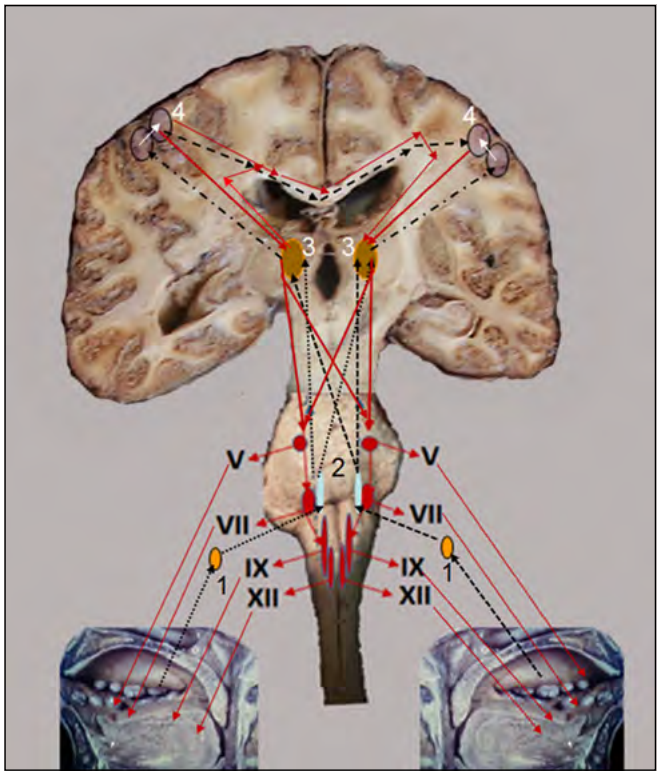


FIGURE 2. Frontal view of schematic diagram over an anatomical specimen representing the neural control of the nutritional oral phase. Black, dotted lines represent the oral afferent pathways that pass through the (1) sensorial ganglion and connect with sensitive nuclei of the solitary tract and nerve V nuclei in the brainstem (2). From there, they connect with the base nuclei (3) through direct and cross pathways. From the base nuclei (3), in nutritious swallowing the signals stimulate the postcentral (sensorial) and precentral (motor) gyruses (4), which start the efferent (motor) pathway. (Note 1: Sensory pathways do not exist in the primary cortical voluntary oral phase). Red, solid lines represent efferent motor pathways from the cortex to the base nuclei (3) and brainstem nuclei (2) where nerves V, VII, IX and XII conduct the stimuli (modulated by the cerebellum) to the oral effectors. (Note 2: In semiautomatic swallowing and while normality is maintained, motor responses are produced without cortical intervention). From the dominant hemisphere, there is an inhibiting pathway (black, dashed line) going to the opposite hemisphere and an excitatory pathway (red, solid line) and also to the base dominant nuclei to the non-dominant side.

Primary cortical voluntary oral phase

This type of oral phase reproduces all dynamic events observed in the nutritive oral phase of swallowing, without having any intraoral content to be qualified. It happens as if the cerebral cortex imagined a bolus with such known features, that the efferent cortical motor area reproduces an oral ejection with the same characteristics and using the same efferent pathways that it would if that imagined bolus could be exposed to oral receptors. Thus, this type of neural control does not have, as an integral part, the afferent signaling coming from the oral receptors to the sensitive cortex. In this way, the sequence from the motor cortex to the oral effectors will be exactly the same[58].

Semiautomatic oral phase

This type of neural control is a temporary substitute for the one that occurs during the nutritional swallowing process. It replaces the voluntary control of the nutritional oral phase when, in a repetitive way, this has its parameters qualified and accepted as usual and within appropriate limits. In such cases, if the attention has been divided with another interest that demands cortical activity, swallowing control can be replaced by a semiautomatic control, which will be processed in subcortical level (base nuclei). Considering the proposed organization for the integration between base nuclei and cortex, we can hold that the base nuclei take control of the oral phase, maintaining its integrative activity, but repressing in their level the information brought from the periphery. Nevertheless, the base nuclei retain the ability to reactivate cortical control at any time, in particular if changes are detected[58]. I believe that the dominant hemisphere controls this semiautomatic process from its base nuclei, also through corpus callosum, on the same way of the inhibitory control.

Subsequent gulps oral phase

Subsequent gulps oral phase swallowing in subsequent gulps implies liquid intake that, in healthy individuals, demands depolarization of fewer motor units, because the necessary ejection force does not require too much effort. The control of this oral phase type of swallowing is, at least for the first gulp, similar to the control of nutritional swallowing. Although the material to ingest is liquid, a proper qualification is necessary, since it may have characteristics unexpected or distinct from the appearance. Taste, temperature and viscosity are assessed during the first gulp and, if accepted, go promptly to semiautomatic coordination, similar to that occurring in the nutritional diet. Here, the semiautomatic dynamics can start without requesting any other cortical attention, and without losing the basic perception of the gulps' characteristics. Like in nutritional swallowing, the resumption of the voluntary cortical control is immediate if desired or if any irregularity is perceived.

Spontaneous oral phase

Spontaneous oral phase is the swallowing that occurs to clarify oral cavity of the saliva produced and released in discrete volumes, but continuously. This type of oral phase occurs repeatedly over the course of the day's 24 hours, with the individual awake or asleep, in the absence of conscious control. These swallowing efforts generate a mechanical sequence similar to the other swallowing types with origin in the oral cavity. However, in some respect it is distinct in its trigger mechanisms. I believe that is possible to assume that this type of swallowing is due to the airways protective mechanism to prevent aspirations and compromising of the respiratory system. It has been demonstrated that the saliva adsorbed to the mucous membrane is capable of lubricating the laryngeal vestibule and vocal folds without producing discomfort. Also, the resulting volume of accumulated saliva would be compressed between the vestibular folds and epiglottis tubercle during swallowing with the adduced vocal folds, resulting in return of the residual saliva to the pharynx[64]. It is possible to believe that spontaneous swallowing is a product of this physiological airways permeation.

The spontaneous swallowing that occurs repeatedly, being the individual awake or during sleep and in the absence of conscious control, seems to be the same semiautomatic swallowing observed in the nutritious swallowing sequence, though with a distinct trigger mechanism, probably related to airway protection.

Besides other functions, saliva is important in the chewing bolus preparation and in the lubrication of the mucous membranes to suitable transport. Saliva is produced in continuous volume and physical-chemical characteristics by the salivary glands, with mediation of parasympathetic fibers conducted by the cranial nerves VII (facial) and IX (glossopharyngeal).

Spontaneous swallowing helps in the distribution of saliva over the oral, pharyngeal and even vestibular mucosa, humidifying these membranes and probably helping to maintain fluid the mucus over the laryngeal ventricles. Inhalation and expiration dry the mucosa by the continuous airflow, and spontaneous swallowing keeps the moisture level of these mucous membranes. Spontaneous swallowing is also important for the control of small volume of liquids adsorbed to the laryngeal vestibule walls, removing any excess over this mucosa. During swallowing, with the adduced vestibule folds, the tubercle of the epiglottis presses against these folds, making the vestibule lumen virtual, expelling to the pharynx any excess existing there[58,64].

NEURAL CONTROL OF THE SWALLOWING PHARYNGEAL PHASE

The reflex pharyngeal phase takes place without voluntary control or direct cortical command. This phase starts from the pharyngeal pressure stimulus transferred by the oral phase. In nutritional swallowing, after bolus qualification, in special in relation to volume and viscosity (mechanoreceptors), the oral ejection will transfer the qualified information (bolus and pressure) to the pharynx. From there the perceived stimulus go to the brainstem (solitary tract nucleus). In the brainstem, in special in the ambiguous nucleus, a motor reflex response will determine sequential muscle contractions in delay line based on the values qualified and transferred by the oral phase[58,65,66]. Delay line is the contractile sequential muscular response of the muscles involved in the pharyngeal phase to a single pressure stimulus, which departs from the pharynx to the posterior sensory portion of the brainstem, and which returns to it via a ventral motor pathway, producing the sequential dynamics of the pharynx contractile activity. Although there is no direct motor cortex influence on the pharyngeal phase, the transferred content can be perceived, for example, for its temperature. This kind of perception means that there is afferent sensitivity, possibly to provide the oral transfer with tolerance limits.

The stimulus that triggers the pharyngeal phase is not the contact produced by the passage of food through the pharynx[67,68], but the pressure that distends it, with or without contents[58,69]. In nutritional swallowing, food and pressure are transferred, but in cortical swallowing, only pressure is, and the pharyngeal response is similar to that of nutritious swallowing, indicating that the pressure distending the pharyngeal walls is the element that stimulates the pharyngeal motor activity[58].

The pharyngeal distention pressure is identified and transferred to the brainstem through sensitive afferent fibers of the pharyngeal plexus (cranial nerves IX, X, XI). The glossopharyngeal (IX) nerves in the oropharynx and vagus and accessory (X and XI) in the laryngopharynx carry to the brainstem dorsal region (solitary tract nucleus – sensitive) the stimulus based on the pressure value transferred from the oral cavity to the pharynx. The dorsal region (sensitive) and the ventral one (motor) are integrated by interneurons of the brainstem's reticular system. A unique stimulus reaches the solitary tract nucleus, and motor reflex response is composed by a sequential action of several muscles in different times, configuring muscular sequential contraction in delay line.

It is reasonable to admit a cerebellum modulation over the pharyngeal reflex responses determined by the brainstem, explaining the sequential muscular contraction in the pharyngeal phase (delay line). Among its main functions, the cerebellum coordinates the temporal sequence of the synergic contraction of the different skeletal striated muscles, with the possibility to generate delay of the motor signals by fractions of a second, creating delay in the muscle contraction sequence[1,8,29].

In a didactic way, and not failing to admit the possibility of a delay line control by inhibitory neurotransmitters, we have considered that the sensory-motor connection in the brainstem would be carried out by distinct amounts of synapses between interneurons connecting sensitive and motor nuclei, generating different transfer times between the solitary tract nucleus to the ambiguous one. Thus, a stimulus perceived by the pharyngeal receptors and transmitted to the solitary tract nucleus as unique would be retransmitted to the ambiguous nucleus, passing by a different and increasing number of interneurons, configuring the delay line observed in the swallowing pharyngeal phase.

Besides the sequence and intensity of muscular contraction determined by the brainstem from pressure reception, the pharyngeal phase incorporates or assimilates, as its functional part, the oral phase developments already in course. The oral phase incorporated elements and the pharyngeal phase will end together. Therefore, the brainstem, during the pharyngeal phase, integrates the sequence of the oral phase with the pharyngeal one. The pharyngeal phase starts by action of the pharyngeal plexus, composed of the glossopharyngeal (IX), vagus (X) and accessory (XI) nerves, with secondary involvement of the trigeminal (V), facial (VII), glossopharyngeal (IX) and the hypoglossal (XII), and also some elements of the cervical plexus (C1, C2). The cervical plexus and the hypoglossal nerve on each side form the *ansa cervicalis*, from which a pathway goes to the geniohyoid muscle, one of the muscles that act in the elevation of the hyoid-laryngeal complex[58,65,70,71].

The accessory (XI) nerve, not always considered among those associated with swallowing, is admitted as having special visceral efferent (motor) fibers originating from the ambiguous nucleus that would follow associated with the vagus nerve, which would also display this type of fiber[1,47]. Thus, the accessory (XI) nerve is also responsible for the motor innervation of the musculature of the palate, pharynx, larynx and esophagus, in association with the vagus nerve.

The pharyngeal phase shows adjustment, over the tongue on each side, of the palatoglossal muscle, innervated by the motor portion of the pharyngeal plexus (X, XI) to prevent pressure from returning to the oral cavity. The tension (V) and elevation of the palate (X, XI) against the first fascicle (pterygo-pharyngeal) of the upper constrictor muscle of the pharynx, innervated by the cranial nerves X and XI, blocks the possible pressure escape from the oropharynx to the rhinopharynx.

The superior, middle and inferior constrictor muscles of the pharynx are each one constituted of distinct parts, with individualized insertions. Each one of these parts is inserted in one side

in anterolateral fixed points, and in the other, in the posterior median line of the pharynx (pharyngeal raphe). As a consequence of the individualization of their motor units, they can contract in sequential mode. The superior constrictor muscle has four parts (pterygopharyngeal, buccopharyngeal, mylopharyngeal and glossopharyngeal), the middle, two parts (chondropharyngeal and ceratopharyngeal), and the inferior, two parts (thyreopharyngeal and cricopharyngeal). The cricopharyngeal presents two fascicles, the upper, oblique, and the lower, transverse, whose fibers seems to cross with each other's in the midline. Between the two fascicles of the cricopharyngeal muscle, there is an anatomically less resistant area due muscular absence[72].

The four parts of the superior constrictor occupy the entire extension of the oropharynx. Thus, it is necessary that only the first portion of its superior (pterygopharyngeal) part perform apposition against the palate, isolating and preventing pressure escapes from the oropharynx to the rhinopharynx. In the same time, the oral pressure can pass to the pharynx without resistance. The sequential contraction of the superior, middle and inferior constrictors' parts do not generate pharyngeal peristalsis, since there is no circular muscle on the pharyngeal wall. With closing of the pharyngeal contiguous cavities except for the pharyngeal-esophageal transition, which opens as a result of the elevation of the hyoid and larynx, there is a constrictors muscle contraction generating a pressure sequence in the cranial-caudal direction. This pressure sequence displaces the transient bolus from the pharynx to the permissive, less resistant esophagus by the opening of the pharyngeal-esophageal transition[42,70].

By definition, peristalsis is a sequential expression produced by a muscle circular layer. In this way this cranial-caudal pressure sequence with distal less resistance without muscle circular layer should not be considered as peristalsis or peristalsis like as is often defined.

The suprahyoid muscles are innervated by the cranial nerves V and VII and by the (C1) cervical plexus, connected via *ansa cervicalis* with the hypoglossal nerve. The mylohyoid branch of mandibular nerve (mixed root of trigeminal – V) innervates the mylohyoid and the anterior belly of the digastric muscles; the posterior belly of the digastric and the stylohyoid muscles, by the facial nerve (VII). The geniohyoid and thyrohyoid muscles are innervated by *ansa cervicalis* (usually C1) through the hypoglossal (XII) nerve. The cervical plexus (usually C2) through the *ansa cervicalis* innervate the other infrahyoid muscles. The suprahyoid muscle group is responsible for the forward and upward movement of hyoid and larynx, with modulation by the infrahyoid group. This action moves the larynx away from the vertebral body and opens the pharyngeal-esophageal transition. Moreover, while moving the larynx away, the suprahyoid group is able to sustain this open condition depending on the bolus volume and viscosity. The opening of the pharyngeal-esophageal transition is also enhanced by the contraction of the longitudinal pharyngeal muscles, the stylopharyngeal ones, innervated by the glossopharyngeal (IX) nerve, and the palatopharyngeal muscle, innervated by motor fibers from cranial nerves X and XI[42,65,71,72].

Still in the oral phase, as a last act, a preventive apnea (swallowing apnea) ensues, being assimilated by the pharyngeal phase and remaining until its end. Associated with the airways resistance produced by apnea, there is independent vocal folds adduction (X, XI), followed by closure of the vestibular folds with the bolus passage through the already open pharyngeal-esophageal transition. The adduction of the vestibular folds is due to the compression of the pre-epiglottic fatty cushion produced by the elevation of the hyoid and larynx, which compresses this cushion contained in the pre-epiglottic fibrous space. This space has, as its point of least resistance, the lateral aspects of the tapered end of the epiglottis, which corresponds to the projection of the vestibular folds on both sides. Thus, the compression produced by this fatty cushion on the sides of the epiglottis causes the medial shift of the vestibular folds, which end up in apposition against the epiglottis tubercle. On its turn, the epiglottis, everted by the tongue, moves posteriorly, adjusting its tubercle against the now adduced vestibular folds[59-62]. At the same time, the constrictor muscles' parts, including the crycopharingeal one, carry out the sequential, cranio-caudal contraction (nerves X and XI), driving the bolus from the pharynx into the esophagus[62,63]. (FIGURE 3).

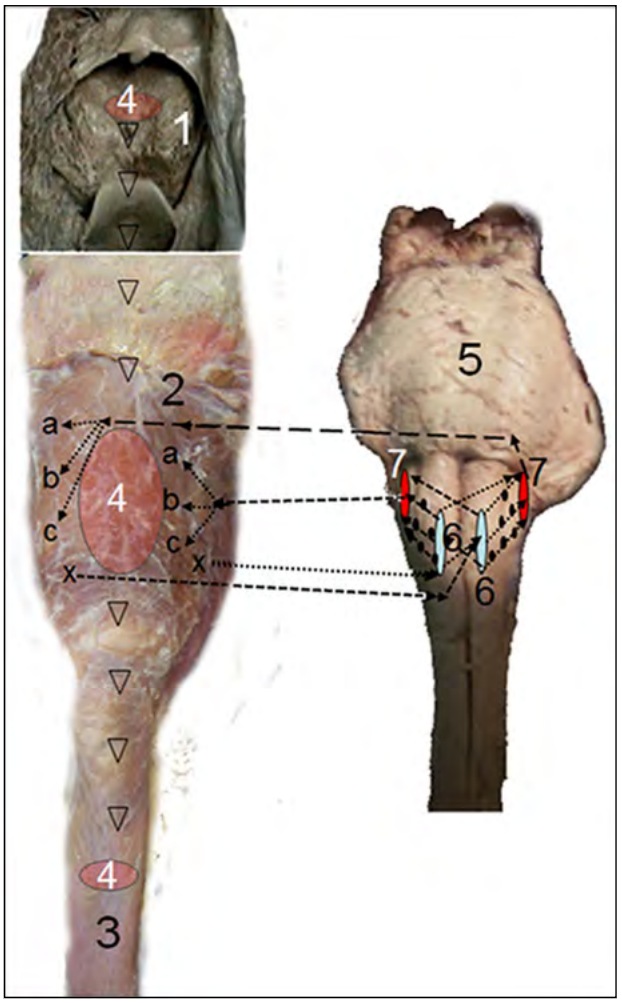


FIGURE 3. Neural control representation of the pharyngeal phase over anatomical specimens where 1 – oral cavity, 2 – pharynx, 3 – esophagus, 4 – swallowed bolus, 5 – brainstem, X – pharyngeal receptors, 6 – solitary tract nucleus, 7 – Ambiguous nucleus. Over 5, lower dotted arrows from six to six – afferent integration, and upper dotted arrows from six to seven – efferent integration. From 6 (sensitive nucleus) to 7 (motor nucleus), multi-dotted arrows are a didactic representation of the growing number of interneurons of the delay line. From 7 (ambiguous nucleus) to a, b, and c on both sides, dashed arrows represent the efferent stimulus to muscle delay line. There is pressure transference from 1 to 2 (pharyngeal distention), represented by widening of 4. Hollow arrowheads show displacement of the bolus (4) from mouth to esophagus.

The pharyngeal and esophageal phases, both reflex, present anatomical and functional relation. The firsts 10 cm of the esophagus are formed by skeletal striated muscle, like the oral and pharyngeal ones. In the distal extremity of this striated segment, by 2 or 3 cm, a muscular distinction is identified macroscopically in fresh anatomical specimens, which is microscopically defined as a mixture of skeletal striated muscle (long and multinucleated fibers) and fibers of smooth muscle (short and mono-nucleated), where the first ganglion of the myenteric plexus appears[73]. (FIGURE 4).

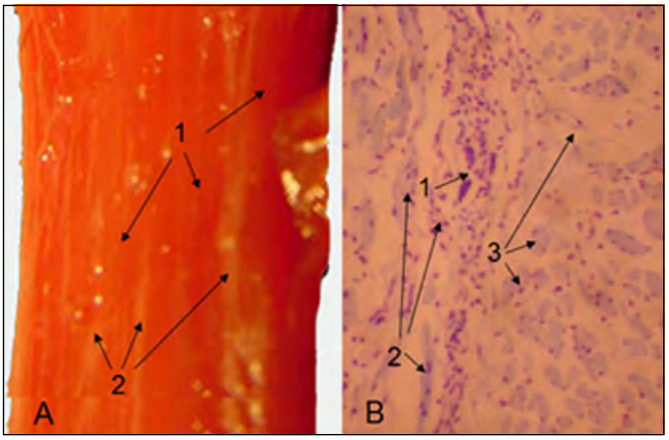


FIGURE 4. A – fresh esophagus segment where there is mixture of 1 – smooth and 2 – striated muscle. **B** – histological specimen obtained from (A), with (1) first ganglion of the myenteric plexus and mixture of long and multinucleated striated muscle fibers (2) and short and mono-nucleated smooth ones (3).

The high-pressure zone designated as the upper esophageal sphincter is located at the distal pharynx, where a tweezer action closes the pharynx between the larynx (cricoid cartilage) and the cervical lordosis at the level of the 5th to 6th cervical vertebrae. Usually this high pressure is considered as due to the maintained contraction of the cricopharyngeal muscle, part of the inferior pharyngeal constrictor. This conception is a severe misunderstanding about the anatomical and functional characteristics of this region. The inferior constrictor of the pharynx is a skeletal striated muscle consisting of two fascicles (thyropharyngeal and the cricopharyngeal). The cricopharyngeal fascicle presents two parts of fibers in its organization, an upper, oblique and a lower, transverse. The upper one inserts on each side of the cricoid cartilage, from where its fibers go from the bottom upwards and from lateral to medial, inserting on the posterior pharyngeal raphe. The lower or transverse part inserts on each side of the cricoid cartilage, with a transverse direction, intercrossing in the midline, where the raphe cannot be seen. The width of the pharyngeal lumen at the level of the transverse cricopharyngeal part is about 17 mm and there is not muscular ring in this region, which can be described as a muscular half-curvature. The divergence between the oblique and transverse parts of the cricopharyngeal muscle creates an intermediary zone without muscular fibers that constitutes an anatomically less resistant point, already described as the Kilian zone, where the posterior pharyngeal diverticulum, known as Zenker's diverticulum, can occur. This anatomically less resistant area is coincidentally the point of higher-pressure values, certainly due to the tweezer action produced by the vertebral body and the larynx[65,71]. (FIGURE 5).

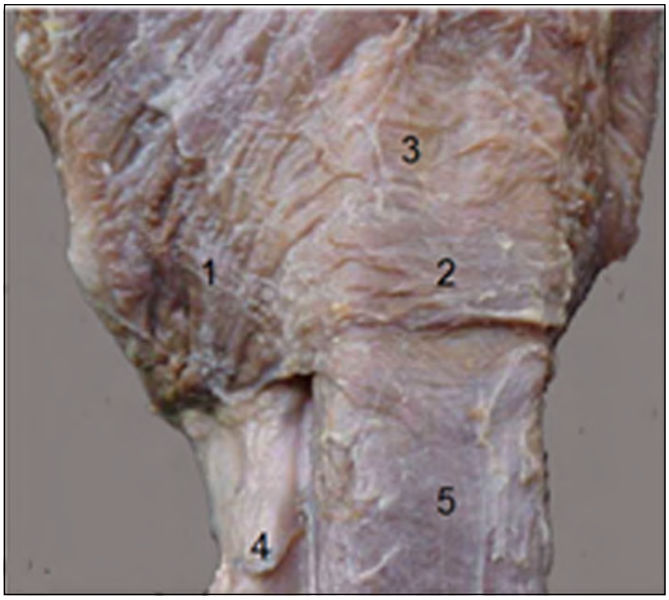


FIGURE 5. Posterior view of anatomical specimen involving the pharynx, larynx, esophagus and trachea, where 1 – Cricopharyngeal muscle, oblique fascicle, 2 – Cricopharyngeal muscle, transverse fascicle, inserted on the larynx cricoid cartilage, 3 – Kilian zone, the anatomically less resistant zone on the posterior pharyngeal wall where the pharyngeal diverticulum described by Zenker occurs. This less resistant zone is due to the divergence of the oblique and transverse fascicles of the cricopharyngeal muscle. 4 – Trachea, 5 – Esophagus.

The cricopharyngeal muscle has been known as a skeletal striated muscle type that demands expressive consumption of ATP (adenosine triphosphate), because it depends on ATP both to contract and to relax. In order to demonstrate that the cricopharyngeal muscle is not contracted at rest, only to relax when the pharyngeal-esophageal transition opens, as believed by many, we performed manometry of the pharyngeal-esophageal transition. This manometry was carried out with a balloon built with a latex glove finger to measure the positive pressure resistance of the pharyngeal-esophageal transition of 12 fresh corpses, in the first 6 to 12 hours postmortem. This research were permitted by an agreement between the Anatomy Department of the Biomedical Sciences Institute of the Federal University of Rio de Janeiro (*Universidade Federal do Rio de Janeiro* – UFRJ) and the Legal Medical Institute of Rio de Janeiro, Brazil.

The balloon traction shows that positive pressure values remain present on the pharyngeal-esophageal transition in all studied fresh corpses. A second pressure verification, with insertion of a metallic prosthesis between the vertebral body and the larynx, shows absence of resistance in this region, where the prosthesis eliminates the tweezer mechanism of the larynx against the vertebral body. Based on the positive values observed in the first measure and absent in the second, with the prosthesis insertion, we concluded that resistance on the pharyngeal-esophageal transition is dependent on the tweezer action of the larynx against the vertebral body. (FIGURE 6).

In two cricopharyngeal muscles, we also carried out electric stimulation, including analysis of tolerance to calcium pump inhibitors (verapamil) and polyacrylamide gel electrophoresis with dodecyl sodium sulfate paired with other striated muscles.

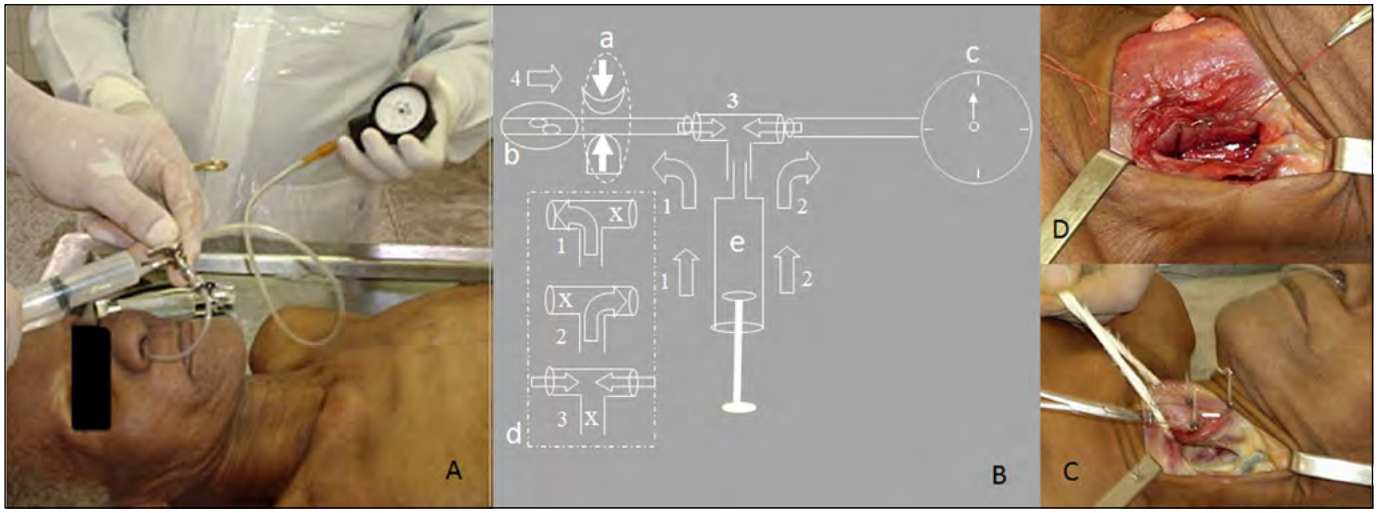
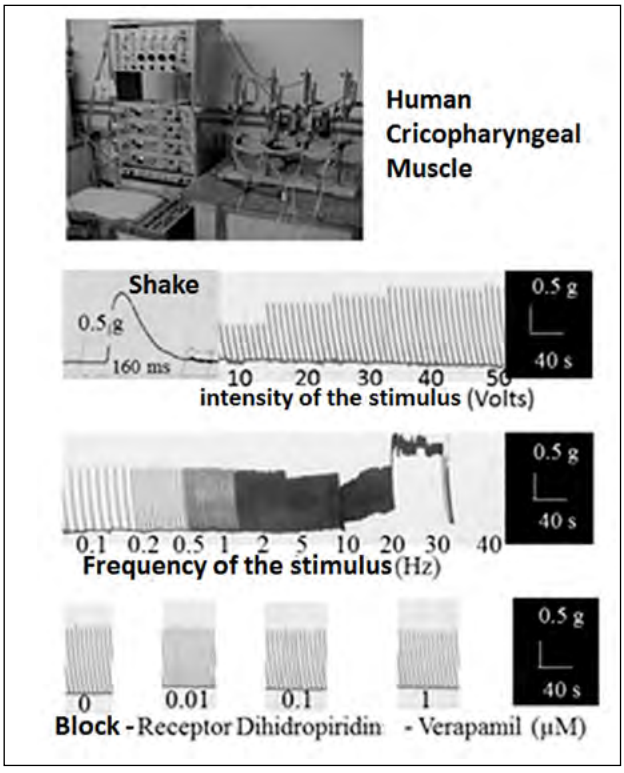


FIGURE 6.A. Manometry on a fresh corpse. **B.** Scheme highlighting (a) – pharynx between tweezer formed by vertebral body and larynx that compresses the pharynx at rest, (b) – elastic and distensible balloon, and (c) – sphygmomanometer. (d) – rectangle containing three possibilities of pressurization of the system, where X represents flow closure, 1 and 2 represent air flow to be balanced with the distended balloon, and 3, the three-way tube that allows the balance of pressures, (e) – syringe, 4 – direction of balloon traction. **C.** After verification of basal pressure (positive in all 12 cases), cervical dissection for passage of a metallic prosthesis separating the larynx from the spine. **D.** Prosthesis installed for re-verification (absence of positive pressure in all 12 cases).

We obtained these two cricopharyngeal muscles from specimens immediately resected from total laryngectomies, with surgical indication and consent. These muscles showed the same characteristics of other striated muscles under electric stimulation, including their tolerance to calcium pump inhibitors. The electrophoresis paired with other striated muscles revealed the same protein patterns and molecular weights. These two experiments allow the conclusion that the cricopharyngeal muscle has morphology and function of a striated muscle. (FIGURES 7 and 8).



The open pharyngeal-esophageal transition intercommunicates the pharynx and esophagus, allowing the video-fluoroscopic examination to show the flow of contrast medium filling both cavities almost simultaneously. One can observe that the pharyngeal and esophageal cavities present a relation with the contrast medium that occurs during the time of the pharyngeal phase. Thus, the beginning of the esophageal phase occurs, practically, in the same time of the pharyngeal phase, demonstrating the clear functional relationship between these reflex phases, which is so much or more consistent than the observed between the oral and pharyngeal phases. This fact demonstrates that the pharyngeal and esophageal phases are responsible for the conduction of the contents transferred by the oral phase[61,74]. (FIGURE 9).

NEURAL CONTROL OF THE SWALLOWING ESOPHAGEAL PHASE

The sequential contraction of pharyngeal muscles leads the bolus transferred by pharyngeal pressure. It results from the special visceral efferent innervation conducted by the vagus nerve, originating in the ambiguous nucleus, also responsible for the striated muscle of the upper portion of the esophagus. The bolus inside the esophagus is conducted by sequential contractions in distal direction, defined as primary peristalsis.

The mechanical relation between bolus and smooth muscle in the esophagus wall will be able to stimulate this kind of muscle, unlike striated one. The smooth muscle in the esophagus wall will

FIGURE 7. Polygraphic record of isometric tension of the cricopharyngeal muscle. On top, the polygraph used. The first bar shows constant increase of the contraction force as the stimuli intensity (Volts) increases. The second bar shows gradual contraction frequency increase of the cricopharingeal muscle with the stimuli pace (Hz) increment, until the installation of tetany. The third bar shows the use of verapamil (calcium pump blocker) in increasing concentrations: both in the absence and with increasing doses of the calcium pump blocker, the muscle behavior is the expected for skeletal striated muscle. The three bars therefore register a skeletal striated muscle behavior.

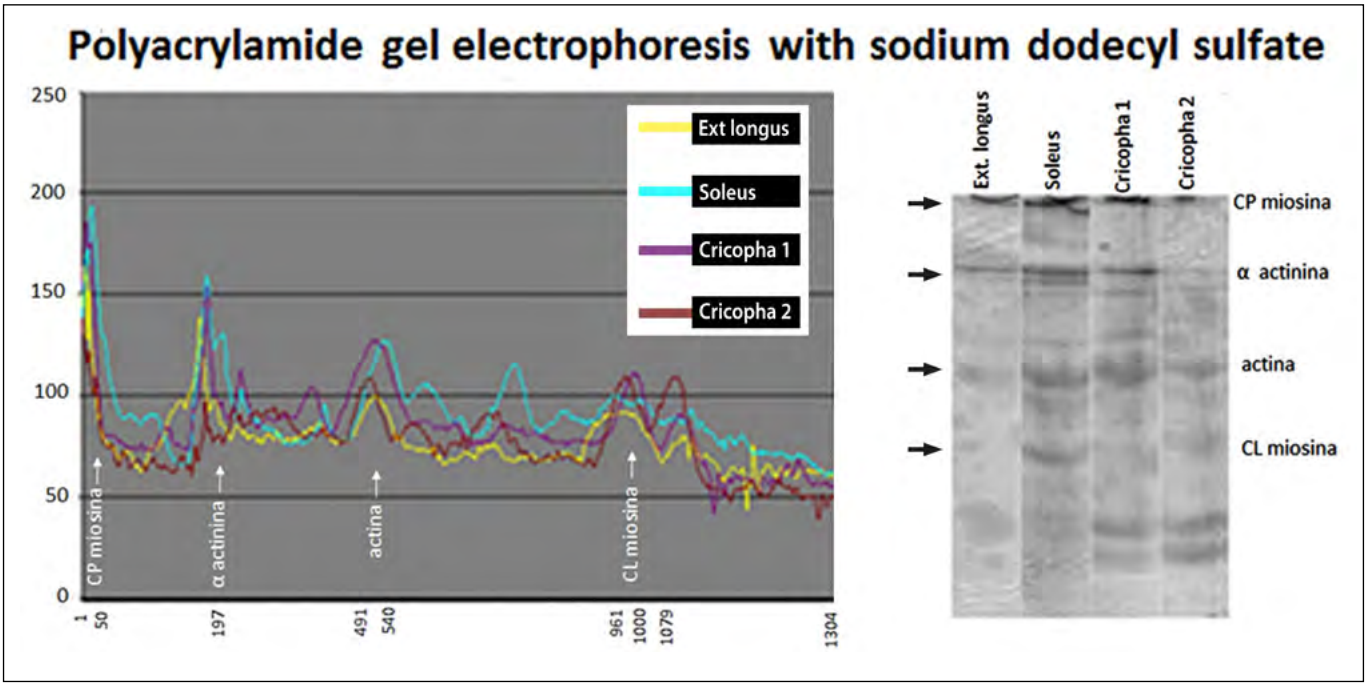


FIGURE 8. Protein Electrophoresis. On the right side, protein fractions distribution near the same plane for the four tested muscle samples, where two are cricopharyngeal samples and two other muscles previous known as striated (extensor halluces longus and soleus muscle). On the left, superposition of the protein weights of the four tested muscle samples, confirming that the cricopharyngeal muscles has the similar protein fractions distribution of the previous known as striated muscle.

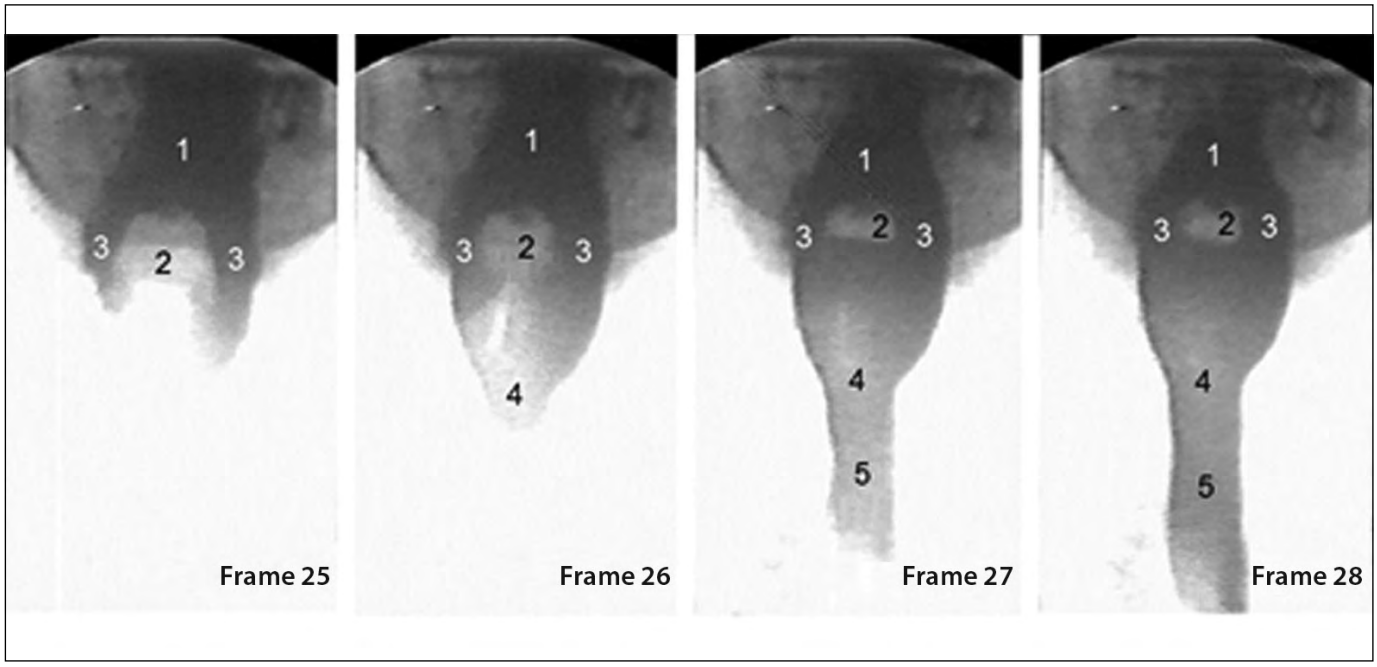


FIGURE 9. Video-fluoroscopic examination of swallowed contrast media. 1 – Oropharynx, 2 – Epiglottis, 3 – Piriform recesses, 4 – Pharyngeal-esophageal transition, and 5 – Esophagus. The pharyngeal phase begins at frame 20 and ends at 50, with total time of 0.99 sec. (each frame lasts 0.033 msec.). After 0.2 to 0.23 sec. (frame 26 to 27), the esophageal phase is already starting in superposition with the pharyngeal one. The epiglottis remains in the vertical position and will only close the pharyngeal-esophageal communication (horizontal position) at the end of the pharyngeal phase, in frame 45. At this time, the pharynx, with residual volume, starts its return to resting position, with closure of the pharyngeal-esophageal transition by the return of the larynx in opposition to the vertebral body and with the epiglottis in vertical position.

be depolarized in a syncytial way, where the depolarization of the muscle cells is freely transferred from one to the other, with contraction processed in the entire extension of the muscle layer. Thus, we can consider, as a hypothetical mechanism, that the contents transferred from the pharynx to the esophagus while in its striated portion are conducted similarly to the way that takes place in the pharynx, by depolarization of motor units. Nevertheless, when the bolus passes through the striated/smooth transition, it is capable of stimulating the myenteric plexus from this transition on, generating syncytial contraction. This syncytial depolarization is able to cause contraction of the longitudinal layer, reducing the resistance of the esophagus as a whole, increasing its complacency and culminating, or at least participating, in the opening of the gastroesophageal transition that occurs in concomitance with the onset of primary peristalsis. It is also possible that the circular musculature depolarizes and contracts during the bolus passage through the striated/smooth transition, in association with the primary peristalsis. This contraction pressurizes the esophageal lumen downwards, leading the bolus in transit through the esophagus[75-76].

The pharynx and the esophagus first portion are both formed by striate muscle innervated by the special visceral efferent (motor) pathway of the vagus nerve. This cranial nerve also has the general visceral efferent (parasympathetic) pathway, which is preganglionic to the myenteric plexus. In this way, another hypothesis would be that the esophageal smooth muscle motor coordination be done by myenteric postganglionic stimulation in sequence with the special visceral efferent pathway (motor to striate muscle) in association with the general visceral efferent pathway (parasympathetic - motor to smooth muscle) of the vagus nerve.

The contents transferred from the pharynx to the esophagus, notably the ones with solid fragments, not always reach the stomach. Sometimes they stop at the level of the esophagus smooth muscle, from where they are able to locally stimulate the submucosal plexus, which transfers an activation command to the myenteric plexus, producing muscle contraction from the retention point on. This downward contractile wave is defined as secondary peristalsis, which ends up conducting the residual esophageal contents to the stomach[73].

It has been considered that the general visceral efferent pathway (parasympathetic fibers) originating in the posterior motor nucleus of vagus as preganglionic fibers will connect to intraparietal ganglia in the esophageal wall, from where postganglionic fibers connect with visceral effectors that release neuro-hormones capable of interfering with the tonus and motility of the smooth portion of the esophagus[1]. It is also believed that the esophagus distal extremity presents resting tonic contraction involving the distal circular musculature. Hormones would regulate this resting tonic contraction in association with intrinsic and extrinsic nerves that generate pressure values around 20 mmHg. This prevailing hypothesis considers that the gastroesophageal transition opens to due muscle relaxation that would occur in association with the primary peristalsis, induced by vagus fibers that would inhibit the tonic contraction of the circular musculature, with possible mediation of VIP (vasoactive intestinal polypeptide) neurotransmitters and NO (nitric oxide)[77].

Despite the prevailing concepts, it has not been identified, in the distal portion of the esophagus, a muscular ring with the classical characteristics observed in smooth muscle sphincters. However, the gastroesophageal transition, without muscular thickening, presents positive resting pressure, which fades away during the primary peristaltic wave that leads the bolus to the stomach. Due to the lack of knowledge about the morphology responsible for the high pressure of this transition defined as cardia, it has been deemed a physiological sphincter. This situation has given rise to speculations that add up to about 27 possible mechanisms, isolated or in association, including those involving the regional muscle organization[74].

The esophagus presents an internal layer, defined as circular, and another external, as longitudinal. The external one, when contracting, reduces the resistance of the esophageal tube, and the internal propels the bolus in sequential contraction. It is possible that the esophageal muscular layers are arranged in a way that the external layer displays long-pitch, spiral fibers, and the internal one, short-pitch, spiral fibers. This morphology, associated with the concept of energy preservation, allows us to admit that the contraction of the external layer would be able to widen the esophagus, decreasing the resistance to the flow, probably also by opening the gastroesophageal transition. On its turn, the internal layer would propel the food downwards by sequential contraction. Thus, during the resting esophageal stage, there would be no energy expenditure[58,73,74]. The opening of the gastroesophageal transition would be an active response to the esophageal peristalsis that would activate the myenteric plexus during the entry of the bolus into the esophagus. Corroborates this hypothesis the fact that the esophagus, when subjected to pure pressure distension, responds differently than in the presence of the concrete bolus.

Costa MMB. Controle neural da deglutição. Arq Gastroenterol. 2018;55(Suppl 1):61-75.

RESUMO – **Contexto** – A deglutição é um processo motor com muitas discordâncias e de difícil estudo quanto a sua neurofisiologia. Talvez por essa razão sejam tão raros os artigos sobre esse tema. **Objetivo** – Descrever o controle neural da mastigação e a qualificação do bolo que se obtém durante a fase oral. Revisar os nervos cranianos envolvidos com a deglutição e suas relações com o tronco cerebral, cerebelo, núcleos de base e córtex. **Métodos** – Revisão da literatura com inclusão de trabalhos pessoais e novas observações buscando dar consistência a necessária revisão dos conceitos, muitas vezes conflitantes. **Resultados e Conclusão** – Em relação a fase oral da deglutição consideramos o controle neural em cinco distintas possibilidades. Fase oral nutricional voluntária, fase oral cortical voluntária primaria, fase oral semiautomática, fase oral em goles subsequentes e fase oral espontânea. Em relação ao controle neural da fase faríngea da deglutição, pode-se observar que o estímulo que dispara a fase faríngea não é o toque produzido pela passagem do bolo, mas sim a distensão pressórica, tenha ou não conteúdo em passagem. Na deglutição nutricional, alimento e pressão são transferidos, mas na fase oral da deglutição primária cortical somente pressão é transferida e temos resposta faríngea similar a nutricional. A fase faríngea incorpora como parte de sua dinâmica as atividades orais já em curso. A fase faríngea se inicia por ação do plexo faríngeo composto pelos nervos glossofaríngeo (IX), vago (X), e acessório (XI), com envolvimento do trigêmeo (V), do facial (VII), glossofaríngeo (IX) e hipoglosso (XII). O plexo cervical (C1, C2), e o nervo hipoglosso, a cada lado, formam a alça cervical de onde, com origem cervical, um ramo segue para o músculo gênio-hioide, um músculo que atua na dinâmica de elevação do complexo hiolaríngeo. Foi também considerado o controle neural da fase esofágica da deglutição. Além de outras hipóteses foi considerado que é possível que a camadas musculares consideradas como longitudinal e circular para o esôfago sejam a longitudinal composta por fibras espirais de passo longo e a circular por fibras espirais de passo curto. Essa morfologia associada ao conceito de preservação de energia, nos permite admitir que a contração da camada longitudinal por seu arranjo espiral seja capaz de alargar o esôfago diminuindo sua resistência ao fluxo e provavelmente e também abrindo a transição esofagogástrica. Desse modo a camada circular, espiral de passo curto, pode propelir o bolo por constrição sequencial de cranial para caudal.

DESCRITORES – Deglutição. Nervos cranianos. Tronco encefálico. Gânglios da base. Córtex cerebral. Vias neurais.

REFERENCES

1. Erhart E A. Neuroanatomia simplificada. 6ed ed. São Paulo: Roca; 1986.
2. Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clin Neurophysiol. 2003;114:2226-44.
3. Miller AJ. Deglutition. Psysiol Rev. 1982;62:129-84.
4. Rosso ALZ. Controle neural da deglutição. In: Temas em deglutição & disfagia: Abordagem multidisciplinar. Rio de Janeiro; 1998. p. 13–6.
5. Roman C. Neural control of deglutition and esophageal motility in mammals. J Physiol. 1989;81:118-31.
6. Bieger D. Rhomboncephalic pathways and neurotransmitters controlling deglutition. Am J Med. 2001;111:85S-89S.
7. Machado A. Neuroanatomia funcional. 2ed ed. Atheneu, editor. São Paulo; 1993.
8. Guyton AC, Hall JE. Textbook of medical physiology. 10 ed. Philadelphia, PA: Saunders Elsevier, 2011.
9. Jean A. Brain stem control of swallowing: neural network and cellular mechanisms. Physiol Rev. 2001;81:929-69.
10. Ertekin C. Electrophysiological evaluation of oropharyngeal dysphagia in Parkinson's disease. Mov Disord. 2014;7:31-56.
11. Jean A, Car A, Roman C. Comparison of afctivity in pontine versus medullary neurons during swallowing. Exp Brain Res. 1975;22:211-20.
12. Jean A. Brainstem organization of the swallowing network. Brain Behav Evol. 1984;25:109-16.
13. Kessler JP, Jean A. Identification of the medullary swallowing regions in the rat. Exp Brain Res. 1985;57:256-63.
14. Umezaki T, Matsuse T, Shin T. Medullary swallowing-related neurons in the anesthetized cat. Neuroreport. 1998;9:1793-8.
15. Ertekin C. Neurogenic Dysfhagia in Brainstem Disorders and EMG Evaluation. J Basic Clin Heal. 2017;1:1-10.
16. Jean A. Control of the central swallowing program by inputs from the principal receptors. A review. J Auton Nerv Syst. 1984;10:225-33.
17. Aydogdu I, Ertekin C, Tarlaci S, Turman B, Kiylioglu N, Secil Y. Dysphagia in lateral medullary infarction (Wallenberg's syndrome): an acute disconnection syndrome in premotor neurons related to swallowing activity. Stroke. 2001;32:2081-7.
18. Jean A, Dallaporta M. Electrophysiologic characterization of the swallowing pattern generator in the brainstem. GI Motil. 2006;9:1-37.
19. Ertekin C, Pehlivan M, Aydogdu I. An electrophysiological investigation of deglutition in man. Muscle Nerve. 1995;18:1177-86.
20. Ertekin C. Voluntary versus spontaneous swallowing in man. Dysphagia. 2011;26:183-92.
21. Ertekin C, Aydogdu I, Yüceyar N. Effects of bolus volumes on the oropharyngeal swallowing: an electrophysiological study in man. Am J Gastroenterol. 1997;92:2049-53.
22. Miller AJ. The neuroscientific principles of swallowing and dysphagia. San Diego, CA/London: Singular Publication Group; 1999.
23. Jean A, Car A. Inputs to swallowing medullary neurons from the peripheral afferent fibers and swallowing cortical area. Brain Res. 1979;178:567–72.
24. Perlman AL, Schlze-Delrieu KS. Deglutition and its disorders: Anatomy, physiology, clinical diagnosis and management. San Diego: Singular Publication Group; 1997.
25. Ertekin C, Aydogdu I, Yüceyar N, Tarlaci S, Kiylioglu N, Pehlivan M. Electrodiagnostic methods for neurogenic dysphagia. Electroenceph Clin Neurophysiol. 1998;109:331-40.
26. Jean A, Amri M, Calas A. Connections between the medullary swallowing area and the trigeminal motor nucleus of the sheep studied by tracing methods. J Auton Nerv Syst. 1983;7:87-96.
27. Costa MMB. Disfagia oral e ou faríngea e os distúrbios referentes. Rio de Janeiro: Medbook; 2013. 180-95 p.
28. Machado A. Nervos cranianos. In: Neuroanatomia funcional. 2ed ed. São Paulo: Atheneu; 2006. p. 119-28.
29. Chusid JG. Neuroanatomia correlativa e neurologia funcional. 18ed ed. Rio de Janeiro: Guanabara Koogan; 1985.
30. Pansky B, Allen DJ. Cranial Nerves. In: Review of neuroscience. New York: MacMillan Publishing; 1980. p. 223-54.
31. Guyton AC. Os sentidos químicos. In: Tratado de fisiologia médica. Rio de Janeiro: Guanabara Koogan; 1992. p. 512-4.
32. Rhodes RA, Pflanzer RG. Sensory systems. In: Human Physiology. 3 ed. Philadelphia: Saunders; 1996. p. 252-97.
33. Lent R. Os sentidos químicos. Estrutura e função do sistema gustatório. In: Cem bilhões de neurônios: conceitos fundamentais. São Paulo: Atheneu; 2001. p. 324-30.
34. Berne RM. The chemical senses. In: Physiology. 4 ed. St. Louis: Mosby; 1998. p. 178-85.
35. Esbérard CA. Sensibilidade especial. In: Fisiologia. Rio de Janeiro: Guanabara Koogan; 1991. p. 246-8.
36. Henkin RI, Christiansen RL. Taste localization on the tongue, palate and pharynx of normal man. J Appl Physiol1. 1967;22:316-20.
37. Estrela F, Schneider FL, Aquini MG, Marrone ACH, Steffani MA, Jotz GP. Controle neurológico da Deglutição. In: Tratado de Deglutição e Disfagia – No adulto e na criança. Rio de Janeiro: Revinter; 2009. p. 20-34.
38. Schiffman S. Taste and smell losses in normal aging and disease. Jama. 1997;278:1357-62.
39. Warwick R, Willians PL. O aparelho gustatório. In: Gray Anatomia. 18ed ed. Rio de Janeiro: Guanabara Koogan; 1979. p. 1016-8.
40. Lindemann B. Receptor and transduction in taste. Nature. 2001;413:219-25.

41. Costa MMB, Santana E, Almeida J. Oral taste recognition in health volunteers. Arq Gastroenterol. 2010;47:152-8.
42. Costa MMB. Fase oral da deglutição. In: Deglutição & Disfagia – Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 70-90.
43. Nanci A. Mucosa oral. In: Tem Cate – Histologia oral: Desenvolvimento, estrutura e função. Rio de Janeiro: Elsevier RJ; 2013. p. 278-310.
44. Bajec MR, Pickering GJ. Thermal taste, PROP responsiveness, and perception of oral sensations. Physiol Behav. 2008;95:581-90.
45. Cruz A, Green BG. Thermal stimulation of taste. Nature. 2000;403:889-92.
46. Bittencourt JC, Costacurta L, Manubens RS, Andrade EP, Zorzetto NL. Estudo anatômico dos ramos linguais do nervo lingual em indivíduos brasileiros adultos. Ver Bras Cien Morfol. 1987;4:115-21.
47. Dantas AM. Nervos cranianos motores. In: Os nervos cranianos – Estudo anátomo-clínico. Rio de Janeiro: Guanabara Koogan; 2005. p. 15-46.
48. Hamdy S, Aziz Q, Rothwell JC, Singh KD, Barlow J, Hughes DG, et al. The cortical topography of human swallowing in health and disease. Nat Med. 1996;2:121-24.
49. Hamdy S, Mikulis DJ, Crawley A, Xue S, Lau H, Henry S, et al. Cortical activation during human volitional swallowing: an event-related fMRI study. Am J Physiol Gastrointes.t Liver Physiol. 1999;277:G219-25.
50. Hamdy S, Rothwell JC, Brooks DJ, Bailey D, Aziz Q, Thompson DG. Identification of the cerebral loci processing human swallowing with H2 15O PET activation. J Neurophysiol. 1999;81:1917-26.
51. Martins RE, Sesse BJ. The role of the cerebral cortex in swallowing. Dysphagia. 1993;8:195-202.
52. Hamdy S, Aziz Q, Rothwell JC, Power M, Singh KD, Nicholson DA, et al. Recovery of swallowing after dysphagic stroke relates of functional reorganization in the intact motor cortex. Gastroenterology. 1998;115:1104-12.
53. Li S, Luo C, Yu B, Yan B, Gong Q, He C, et al. Functional magnetic resonance imaging study on dysphagia after unilateral hemisferic stroke: a preliminar study. J Neurol Neurosurg Psychiatry. 2009;80:1320-9.
54. Teismann IK, Suntrup S, Warnecke T, Steinstrater O, Fischer M, Floel A, et al. Cortical swallowing processing in early subacute stroke. BMC Neurol. 2011;11:34.
55. Penfield W, Jasper H. Epilepsy and the functional anatomy of the human brain. Ed. Oxford. England: Little, Brown & Co; 1954.
56. Hogan RE, English EA. Epilepsy and brain function: commons ideas of Hughlings-Jckson and wilder Penfield. Epilepsy Behav. 2012;24:311-3.
57. Costa MMB. Dinâmica da deglutição. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 38-45.
58. Costa MMB. Controle neural da deglutição. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 48-68.
59. Costa MMB. Mecanismos de proteção das vias aéreas. In: Disfagia: Abordagem clínica e cirúrgica – criança, adulto e idoso. Rio de Janeiro: Elsevier; 2017. p. 23-32.
60. Costa MMB. Mecanismo de proteção de vias aéreas. In: Tópicos em deglutição & Disfagia. Rio de Janeiro: MEDSI; 2003. p. 163-73.
61. Costa MMB. Proteção de vias aéreas. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 38-45.
62. Costa MMB, Silva RI, Lemme EM, Tanabe R. Apneia de deglutição no homem adulto. Gastroenterology. 1998;35:32-9.
63. Costa MMB, Lemme EM. Coordination of respiration and swallowing: functional pattern and relevance of vocal folds closure. Arq Gastroenterol. 2010;47:42-8.
64. Costa MMB, Maliska C. A New Hypothesis for Fluidification of Vocal-Fold Mucus: Scintigraphic Study. J Voice. 2012;26:276-9.
65. Costa MMB, Moscovi M, Koch HA, Pereira AA. Avaliação videofluoroscópica da transição faringe-esofágica e esfincter esofágico superior. Radiol Bras. 1992;25:11-8.
66. Dantas RO, Dodds WJ, Massey BT, Kern MK. The effect of high- vs low-density barium preparations on the quantitative features of swallowings. Am J Roentgenol. 1989;153:1191-5.
67. Pommerenke WT. A study of the sensory areas eliciting the swallowing reflex. Am J Physiol. 1928;84:36-41.
68. Fujiu M, Toleikis JR, Logemann JA, Larson CR. Glossopharyngeal evoked potentials in normal subjects following mechanical stimulation of the anterior faucial pillar. Electroenceph Clin Neurophysiol. 1994;92:183-95.
69. Alvite MFL, Lopes RLC, Costa MMB. Estimulação mecânico-térmica dos pilares palatoglosso. Arq Gastroenterol. 2007;44:221-6.
70. Costa MMB. Fase faríngea da deglutição. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. 2013. p. 91-112.
71. Costa MMB. Dinâmica esfincteriana. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 133-47.
72. Lockhart RD, Hamilton GF, Fyfe FW. Anatomy of the human body. Philadelphia: Lippincott; 1960.
73. Costa MMB. Fase esofágica da deglutição. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 163-78.
74. Costa MMB. Esôfago: anatomia médico-aplicada. In: Esôfago. Rio de Janeiro: Ed Rubio; 2005. p. 1-12.
75. Rhoades RA, Pflanzer RG. Muscle. In: Human Physiology. 3ed ed. Orlando; 1996. p. 466-507.
76. Costa MMB. Bases biofísico-químicas aplicáveis a dinâmica da deglutição. In: Deglutição & disfagia- Bases morfofuncionais e videofluoroscópicas. Rio de Janeiro: Medbook; 2013. p. 1-26.
77. Berne RM, Levy MN. Gastrointestinal motility. In: Physiology. 4ed ed. St. Louis: Mosby; 1998. p. 589-616.

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Prolonged gastroesophageal reflux monitoring by impedance-pHmetry: a review of the subject pondered with our experience with 1,200 cases

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ABSTRACT – **Background** – Prolonged monitoring increased our knowledge on gastroesophageal reflux (GER), and the disease became known as gastroesophageal reflux disease (GERD). Prolonged reflux monitoring permits the diagnosis of GERD when endoscopic findings are not enough to characterize it. **Objective** – The objective of this paper is to review the current knowledge on impedance-pH monitoring, taking into account the published literature and the authors experience with 1,200 exams. **Methods** – The different types of prolonged reflux monitoring, namely: conventional pHmetry, catheter-free pHmetry and impedance-pHmetry will be briefly described. The new possibilities of evaluation with impedance-pHmetry are emphasized, namely: the study of symptomatic patients in use of proton pump inhibitors (PPIs); evaluation of patients with symptoms suggestive of GERD although with normal endoscopy and normal pHmetry, diagnostic elucidation of patients with atypical symptoms or supra-esophageal symptoms, mainly chronic cough, study of patients complaining of belch, differentiating gastric and supra-gastric belching, and the proper work-up before anti-reflux surgery. **Results** – When impedance was associated to pH monitoring, an impressive technological evolution became apparent, when compared to pH monitoring alone. The main advantages of impedance-pHmetry are: the ability to detect all types of reflux: acid, non-acid, liquid, gaseous. In addition, other important measurements can be made: the ability of the esophagus in transporting the bolus, the measurement of basal mucosal impedance and the evaluation of primary peristalsis post reflux. **Conclusion** – Impedance-pHmetry is a promising method, with great advantages over conventional pHmetry. The choice between these two types of monitoring should be very judicious. The authors suggest the importance of careful evaluation of each reflux episode by the physician responsible for the examination, necessary for the correct interpretation of the tracings.

HEADINGS – Gastroesophageal reflux. Esophageal pH monitoring. Electric impedance.

INTRODUCTION

Prolonged reflux monitoring, introduced in clinical practice in the mid 70s, enlarged our knowledge on GER. Until then, reflux was recognized only when it provoked inflammation of the esophageal mucosa, identified during endoscopy. The disease caused by reflux, was then designated as reflux esophagitis. With the introduction of prolonged pH monitoring the quantification of reflux in healthy volunteers was established and named physiologic reflux. Reflux above this level was named pathologic reflux and classified according to body position, in three types: upright (the most common type), supine and combined. A large portion of patients with symptomatic pathologic reflux did not have esophagitis identified by endoscopy.

Therefore, the concept of this disease became known as GERD, which can be diagnosed by endoscopic changes suggestive of reflux such as erosive esophagitis and/or pathologic reflux, identified by prolonged reflux monitoring.

The initial monitoring tool in clinical use – esophageal pHmetry- identified only episodes of acid reflux. With the evolution of this method, represented by impedance–pH monitoring, other types of reflux such as non-acid and gaseous reflux were recognized. They can also provoke symptoms and are not shown by conventional pHmetry alone. The purpose of this paper is to review reflux monitoring by impedance-pHmetry, taking into account data of the literature, and the experience of the authors with this method in 1,200 exams.

TYPES OF PROLONGED REFLUX MONITORING

Prolonged reflux monitoring can be done by catheter pHmetry or by catheter-free pH testing, using a telemetric capsule placed by endoscopy in the distal esophagus; when associated with impedance (impedance-pHmetry), it identifies non-acid reflux (pH above 7) and slightly acid (pH between 4 and 7). Impedance-pH monitoring has excellent sensitivity (77%–100%) and specificity (85%–100%) for the diagnosis of pathologic reflux[1]. Therefore, this method is considered the gold standard by many authors[2,3].

Standard catheter pHmetry

PHmetry is done through a catheter introduced trans-nasally, with one or more pH sensors. The distal sensor is positioned 5 cm above the upper limit of the lower esophageal sphincter (LES), previously identified by manometry. The catheter is connected to a portable data logger, that register pH data every 4 sec during a

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18 to 24 hour period. The patient registers the beginning and end of meals, upright and supine periods, as well as the occurrence of symptoms. Acid reflux is defined as a fall of esophageal pH below 4; the time percentage of pH<4 during the total time is the most reliable measurement for the diagnosis of GERD, considering the upper limit of normal between 4% and 5.5%[4].

Catheter-free pHmetry

Catheter-free pHmetry is done with a device, the size of a capsule, which is fixed to the esophageal mucosa, usually during endoscopy, 6 cm above the Z line[5]. This technique was developed, aiming to reduce patient discomfort, thereby permitting more prolonged monitoring, and increasing the sensitivity of the test, since the patient can go through normal daily activities without the discomfort of the trans-nasal catheter. Nevertheless, a Brazilian study published in 2012, showed that, although catheter-free revealed a larger percentage of time of reflux than conventional pHmetry, both methods were comparable in the diagnosis of pathologic reflux and its correlation with symptoms[6].

Impedance-pHmetry

Esophageal impedance is a method that allows to follow the ante-grade (bolus transport) and retro-grade movements (reflux) of intraluminal contents[7]. When impedance is associated with pHmetry – esophageal impedance-pHmetry (imp-pH), we can evaluate the retrograde movement of the refluxed material, characterizing its physical and chemical nature. Therefore, we can determine if there is reflux, if it is liquid, gaseous or mixed, acid or non-acid, and mainly, to correlate symptoms with all types of reflux[8,9]. Since the method identifies reflux regardless of its pH, it can be done while on anti-secretory drugs.

The imp-pH catheter has the same diameter of the conventional pHmetry catheter (2 mm), with one or two pH sensors and six pairs of metallic electrodes, allowing several configurations. The catheter is connected to a portable data-logger, and this data is kept in a memory card. At the end of the examination, the data is transferred to a computer to be analyzed by a dedicated software.

The method is based on the measurement of alterations in the resistance to alternating electric current (measured in Ohms), which occur between pairs of metallic electrodes, distributed along the catheter, positioned inside the esophagus. The electric conductance is directly related to the concentration of ions inside the esophageal lumen. When the content has a high concentration of ions (food, saliva, gastric contents), the electrical conductivity is high, and therefore, the impedance is low. When the intraluminal contents have a low ionic concentration (absence of bolus or presence of air), the electrical conductivity is low and, therefore, the impedance is high. Observing the impedance changes along the catheter, we can verify if the direction of the bolus is ante-grade, such as during food ingestion, or retrograde, as occurs during reflux. When a pH sensor is attached to this catheter, we can identify the acid or non-acid nature of the refluxed material[10]. (FIGURE 1).

MAIN INDICATIONS FOR IMPEDANCE-PHMETRY

Impedance-pHmetry is the method with the best sensitivity to detect all reflux episodes, as well as its distribution in the esophagus and pharynx, composition and clearance[11-13]. It was validated in the detection of acid reflux, identifying 97% to 98% of acid refluxes detected by pHmetry, not only in patients with GERD, but also in healthy controls, and in the identification of non-acid refluxes, detecting more than 93% of non-acid refluxes and in superimposed refluxes ("re-reflux"). This method, nevertheless, does not allow detection of very small volume refluxes (<1mL); but such episodes are less frequent in clinical practice. Next are the main indications and advantages of the method.

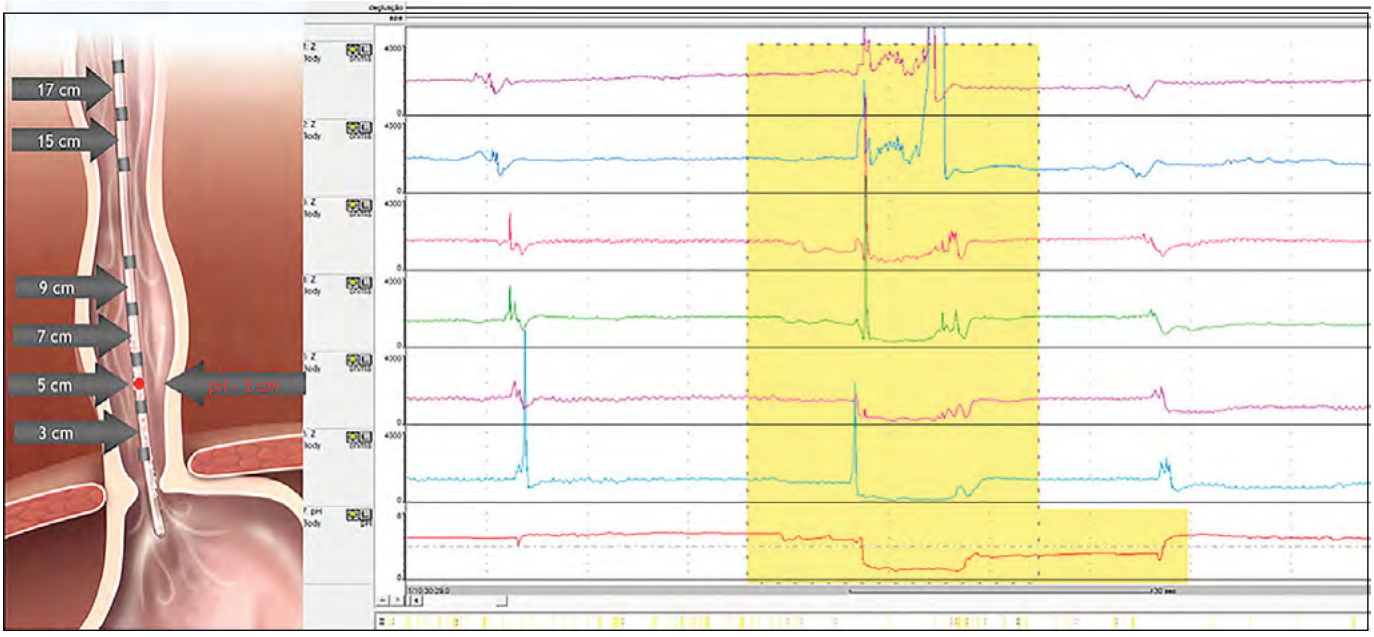

FIGURE 1. On the left, an intra-esophageal catheter is depicted; on the right, there is a graphic representation of a reflux episode mainly liquid (shown by the decrease in impedance), acid (demonstrated by the fall of pH in the lower tracing), with proximal extension up to the pharynx. It is also shown that this reflux episode is cleared by primary peristalsis, seen by the descending movement of liquid content.

Assessment of non-acid reflux

As already mentioned, esophageal pHmetry evaluates properly acid GER, but is not so with non-acid reflux. About 30% of patients continue having symptoms, in spite of anti-secretory drugs, have their symptoms due to non-acid reflux, not detected by conventional pHmetry. The term non-acid reflux is not very precise, since the majority of these refluxes have pH between 4 and 7. This aspect was discussed in an international consensus on the definition of reflux, and it was suggested that the term non-acid reflux should be used when pH is above 7, and refluxes with pH between 4 and 7 should be called slightly acidic refluxes[9]. Nonetheless, in clinical practice the term non-acid is used whenever a reflux has pH>4, all of them not detected by conventional pHmetry.

Several studies in adults and children, indicate that impedance-pHmetry is the gold standard for the diagnosis of GER. Tutuian R and Castell DO, in a review on this subject[14], claim that the presence and proximal extension of non-acid reflux (which occur mainly in the post-prandial period when gastric acidity can be neutralized by food, and during treatment with anti-secretory drugs), can now be adequately studied. The possibility of correlating clinical symptoms and non-acid reflux is of great value, especially in patients who remain symptomatic while in use of anti-secretory drugs.

Other methods for the detection of non-acid reflux (scintigraphy and bilimetry) have several limitations. Scintigraphy involves radiation and can only be done over short periods of time, allowing a momentaneous analysis of reflux. Bilimetry does not correlate well with intra-gastric pH, and does not detect reflux without bilirubin, which amounts to more than 90% of non-acid refluxes[15]. Pace F et al.[16], evaluating bilimetry together with impedance-pH, noted that there is no significant relation between bile reflux and non-acid reflux. The majority of bile reflux are associated with acid reflux.

Assessment of proximal extension and composition of reflux

Regarding proximal extension, refluxes are limited to the distal esophagus, or ascend proximally to the upper esophagus. Neither pHmetry, nor impedance-pHmetry can measure volume. The measurement of proximal extension is a surrogate for volume, since larger volume of reflux, occupying more space, extends proximally. This measurement of proximal extension (by impedance) is important, since there are symptoms that are not due to its acidity, but to the volume of refluxed material, such as regurgitation, chest pain and cough. Moreover, the increased proximal extension of reflux can be the reason of refractory symptoms in patients with hypersensitive esophagus[17].

Regarding the composition of reflux, we observe a similar proportion of liquid (51%) and mixed refluxes (49%). Regarding esophageal clearance, it is noted that the necessary time to pH to return to a level above 4, is twice longer than the time to impedance to return to previous level. There are some publications on normal values for imp-pH; among them we emphasize: Zerbib F et al., with 68 asymptomatic controls[18] and Zentilin P et al., with 25 controls[19].

It is important to stress that symptoms often do not depend on the chemical composition of the reflux, but on its physical composition (liquid, gaseous or mixed content). In these cases, symptoms are not due to stimulation of chemoreceptors, but on mechanoreceptors. The association of symptoms with gaseous distention, can only be detected by impedance-pHmetry. It is worth mentioning that gaseous content of reflux is an important factor in the proximal extension and development of extra-esophageal complaints.

Imp-pH also permits the diagnosis of "re-reflux" (superimposed acid reflux). It represents a new episode of reflux that occurs while the pH is still below 4. Conventional pHmetry can not distinguish a "re-reflux" from a prolonged reflux episode[20]. Acid reflux is twice more frequent than non-acid reflux, and superimposed reflux ("re-reflux") occurs in an even smaller frequency.

Assessment of patients with refractory symptoms in spite of anti-secretory drugs

When imp-pH is indicated in the evaluation of patients not responding well to the use of anti-secretory drugs, the exam should be preferably done during treatment to establish if symptoms are due to acid reflux not adequately blocked, if symptoms are due to non-acid reflux, or not due to reflux at all. In a classic study with imp-pH in symptomatic patients in spite of anti-secretory drugs, it was shown that 11% of them had their symptoms due to acid reflux not adequately neutralized by anti-secretory drugs (these cases could be identified by conventional pHmetry). Nevertheless, 37% of patients had symptoms related to non-acid reflux (detectable only by impedance-pH). In the remaining 52% of the patients, symptoms were not related to reflux[21].

When imp-pH is indicated for the diagnosis of GERD, it is preferable to withhold medication for at least one week. By doing so, we can assess the total number of refluxes and their distribution in acid or non-acid. We can determine the percentage of time of acid exposure, which is considered pathologic when greater than 6%. Another reason is that with a tendency for an increase in the number of symptoms when off medication, there is a greater chance for symptom correlation with reflux.

When evaluating asymptomatic controls without anti-secretory drugs, it is noted that 2/3 of reflux is acid and 1/3 is non-acid. When patients are taking anti-secretory drugs, we do not notice a significant reduction in the total number of reflux episodes, but there is a significant change in the distribution, and non-acid refluxes predominate.

Vela et al., in a classic publication on this subject[22], evaluated the effect of omeprazole in 12 patients, submitted to impedance-pHmetry, before and during the use of this drug. They observed that before treatment, 55% of the refluxes were non-acid and 45% were acid. During the use of omeprazole, the total number of reflux was the same, but there was a great change in the distribution; 97% of the refluxes became non-acid, and 3% remained acid.

Evaluation of atypical symptoms

Ambulatory impedance-pH monitoring has become a great diagnostic tool in the evaluation of atypical GERD symptoms like chronic cough and belching.

According to a systematic review and meta-analysis of randomised controlled trials 21% to 41% of chronic cough without an underlying respiratory disease is associated with gastro-oesophageal reflux[23]. Sifrim et al.[24] analyzing 22 patients suffering from chronic cough has observed that 22.7% had chronic cough related to acid reflux, 13.6% related to weakly acid reflux and 9% related to both. In this study, the ability in determination of temporal association between cough and reflux was observed in 31.5% for pH-monitoring alone and in 45.5% for impedance-pH. Besides, a subgroup of patients with chronic cough clearly associated with weakly acidic re-

flux was identified. In another case series, the same author analyzed a total of 100 patients with chronic cough. It was demonstrated that acid reflux could be a potential mechanism for cough in 45 patients, weakly acidic reflux could be a potential mechanism for cough in 24 patients and reflux could not be identified as a potential mechanism for cough in 31 patients[25].

One of the mechanisms that have been proposed to explain unexplained chronic cough refractory to PPI is the occurrence of esophageal distension by weakly acidic reflux[21]. Impedance-pH-monitoring identified patients in whom cough can be related to reflux that would have been disregarded using the standard diagnostic criteria for acid reflux.

In patients with excessive belching, impedance-pH can differentiate patients who present belching from the gas content of the stomach through the esophagus, those who expulse swallowed air and those who expulse air stored in the esophagus itself. Such differentiation is important in therapeutic management.

Belching (eructation) is classically defined as a physiological mechanism that prevents the accumulation of gas in the stomach due to the venting of the accumulated intragastric air into the esophagus followed by oral expulsion[26]. However, with the use of esophageal impedance monitoring, supragastric belching has been identified. During this type of belch, air is rapidly brought into the esophagus and immediately followed by a rapid expulsion. Impedance tracers demonstrate an increase in impedance level starting in the proximal channel and progressing to the most distal channel. The air is then cleared from the esophagus in oral direction that is seen as a return to the baseline impedance level, starting in the most distal channel and progressing to the proximal channel. On the other hand, gastric belch is characterized by an increase in impedance level starting in the distal channel and progressing to the most proximal channel accompanied by lower esophageal sphincter relaxation[27].

Differential diagnosis of functional disorders

Symptomatic reflux, abnormal acid exposure, and mucosal acid sensitivity are separate, though related, aspects of GERD. It is known that 10%-40% of patients presenting heartburn do not respond to proton pump inhibitor (PPI) use and that a proportion of those patients have normal esophageal acid exposure and no correlation between reflux events and symptoms[28]. This group is named "functional heartburn"[29].

According to Rome IV criteria, diagnosis of functional heartburn must include all of the following: burning retrosternal discomfort or pain; no symptom relief despite optimal antisecretory therapy; absence of evidence that gastroesophageal reflux or EoE is the cause of symptoms and absence of major esophageal motor disorders[30].

In other hand, reflux hypersensitivity refers to patients with esophageal symptoms (heartburn or chest pain) triggered by physiologic reflux[30].

Thus, it is observed that imp-pH is essential for the diagnosis of functional heartburn and hypersensitivity to reflux[30]. Classifying patients with symptomatic nonacid reflux as having a hypersensitive esophagus decreases the number of patients with functional heartburn[31]. This characterization is important considering that patients with functional heartburn may not respond to antisecretory drugs[29].

Identification of candidates for surgical treatment

It is well established that GERD is a disease of acid escape and not acid production and that transient lower esophageal sphincter relaxation (TLESR) is one of the main mechanism of gastroesophageal reflux disease. Although TLESRs number are not consistently increased in GERD patients compared to controls, it is known that TLESRs are more frequently associated with reflux episodes in GERD patients[32,33].

Fundoplication results in significant decrease in TLESR frequency compared to GERD and normal patients, and less TLESRs associated with reflux events[34]. Moreover, fundoplication can restore the disrupted anatomy of esophagogastric junction (EGJ) in case of hiatus hernia. However, because of the invasive nature of the operation, it is not considered as first-line therapy to GERD patients. Thus, patient selection is the key role for surgery success. The best candidates are those with typical symptoms who respond to PPI therapy[35]. However, non-responders can also be candidates when they have positive correlation between symptoms and acid or weakly acid reflux. In a study of 200 patients with persistent symptoms despite PPIs twice daily, 18 patients with positive correlation of symptoms with reflux underwent laparoscopic Nissen fundoplication. Seven of these patients complaining of chronic cough had their symptoms related to non-acid reflux, and all of them remained asymptomatic at 14 months follow-up[36]. This indicates that, unlike the treatment with antisecretor[36,37], surgical management can also treat non-acid reflux.

Imp-pH could also demonstrate that the drugs used to reduce transient relaxation of the esophageal lower sphincter, especially baclofen, reduce the total number of reflux episodes and not only change their chemical composition, as do the antisecretor[38]. However, their important side effects may limit their clinical use.

AUTHORS' EXPERIENCE WITH THE METHOD

We have started the use of imp-pH in 2005 carrying out 1,200 procedures. We advocate that the main indication of the method is the study of symptoms refractory to the clinical treatment of GERD. Analyzing a series of 20 consecutive patients, with predominant typical complaints, we observed that 19 (95%) had symptoms during the examination; (31.6%) with no reflux, 6 (31.6%) related to non-acid reflux, 6 (31.6%) related to non-acid reflux and 2 (10.5%) related with both. Roughly, we can say that among patients with refractory GERD, 1/3 has symptoms due to acid reflux, 1/3 due to non-acid reflux and in 1/3 it is not possible to relate persistent symptoms to any reflux modality.

In our series, the main indications of the method were: antisecretors symptom refractory patients, atypical or extraesophageal complaints and patients with clinical suspicion of GERD not confirmed by endoscopy or by conventional pHmetry. Kline MM et al.[39] evaluating 37 patients with typical GERD symptoms with normal endoscopy and pHmetry, have found that 10 (27%) presented acid reflux and 14 (38%) acid reflux and non-acid reflux symptoms demonstrating incremental value of imp-pH over conventional pHmetry in diagnostic performance.

Additional advantages of impedance-pH versus pHmetry

A recently published consensus on the diagnosis of GERD, Lyon consensus[40], interesting statements are set regarding the monitoring of GERD. The authors advocated that the most

relevant parameter in monitoring by pHmetry is the percentage of total reflux time; percentages above 6 should be considered pathological, less than 4 physiological and between 4 and 6 inconclusive. Regarding imp-pH monitoring, the number of episodes of reflux has been highlighted; pathological over 80, physiological below 40 and inconclusive between 40 and 80. The authors have emphasized that imp-pH, considering all reflux modalities, has a greater chance of relating clinical symptoms with reflux than conventional pH monitoring. Three additional advantages of imp-pH monitoring in relation to conventional pHmetry are pointed out: analysis of bolus transport, basal esophageal impedance and post reflux peristalsis. We have evaluated the transport of the bolus since the beginning of our experience; and, in the last three years, we added the analysis of baseline impedance and peristalsis post reflux in all performed procedures. The importance of these three measurements is demonstrated as follows.

• Analysis of the bolus transport

At the beginning of recording, with the patient in recumbent position, 10 oral instillations of 5 ml of saline are made, 30 seconds interval between them. The following day, after removal of the equipment, it is verified, by impedance, if there is complete transport of the bolus. Adequate transport of at least eight (80.0%) of the swallows studied is considered normal[41]. FIGURE 2 shows an adequate transport record of the ingested bolus. This information is important in the preoperative evaluation, since complete bolus transport is indicative of the efficacy of the contractile activity of the esophagus, even if there is hypocontractility of the esophageal body on manometric study.

In our experience, retrospectively reviewing the last 1,000 cases, we found abnormal bolus transport (<80%) in 31 (3.1%) cases. There were several causes for impairment of bolus transport; among them: relevant motor disorders of the esophagus, dysphagia after fundoplication and large gastric herniations. In 12 (1.2%) cases the analysis of the bolus transport was impaired by very low baseline impedance in the esophageal body. The most common causes for the difficulty of bolus transport analysis due to low baseline impedance were: long Barrett's esophagus, esophageal involvement due to collagen disease and megaesophagus. In our view, the study of bolus transport by impedance-pHmetry provides important reference information; however, it does not represent a specific and sensitive method for definitive characterization of esophageal transport function. For a more specific analysis of this question, a radiological contrast study is recommended. A radiological contrast study of the esophagus can be performed in two ways: conventional and dynamic. The dynamic study, with film of the passage of contrast material through the esophagus, has a higher diagnostic sensitivity than the conventional study.

• Basal impedance

When the esophagus is empty, the intraluminal impedance recorded corresponds to that of the esophageal mucosa. In the presence of active inflammation of the same, Barrett's esophagus and esophageal involvement in collagenosis, the basal impedance is very much reduced. Therefore, by the analysis of the basal impedance (BI) one can infer about the integrity of the mucosa. In the presence of liquid-alimentary residue in the esophagus, the baseline impedance is also reduced, impeding adequate evaluation of reflux[42]. FIGURE 3 shows a record of both low and normal BI in the lower esophagus. The BI should be evaluated during sleep, when the impedance is more stable, as there are fewer refluxes and deglutition. This is calculated as an average of three periods of 10 minutes.

In our experience, it has been noted that low baseline impedance makes it difficult to interpret reflux episodes; however, we have observed a relationship between the percentage of exposure time to acid and baseline impedance and also that the reduced BI tends to normalize with anti-secretory use. Baseline impedance has been considered a good marker of esophageal mucosal lesion[43].

Mucosal integrity and BI are longitudinal evidences, that is, over time, reflects exposure to acid. Reduced BI, in the absence of stasis, indicates impairment of esophageal mucosal integrity. Obviously, mucosal integrity can also be assessed by upper digestive endoscopy; however, it must be emphasized that there may be involvement of the mucosa without visible endoscopic alterations. When biopsies are performed to identify microscopic esophagitis, mucosal integrity can be assessed in greater detail. However, macroscopic esophagitis may be present in up to 15% of healthy individuals[44].

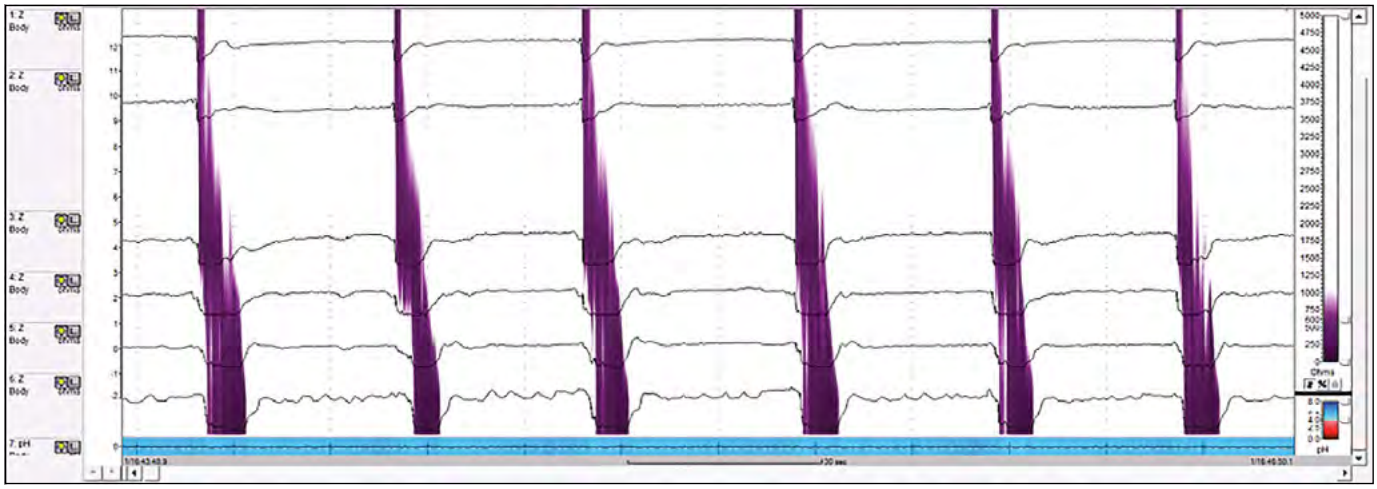

FIGURE 2. Analysis of the bolus transport.

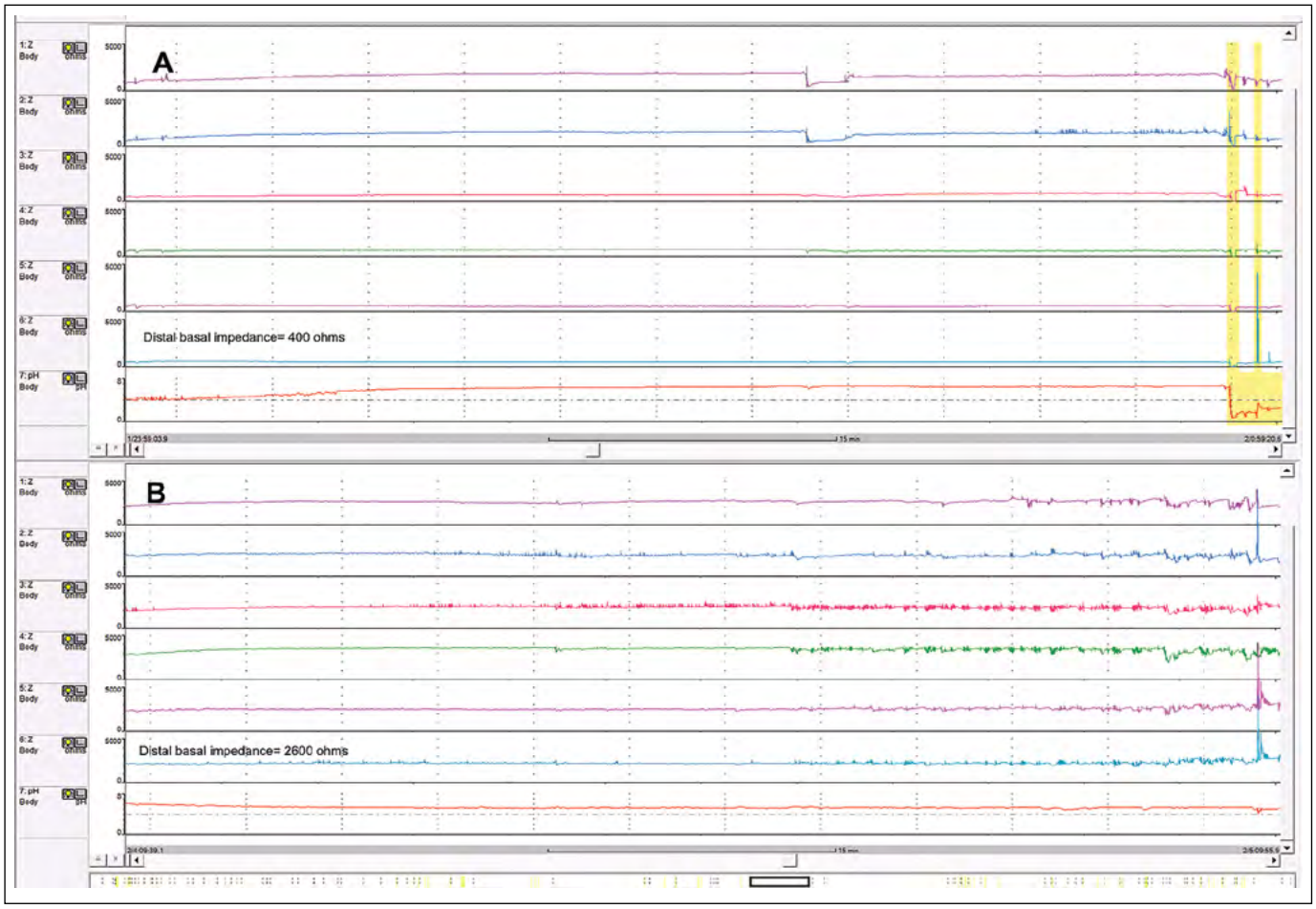

FIGURE 3. Demonstration of both low and normal basal impedance in the lower esophagus.

• Peristalse post reflux

Here we stop worrying only about the reflux and we begin to worry about what happens after the reflux, that is, with its clearance. It is known that acid reflux triggers esophageal-salivary reflex[45]. After an episode of reflux, one can identify, by impedance-pH, whether there is esophageal peristalsis. By analyzing the reflux episodes individually, we observed how many elicited esophageal peristalsis in the 30 seconds following reflux. With this, one can analyze the percentage of refluxes that trigger peristalsis after reflux; that is, the so-called post reflux peristalsis index (PRPI). Initial publications on the subject have pointed out that this index reflects the capacity of clearance of the esophagus. Normal indices (greater than or equal to 61%) suggest good capacity of esophageal clearance of the refluxed material. Relating this index to the degree of mucosal lesion, lower rates of erosive GERD, intermediate non-erosive and normal asymptomatic controls have been noted[46]. FIGURE 4 shows post-reflux peristalsis promoting acidity clearance of reflux.

It has been noted that the rate of peristalsis post reflux is more reduced in patients with Barrett's esophagus with dysplasia[47]. Barrett's neoplastic degeneration seems to relate more to low PRPI than to inadequate response to antisecretors. Quantifying reflux may be dispensable in Barrett because the diagnosis is already established; however, the evaluation of PRPI may justify the achievement of impedance-pH in these cases. The evaluation of PRPI is also important in patients who undergo lung transplantation; the risk of rejection is greater when there is reduced PRPI[48]. The measurement of the PRPI has not yet been incorporated into the software; therefore, careful visual analysis of all acid or mildly acid reflux episodes is necessary. Episodes of gas reflux are not considered in the calculation of PRPI because they do not trigger esophageal-salivary reflux.

INDICATIONS OF IMPEDANCE-PHMETRY

1. Study of patients who remain symptomatic during the treatment of reflux with anti-secretory drugs. In these cases, the test should be performed during the period on medication.
2. Patients with symptoms suggestive of GERD who do not present esophagitis at endoscopic examination and who have normal pHmetry. In these cases, the test should be performed without the use of anti-secretory agents.
3. Diagnostic clarification of patients with atypical symptoms and supra-esophageal symptoms, not explained by other causes. Principally: coughing and belching.
4. Assistance in the indication of surgical treatment of reflux.

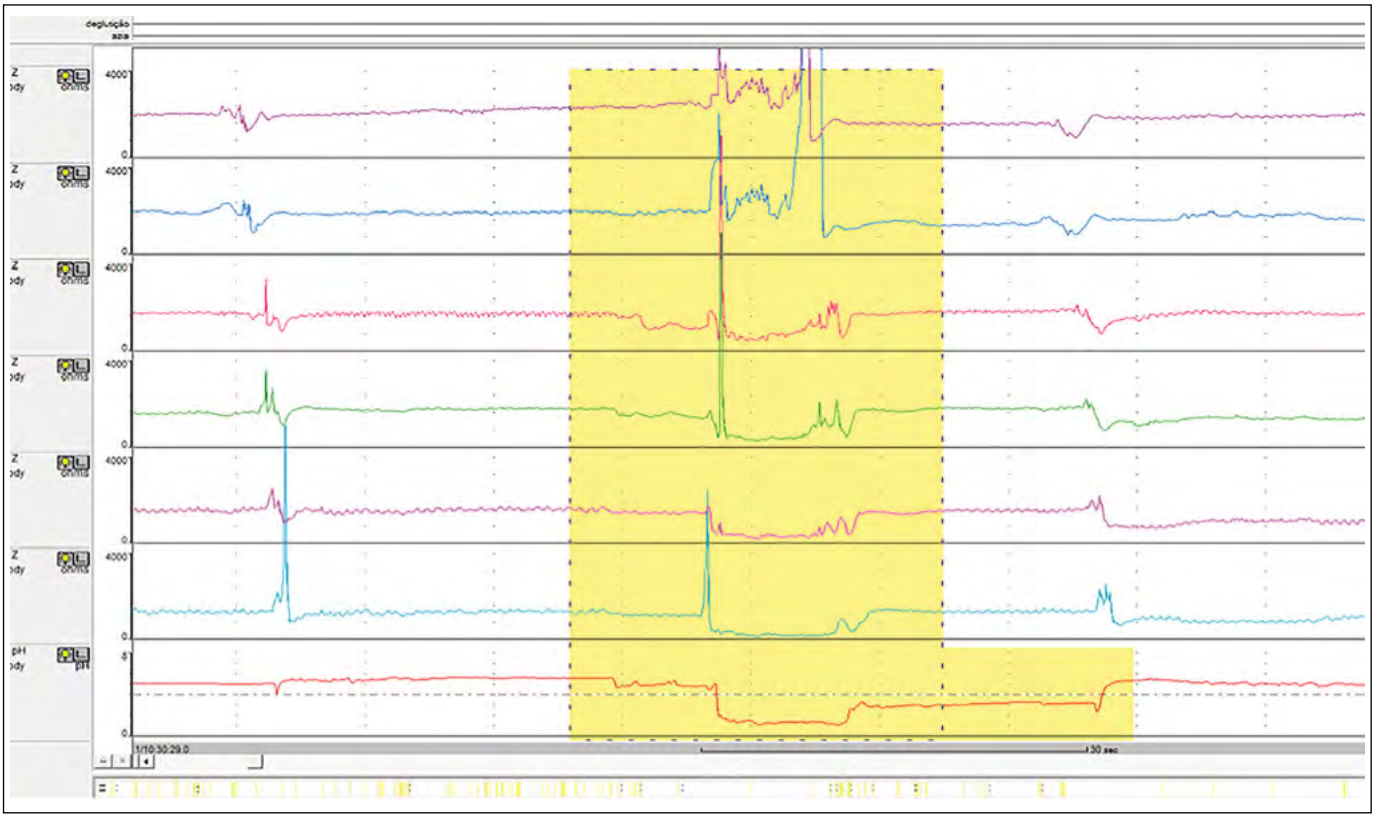

FIGURE 4. Demonstration of post-reflux peristalsis promoting acidity clearance of reflux.

CONCLUSION

Prolonged monitoring increased knowledge about gastroesophageal reflux; the condition resulting from it, has been renamed Gastroesophageal reflux disease. Monitoring allows the diagnosis of GERD in cases without sufficient endoscopic alterations to characterize the condition.

The choice of the type of monitoring to be used should be judicious. The main advantages of impedance-pHmetry to pH-monitoring alone are: the possibility of evaluating all reflux modalities; i.e. acid, non-acid, liquid and gaseous and also the possibility of studying other important variables; i.e., bolus transport capacity, basal impedance of the esophagus and peristalsis post reflux.

The main indications of impediment-pH monitoring in clinical practice are: the study of symptoms refractory to the clinical treatment of GERD, the study of atypical reflux manifestations; among them, in particular, the chronic cough and the study of the eructations differentiating them in gastric and supragastrics.

Our experience with the method is encouraging. It should be noted, however, that the method is much more labor intensive than conventional pHmetry. The automatic reflux analysis by the computer program often misinterprets impedance traces, considering as reflux what in reality is an anterograde flow (deglutition). Therefore, one should analyze all episodes referred to as reflux for correct interpretation; only the retrograde propagation pattern is indicative of reflux. The characterization of the reflux should not be left on account of the computer program. Finally, it is emphasized that the study of the bolus transport capacity, the measurement of the nocturnal basal impedance and the post reflux peristalsis have become important components of the prolonged monitoring of impedance-pH monitoring[49].

Authors' contribution

All authors contributed equally in writing of text.

Nasi A, Queiroz NSF, Michelsohn NH. Monitorização prolongada do refluxo gastroesofágico por impedancio-pHmetria esofágica: uma revisão sobre o tema ponderada com nossa experiência de 1.200 casos com o método. Arq Gastroenterol. 2018;55(Suppl 1):76-84.

RESUMO – **Contexto** – A monitorização prolongada ampliou o conhecimento sobre o refluxo gastroesofágico; a afecção decorrente do mesmo, passou a ser designada por doença do refluxo gastroesofágico (DRGE). O estudo prolongado do refluxo viabiliza o diagnóstico da DRGE nos casos sem alterações endoscópicas suficientes para caracterização da afecção. **Objetivo** – O objetivo do presente trabalho é apresentar uma revisão sobre a monitorização do refluxo por impedância-pHmetria, ponderando-se os dados de literatura com a experiência dos autores com o método em 1.200 exames realizados. **Métodos** – São apresentados detalhes dos diferentes tipos de monitorização prolongada do refluxo; ou seja, a pHmetria convencional, a pHmetria sem cateter e a impedância-pHmetria. Salientam-se as novas possibilidades de avaliação que a impedância-pHmetria propicia e suas principais indicações: estudo de pacientes que permanecem sintomáticos durante o tratamento do refluxo com antissecretores; análise de pacientes com sintomas sugestivos de DRGE que não apresentem esofagite ao exame endoscópico e que tenham pHmetria normal; esclarecimento diagnóstico de pacientes com sintomas atípicos e supraesofágicos – em especial na tosse crônica; estudo da eructação diferenciando-as em dois grupos: gástricas e supragástricas e no auxílio na indicação do tratamento cirúrgico do refluxo. **Resultados** – A monitorização associando duas modalidades de avaliação: a impedancio-pHmetria representa evolução tecnológica expressiva em relação à modalidade baseada apenas na análise do pH (pHmetria). As principais vantagens da impedância-pHmetria são: possibilidade de avaliação de todas modalidades de refluxo; ou seja, ácido, não-ácido, líquido e gasoso e também a possibilidade de estudo de outras variáveis importantes; ou seja: capacidade de transporte do bolus, impedância basal do esôfago e peristalse pós refluxo. **Conclusão** – A impedancio-pHmetria é um método promissor, com grandes vantagens sobre a pHmetria convencional. A escolha do tipo de monitorização a ser utilizada, deve ser criteriosa. Os autores destacam a importância da análise cuidadosa de cada episódio de refluxo, pelo médico responsável pela execução do exame, para correta interpretação e valorização dos dados obtidos.

DESCRITORES – Refluxo gastroesofágico. Monitoramento do pH esofágico. Impedância elétrica.

REFERENCES

1. Hirano I, Richter JE, Practice Parameters Committee of the American College of Gastroenterology. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol. 2007;102:668-85.
2. Lacy BE, Weiser K, Chertoff J, Fass R, Pandolfino JE, Richter JE, et al. The diagnosis of gastroesophageal reflux disease. Am J Med. 2010;123:583-92.
3. Richter JE. Diagnostic tests for gastroesophageal reflux disease. Am J Med Sci. 2003;326:300-8.
4. Leme EMO. Parte II – pHmetria Esofágica Prolongada. Nasi A, Michelsohn N, eds. São Paulo: Editora Roca; 2001.
5. Pandolfino JE, Richter JE, Ours T, Guardino JM, Chapman J, Kahrilas PJ. Ambulatory esophageal pH monitoring using a wireless system. Am J Gastroenterol. 2003;98:740-9.
6. Azzam RS, Sallum RAA, Brandao JF, Navarro-Rodriguez T, Nasi A. Comparative study of two modes of gastroesophageal reflux measuring: conventional esophageal pH monitoring and wireless pH monitoring. Arq Gastroenterol. 2012;49:107-12.
7. Silny J. Intraluminal Multiple Electric Impedance Procedure for Measurement of Gastrointestinal Motility. Neurogastroenterol Motil. 1991;3:151-62.
8. Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: A multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol. 2004;99:1037-43.
9. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut. 2004;53:1024-31.
10. Bredenoord AJ, Smout AJPM. Advances in motility testing--current and novel approaches. Nat Rev Gastroenterol Hepatol. 2013;10:463-72.
11. Sifrim D, Holloway R, Silny J, Tack J, Lerut A, Janssens J. Composition of the postprandial refluxate in patients with gastroesophageal reflux disease. Am J Gastroenterol. 2001;96:647-55.
12. Shay SS, Bomeli S, Richter J. Multichannel intraluminal impedance accurately detects fasting, recumbent reflux events and their clearing. Am J Physiol Gastrointest Liver Physiol. 2002;283:G376-83.
13. Sifrim D, Silny J, Holloway RH, Janssens JJ. Patterns of gas and liquid reflux during transient lower oesophageal sphincter relaxation: a study using intraluminal electrical impedance. Gut. 1999;44:47-54.
14. Tutuian R, Castell DO. Use of multichannel intraluminal impedance to document proximal esophageal and pharyngeal nonacidic reflux episodes. Am J Med. 2003; Suppl 3A:119S-123S.
15. Just RJ, Leite LP, Castell DO. Changes in overnight fasting intragastric pH show poor correlation with duodenogastric bile reflux in normal subjects. Am J Gastroenterol. 1996;8:1567-70.
16. Pace F, Sangaletti O, Pallotta S, Molteni P, Porro GB. Biliary reflux and non-acid reflux are two distinct phenomena: A comparison between 24-hour multichannel intraesophageal impedance and bilirubin monitoring. Scand J Gastroenterol. 2007;42:1031-9.
17. Rohof WO, Bennink RJ, de Jonge H, Boeckxstaens GE. Increased Proximal Reflux in a Hypersensitive Esophagus Might Explain Symptoms Resistant to Proton Pump Inhibitors in Patients With Gastroesophageal Reflux Disease. Clin Gastroenterol Hepatol. 2014;12:1647-55.
18. Zerbib F, des Varannes SB, Roman S, Pouderoux P, Artigue F, Chaput U, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subjects. Aliment Pharmacol Ther. 2005;22:1011-21.
19. Zentilin P, Iiritano E, Dulbecco P, Bilardi C, Savarino E, De Conca S, et al. Normal values of 24-h ambulatory intraluminal impedance combined with pH-metry in subjects eating a Mediterranean diet. Dig Liver Dis. 2006;38:226-32.
20. Shay SS, Johnson LF, Richter JE. Acid rereflux: A review, emphasizing detection by impedance, manometry, and scintigraphy, and the impact on acid clearing pathophysiology as well as interpreting the pH record. Dig Dis Sci. 2003;48:1-9.
21. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: A multicentre study using combined ambulatory impedance-pH monitoring. Gut. 2006;55:1398-402.
22. Vela MF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: Effect of omeprazole. Gastroenterology. 2001;120:1599-606.
23. Chang AB, Lasserson TJ, Kiljander TO, Connor FL, Gaffney JT, Garske LA. Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. BMJ. 2005;332:11-17.
24. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. Gut. 2005;54:449-54.
25. Blondeau K, Dupont LJ, Mertens V, Tack J, Sifrim D. Improved diagnosis of gastro-oesophageal reflux in patients with unexplained chronic cough. Aliment Pharmacol Ther. 2007;25:723-32.
26. Wyman JB, Dent J, Heddle R, Dodds WJ, Toouli J, Downton J. Control of belching by the lower oesophageal sphincter. Gut. 1990;31:639-46.
27. Kessing BF, Bredenoord AJ, Smout AJPM. The pathophysiology, diagnosis and treatment of excessive belching symptoms. Am J Gastroenterol. 2014;10(8).
28. Fass R, Sifrim D. Management of heartburn not responding to proton pump inhibitors. Gut. 2009;58:295-309.

29. Hachem C, Shaheen NJ. Diagnosis and Management of Functional Heartburn. Am J Gastroenterol. 2016;111:53-61.
30. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Esophageal disorders. Gastroenterology. 2016;150:1368-79.
31. Savarino E, Zentilin P, Tutuian R, Pohl D, Casa DD, Frazzoni M, et al. The role of nonacid reflux in NERD: Lessons learned from impedance-pH monitoring in 150 patients off therapy. Am J Gastroenterol. 2008;103:2685-93.
32. Iwakiri K, Hayashi Y, Kotoyori M, Tanaka Y, Kawakami A, Sakamoto C, Holloway RH. Transient lower esophageal sphincter relaxations (TLESRs) are the major mechanism of gastroesophageal reflux but are not the cause of reflux disease. Dig Dis Sci. 2005;50:1072-7.
33. Trudgill NJ, Riley SA. Transient lower esophageal sphincter relaxations are no more frequent in patients with gastroesophageal reflux disease than in asymptomatic volunteers. Am J Gastroenterol. 2001;96(Suppl.9):2569-2574.
34. Kessing BF, Bredenoord AJ, Schijven MP, van der Peet DL, van Berge Henegouwen MI, Smout AJPM. Long-term effects of anti-reflux surgery on the physiology of the esophagogastric junction. Surg Endosc Other Interv Tech. 2015;29:3726-32.
35. Campos GM, Peters JH, DeMeester TR, Oberg S, Crookes PF, Tan S, et al. Multivariate analysis of factors predicting outcome after laparoscopic Nissen fundoplication. J Gastrointest Surg. 1999;3:292-300.
36. Mainie I, Tutuian R, Agrawal A, Adams D, Castell DO. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. Br J Surg. 2006;93:1483-7.
37. Tutuian R, Mainie I, Agrawal A, Adams D, Castell DO. Nonacid reflux in patients with chronic cough on acid-suppressive therapy. Chest. 2006;130:386-91.
38. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther. 2003;17:243-51.
39. Kline MM, Ewing M, Simpson N, Laine L. The Utility of Intraluminal Impedance in Patients With Gastroesophageal Reflux Disease-Like Symptoms But Normal Endoscopy and 24-Hour pH Testing. Clin Gastroenterol Hepatol. 2008;6:880-85.
40. Gyawali CP, Kahrilas PJ, Savarino E, Zerbib F, Mion F, Smout AJPM, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut. 2018:67:1351-62.
41. Hila A, Chowdhury N, Hajar N, Castell DO. Swallow evaluation during multichannel intraluminal impedance and pH: An alternate method to assess esophageal transit. J Clin Gastroenterol. 2011;45:862-6.
42. Kandulski A, Weigt J, Caro C, Jechorek D, Wex T, Malfertheiner P. Esophageal Intraluminal Baseline Impedance Differentiates Gastroesophageal Reflux Disease From Functional Heartburn. Clin Gastroenterol Hepatol. 2015;13:1075-81.
43. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJM, Loots CM, Smout AJPM. Esophageal acid exposure decreases intraluminal baseline impedance levels. Am J Gastroenterol. 2011;106:2093-7.
44. Vaezi MF, Sifrim D. Assessing Old and New Diagnostic Tests for Gastroesophageal Reflux Disease. Gastroenterology. 2018;154:289-301.
45. Woodley FW, Fernandez S, Mousa H. Diurnal Variation in the Chemical Clearance of Acid Gastroesophageal Reflux in Infants. Clin Gastroenterol Hepatol. 2007;5:37-43.
46. Frazzoni M, Savarino E, de Bortoli N, Martinucci I, Furnari M, Frazzoni L, et al. Analyses of the Post-reflux Swallow-induced Peristaltic Wave Index and Nocturnal Baseline Impedance Parameters Increase the Diagnostic Yield of Impedance-pH Monitoring of Patients With Reflux Disease. Clin Gastroenterol Hepatol. 2016;14:40-6.
47. Frazzoni M, Bertani H, Conigliaro R, Frazzoni L, Losi L, Melotti G. Neoplastic progression in short-segment Barrett's oesophagus is associated with impairment of chemical clearance, but not inadequate acid suppression by proton pump inhibitor therapy. Aliment Pharmacol Ther. 2014;40:835-42.
48. Tangaroonsanti A, Jones DR, Lee AS, Vela MF, DeVault KR, Houghton LA. 534 Post-Reflux Swallow-Induced Peristaltic Wave (PSPW) Index, a Measure of Esophageal Chemical Clearance Is a Predicator of Allograph Failure After Lung Transplantation. Gastroenterology. 2016;150:S111-S112. Doi: https://doi.org/10.1016/S0016-5085(16)30480-2.
49. Smits MJ, Loots CM, van Wijk MP, Bredenoord AJ, Benninga MA, Smout AJPM. An expert panel-based study on recognition of gastro-esophageal reflux in difficult esophageal pH-impedance tracings. Neurogastroenterol Motil. 2015;27:637-45.

REVIEW

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Are the persistent symptoms to proton pump inhibitor therapy due to refractory gastroesophageal reflux disease or to other disorders?

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ABSTRACT – **Background** – Gastroesophageal reflux disease (GERD) is a clinical condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Transient lower esophageal sphincter relaxation is the main pathophysiological mechanism of GERD. Symptoms and complications can be related to the reflux of gastric contents into the esophagus, oral cavity, larynx and/or the lung. Symptoms and other possible manifestations of GERD are heartburn, regurgitation, dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma and dental erosions. The proton pump inhibitor (PPI) is the first-choice drug and the most commonly medication used for the treatment of GERD. The most widespread definition of Refractory GERD is the clinical condition that presents symptoms with partial or absent response to twice-daily PPI therapy. Persistence of symptoms occurs in 25% to 42% of patients who use PPI once-daily and in 10% to 20% who use PPI twice-daily. **Objective** – The objective is to describe a review of the current literature, highlighting the causes, diagnostic aspects and therapeutic approach of the cases with suspected reflux symptoms and unresponsive to PPI. **Conclusion** – Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage and emphasizing the recommendations on lifestyle modification change, avoiding food and activities that trigger symptoms. PPI decreases the number of episodes of acid reflux; however, the number of "non-acid" reflux increases and the patient continues to have reflux despite PPI. In this way, it is possible to greatly reduce greatly the occurrence of symptoms, especially those dependent on the acidity of the refluxed material. Response to PPI therapy can be evaluated through clinical, endoscopic, and reflux monitoring parameters. In the persistence of the symptoms and/or complications, other causes of Refractory GERD should be suspected. Then, diagnostic investigation must be initiated, which is supported by clinical parameters and complementary exams such as upper digestive endoscopy, esophageal manometry and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring). Causes of refractoriness to PPI therapy may be due to the true Refractory GERD, or even to other non-reflux diseases, which can generate symptoms similar to GERD. There are several causes contributing to PPI refractoriness, such as inappropriate use of the drug (lack of patient adherence to PPI therapy, inadequate dosage of PPI), residual acid reflux due to inadequate acid suppression, nocturnal acid escape, "non-acid" reflux, rapid metabolism of PPI, slow gastric emptying, and misdiagnosis of GERD. This is a common cause of failure of the clinical treatment and, in this case, the problem is not the treatment but the diagnosis. Causes of misdiagnosis of GERD are functional heartburn, achalasia, megaesophagus, eosinophilic esophagitis, other types of esophagitis, and other causes. The diagnosis and treatment are specific to each of these causes of refractoriness to clinical therapy with PPI.

HEADINGS – Gastroesophageal reflux. Proton pump inhibitor. Refractory gastroesophageal reflux disease. Refractory symptoms.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications[1]. GERD is a common disease attended by the gastroenterologist[2]. A systematic review found a prevalence of GERD of 10% to 20% in the Western World (Western Europe and North America) with a lower prevalence in Asia[3,4]. However, epidemiologic estimates of the prevalence of GERD are based primarily on symptoms of heartburn and regurgitation. These are the typical symptoms of GERD and the frequency of heartburn and regurgitation in GERD is 75%-98% and 48%-91%, respectively[1].

Symptoms and complications can be related to the reflux of gastric contents into the esophagus, oral cavity, larynx and/or the lung[2]. Other possible manifestations of GERD are dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma, dental erosions and epigastric pain[1]. However, many patients empirically treated empirically with the proton pump inhibitor (PPI) for suspected reflux symptoms do not respond to this medication[2]. Furthermore, all these symptoms (typical symptoms and other manifestations) can have causes unrelated to reflux[1].

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The diagnosis of GERD is achieved by using some combination of reported symptoms, responsiveness to antisecretory therapy, and objective testing with endoscopy and ambulatory reflux monitoring (pH monitoring or impedance-pH monitoring)[2]. GERD can be classified by the endoscopy examination as Nonerosive Reflux Disease (NERD) or Erosive Reflux Disease (ERD) when there is presence of symptoms without erosions on endoscopic examination or with erosions present, respectively[2].

The PPI is the first choice drug and the most commonly medication used for the treatment of GERD[5]. Among the available drugs, PPI blocks gastric acid secretion more effectively and presents better rates of symptom relief, healing of esophagitis and prevention of complications[6,7]. Although it does not significantly reduce the number of reflux episodes, it leads to a significant change in their acidity. That is: there is still reflux; however, episodes of reflux become less acidic. In this way, it is possible to reduce greatly the occurrence of symptoms, especially those dependent on the acidity of the refluxed material[8].

Refractory GERD was defined, by the majority of researchers, as the condition that presents a missing or partial response after four to eight weeks of twice-daily PPI treatment[9-11]. However, the concept of Refractory GERD is controversial, since some publications suggest that the absence of a satisfactory symptomatic response to PPI once-daily would be sufficient to consider refractoriness[12].

Refractory GERD is a frequent cause of medical care in Gastroenterology. Despite the use of PPI, a large group of patients continues with clinical manifestations. It is estimated that 20% to 40% of patients with GERD symptoms do not respond well to PPI treatment[13,14]. Regarding the failure to respond to treatment, total or partial persistence of symptoms occurs in 25% to 42% of patients who use PPIs once-daily and in 10% to 20% of patients who use PPI twice-daily[11,15].

There are several factors involved in refractoriness. Classically, it is considered that there is influence of the type of GERD. Several publications report greater refractoriness in the NERD compared to ERD. After four weeks of once-daily PPI treatment, symptomatic response failure was 44% in the group of patients with ERD and significantly greater (63%) in the NERD group. However, recent studies, with a better characterization of reflux, indicate similar refractoriness rates, around 20%, in the NERD and in the ERD[16]. Among the erosive forms, it is emphasized that the occurrence of refractoriness is directly proportional to the degree of esophagitis. That is, it is greater in the most intense forms[5]. Furthermore, the Refractory GERD produces significant reduction on the quality of life, regarding the physical and mental health[17].

From a practical point of view, it is considered that there is PPI refractoriness when the patient persists with symptoms during the treatment. Nevertheless, response to therapy of Refractory GERD can be evaluated through clinical, endoscopic and ambulatory reflux monitoring parameters. Thus, Refractory GERD can occur in relation to the presence of persistent symptoms (heartburn, regurgitation and/or other manifestations), erosive esophagitis and pathological gastroesophageal reflux (GER). Symptoms can be evaluated for persistence (complete or incomplete), frequency and intensity.

Hereafter, our purpose is to describe a review of the current literature of the causes and treatment of suspected reflux symptoms unresponsive to PPI.

CAUSES AND TREATMENT OF REFRACTORINESS TO PPI

Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage and emphasizing the recommendations on lifestyle modification, before indicating diagnostic exams, except in the presence of alarm symptoms. Lifestyle modification consists of dietary and behavioral orientations for GERD, avoiding food and activities that trigger symptoms.

In the persistence of the symptoms, in spite of this described management, other causes of Refractory GERD should be suspected. Then, diagnostic investigation must be initiated, which is supported by complementary exams such as upper digestive endoscopy, esophageal manometry, ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring) and, eventually, scintigraphy for evaluation of gastric emptying.

Causes of refractoriness to PPI therapy may be due to the true Refractory GERD or even other non-reflux diseases, which can generate symptoms similar to GERD.

There are several causes of PPI refractoriness, such as inappropriate use of the drug (lack of patient adherence to PPI therapy, inadequate dosage of PPI), residual acid reflux due to inadequate acid suppression, nocturnal acid escape, "non-acid" reflux, rapid metabolism of PPI, slow gastric emptying and misdiagnosis of GERD. This is a very common cause of clinical treatment failure and the causes are functional heartburn, achalasia, megaesophagus, eosinophilic esophagitis, other types of esophagitis and other causes. The diagnosis and treatment is specific to each of these causes of refractoriness to clinical therapy with PPI.

These etiologies and differential diagnoses of Refractory GERD will be described below, with their respective diagnostic exams and specific treatments.

Inappropriate use of the drug

In cases of refractoriness, the first step is to check whether the patient is using the prescribed PPI correctly. It should be noted that, in some cases, physicians prescribe PPI incorrectly. Lack of patient adherence to PPI therapy and inadequate dose of PPI are inappropriate use of this drug that can cause persistence of symptoms and will be described separately below.

Lack of adherence

Adherence to treatment is the agreement between the patient's behavior and the prescribed medical orientation. It can be classified as non-adherence, low or high adherence. The patient's lack of adherence to PPI therapy is an important cause of pharmacotherapeutic failure of GERD to be considered, and a great challenge for gastroenterologists.

A recent prospective study, evaluating the degree of adherence to PPI treatment in 240 patients with GERD, revealed a high rate of low adherence to omeprazole once-daily or twice-daily: 114 (47.5%) patients had low adherence and 126 (52.5%) high adherence[18]. It should be noted that the main causes of low adherence were forgetting to take PPI in 129 (53.8%) patients, change of the ideal time of use in 124 (51.7%), stopping taking PPI after clinical improvement in 72 (30.0%) and interruption of PPI due to side effects occurred in only 7.1% of cases. The risk factors for low adherence were age under 60 years, married civil status and symptomatic patient[18]. Other literature studies have shown similar rates of low adherence to PPI. The continuity of daily use of PPI occurs

in 55% of patients after one month of treatment and decreases to only 30% after six months.

In this way, first of all, it is important to check that the patient is effectively using the prescribed PPI in an appropriate manner. Identify the presence and reasons for the lack of adherence to PPI. Emphasize the importance of high adherence, motivating the patient to ingest the PPI regularly and daily. A good doctor-patient relationship is essential. Explain to the patient the chronic characteristic of GERD and the importance of the PPI function.

Inadequate dosage

Adequate dose, time of administration and duration of treatment, as well as PPI quality, are essential for therapeutic success. Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole and pantoprazole magnesium are the PPI options available in Brazil. The standard or full dose of the PPI is once-daily and should be taken in fasting, 30 minutes before breakfast, in order to obtain the maximum power of gastric acid suppression. The double dose is twice-daily and the second dose of the PPI should be taken 30 minutes before dinner.

However, in part, because they do not receive adequate orientation, the majority (54%) of patients take the PPI incorrectly; of these, 39% take it before bed, and 4% as needed. In the USA, 70% of the general physicians and 20% of the gastroenterologists report in an inappropriate manner the PPI administration[19]. A study evaluating the medical prescriptions of the Clinical Hospital of Sao Paulo University has shown that PPI was incorrectly prescribed in 60% of the cases, in relation to dose or time of administration[20]. In patients with persistent symptoms to once-daily PPI, initial treatment includes emphasizing the correct dosage orientations, respecting the dosage of each PPI, the time of administration and duration of treatment. Verify the quality of the drug used, in relation to the manufacturer and the type, such as compounded or industrialized (generic, similar or reference). Doubling PPI dose or replacing it with another PPI allows for a 25% improvement in the satisfactory response[21].

Residual acid reflux

Residual acid reflux (RAR) is the remaining acid gastroesophageal reflux (GER) despite the use of PPI, due to inadequate gastric acid suppression. Approximately 10% to 15% of patients refractory to PPI have symptoms due to acid GER that were not adequately blocked by the drug in use. The RAR can be detected through the pH sensor of the esophageal pH monitoring or impedance-pH monitoring, performed on PPI therapy. Most digestive motility laboratories use the same normal values for the pH analysis performed with or without the use of PPI. More rigorous criteria with PPI use is a cut-off level of 1.6% for the percentage of the total reflux time that was proposed by a study evaluating healthy individuals using PPI[22].

RAR is less common in Refractory GERD, since using PPI, the majority of patients with persistent symptoms present normal esophageal pH monitoring. On PPI therapy, acid GER was pathological in only 4% to 16% of patients with Refractory GERD who used twice-daily PPI and in 31% to 36% of patients who used once-daily PPI[23-25].

Furthermore, several studies have demonstrated that the characteristics of RAR are similar between responders and non-responders to PPI, raising questions as to the real role of RAR in Refractory GERD, and the need for indication of esophageal pH monitoring during the use of IBP. The hypothesis is that the persistence of symptoms would be caused by the phenomenon of hypersensitivity of the esophagus, gas presence in reflux, and proximal migration of acid or non-acid reflux.

In such cases, one may increase the dose of PPI in use or change the type of PPI. In practice, the dose is initially increased and the exchange of PPI is reserved for cases that do not respond well to this initial management. Also, follow the orientations of the topics "Lack of adherence" and "Inadequate dosage". If RAR persists, continue investigation of other causes of Refractory GERD.

Nocturnal acid escape

The nocturnal acid escape (NAE) is defined as gastric pH<4, lasting more than 60 minutes at night. NAE is diagnosed by intragastric pH monitoring, which uses one sensor in the stomach and another in the distal esophagus. However, NAE investigation has not been performed routinely because of the lack of significant evidence of its correlation with the nocturnal symptoms of GERD, and the failure to respond to PPI.

With regard to treatment, administer nocturnal dose of PPI or histamine H2-receptor antagonist (H2-RA). The nocturnal dose of H2-RA varies according to its type: cimetidine (400 mg), ranitidine (150 mg), famotidine (20 mg), nizatidine (150 mg). H2-RA can be administered intermittently or on demand, in order to avoid the phenomenon of tachyphylaxis (reduction of the therapeutic effect due to prolonged use).

Non-acid reflux

Symptoms can arise from "non-acid" reflux (NAR). In clinical practice, GER was categorized as acid reflux (AR) when pH <4 and NAR when pH >4. This is the most widely used practical concept. However, it was defined as AR (pH <4), weakly acid reflux (pH >4 and <7) and NAR (pH >7). NAR represents about 10% to 30% of all GER episodes in normal subjects and has higher rates in patients with GERD. About 30% to 40% of Refractory GERD patients have symptoms resulting from NAR.

Transient lower esophageal sphincter relaxation (TLESR) is the main mechanism of AR and NAR. Studies on the pathophysiology of GERD suggest that NAR plays no role in the development of esophageal or extraesophageal lesion, but it is a cause of symptoms, especially in patients with NERD or Refractory GERD.

The suggested hypotheses for triggering the symptoms are esophageal distension due to NAR volume and the hypersensitivity to NAR. The PPI decreases the number of AR episodes, however the number of NAR increases, and therefore the total number of GER episodes (AR and NAR) is similar with or without PPI[26]. That is, the patient continues to reflux despite the PPI, which may be the cause of the symptoms refractoriness in GERD.

The impedance-pH monitoring allows evaluating the following reflux characteristics: chemical composition (AR, weakly acid or NAR), physical composition (liquid, gaseous or mixed) and reflux migration to the proximal esophagus[27]. This diagnostic method made it possible to detect, for example, that the proximal extension of AR and NAR is greater in GERD than in healthy individuals; however, the proximal extension of the NAR is significantly smaller than the AR. Impedance-pH monitoring improves the detection and characterization of GER, as it can correlate "non-acid" reflux with the presence of symptoms[28]. The impedance-pH monitoring has been considered the best diagnostic method for GERD, but it does not measure the reflux volume, it is costly and little available, even at large university centers.

In such cases, it would be useful to have drugs that could effectively reduce the occurrence of reflux and not simply, as PPIs do, reduce their acidity. Baclofen (GABA-B agonist) falls into this category of drugs: modulators of the action of the lower esophageal sphincter (LES). It is known that the transient relaxations of the LES represent the main mechanism favoring reflux. Such drugs have the effect of reducing the occurrence of this type of sphincter relaxation and, consequently, effectively reduce the occurrence of reflux[29].

The dose of baclofen described in the literature is 5 to 10 mg three times a day, with a gradual increase up to 20 mg three times a day, but it has important side effects such as somnolence, nausea, vertigo, asthenia and tremors[30]. Due to the large number of these side effects that usually result, it has very limited clinical use. It is hoped that in the future there may be new drugs with the same action without significant side effects.

Well-selected patients, with symptoms arising from NAR, may be good candidates for surgical treatment of reflux. Thus, in patients with NAR, the proposed therapies, still in the research phase – such as TLESR reducers (agonist of GABA-B receptor), pain modulators and antireflux surgery – should be considered[10].

Rapid metabolism of PPI

Rapid metabolism of PPI may predispose to reflux symptoms due to inadequate acid suppression. PPI is metabolized in the liver by the cytochrome P450 (CYP) enzyme complex, mainly through the CYP2C19 and CYP3A4 isoenzymes. The activity of these enzymes is influenced by endogenous and exogenous factors. The ability to metabolize depends on genotypical differences and type of PPI. The polymorphism of CYP2C19, due to genetic alterations, causes large individual pharmacokinetic variations, producing variability in acid suppression, drug interactions and therapeutic efficacy of PPI[31,32].

The genotypes of CYP2C19 were classified into three phenotypes: rapid metabolisers (RM), intermediate metabolisers (IM) or slow metabolizers (SM). RM, also called extensive metabolisers, have wild alleles and the SM or poor metabolisers have mutant alleles. RM has a high prevalence: 60% to 70% in Caucasians and 28% to 42% in Asians. In RM, PPI has rapid metabolism and low plasma level, gastric acid suppression is insufficient and symptoms persist, causing Refractory GERD.

Blood genetic testing performs CYP2C19 genotyping. The DNA is extracted from a peripheral blood sample and amplified by conventional polymerase chain reaction (PCR), directed to the specific target alleles. The drug options for the treatment of RM are esomeprazole or rabeprazole[14]. Esomeprazole is metabolized more slowly than omeprazole. Rabeprazole is also metabolized non-enzymatically and is less affected by the genetic polymorphism of the CYP2C19[32].

Slow gastric emptying

Slow gastric emptying (SGE) may predispose to reflux of gastric contents. SGE is associated in up to 40% of GERD and in up 20% of Refractory GERD cases. SGE has non-specific symptoms, such as early satiety, gastric fullness, regurgitation, epigastric pain, nausea and vomiting. Initially, gastric and other gastrointestinal organ damage should be excluded.

SGE is evaluated by direct, non-invasive methods (contrasted radiological exam, ultrasound or scintigraphy) or indirect (absorption of paracetamol or respiratory tests with carbon-13 or carbon-14). Ultrasonography is non-invasive and can evaluate the sectional area or the volume of the gastric antrum, after time intervals of the ingestion of liquid or semi-liquid meal, determining the time of the gastric emptying. Gastric scintigraphy is considered the gold standard method for evaluation of the gastric emptying. It uses a low dose of radiation and quantifies gastric emptying of liquid, pasty or solid diets. It allows to evaluate velocity of the gastric emptying [slow, fast or mixed (fast initial phase and slow late phase)]; intragastric distribution of the bolus; and antral contractility pattern[33]. However, the method has low availability, high cost and impossibility of use in children and pregnant women.

Dietary orientation aimed at improving SGE and treatment using prokinetics drugs can improve the symptoms of GERD. An experimental alternative, botulinum toxin was applied in a few cases, resulting in a short period (five months) of symptomatic improvement of GERD.

Misdiagnosis of GERD

Although not presented at the beginning of this text, the wrong diagnosis of GERD represents a very common cause of failure of the clinical treatment. One of the initial steps in refractoriness analysis is to assess whether there is actually proven GERD. Patients with other conditions such as functional heartburn, eosinophilic esophagitis, esophagitis of other causes, and even achalasia or megaesophagus can be mistakenly characterized as having GERD. In these cases, the problem is not the treatment but the diagnosis. Some causes of misdiagnosis of GERD will be described below.

Functional heartburn

In clinical practice, patients who present heartburn with normal esophagus at the digestive endoscopy, physiological reflux and normal symptom index at the reflux monitoring test (pH monitoring or impedance-pH monitoring), are supposedly characterized as having Functional Heartburn (FH) and need specific approach[5].

FH was defined in the Rome IV Consensus as burning retrosternal discomfort or pain, without relief despite optimal antisecretory therapy, in the absence of GERD, eosinophilic esophagitis or esophageal motor disorders. All these diagnostic criteria must be present in the last three months, with symptom onset at least six months before diagnosis, with a frequency of at least twice a week[34,35]. Structural, histopathological and metabolic changes should be excluded prior to the diagnosis of FH. The absence of GERD should be suggested through normal exams (upper gastrointestinal endoscopy without esophageal lesions and esophageal pH monitoring demonstrating physiological reflux unrelated to symptoms) and absence of symptomatic improvement with the PPI therapeutic test.

FH is the most common cause of Refractory DRGE and corresponds to up to 58% of patients refractory to twice-daily PPI. Of patients with heartburn and without esophagitis, 20% to 60% belong to the FH group and 40% to 80% to the NERD group.

FH predominates in women, and the presence of other functional gastrointestinal disorders is frequent, such as functional dyspepsia and irritable bowel syndrome. The pathophysiological mechanism of FH is not yet established, however, the main factor suggested is the phenomenon of visceral hypersensitivity. Studies have shown increased sensitivity of the esophagus to mechanical and electrical stimuli.

The treatment consists of behavioral and pharmacological therapy. Tricyclic antidepressants (amitriptyline, clomipramine,

nortriptyline), trazodone and selective serotonin reuptake inhibitors (fluoxetine, paroxetine) can be used in smaller doses and act as modulators of visceral sensitivity. Histamine H2-receptor antagonist (H2-RA), commonly used as antisecretor drugs, may play some role in the treatment of FH because of its likely modulation effect on visceral sensitivity. GABA-B receptor agonists (baclofen and lesogaberan), which decrease the transient relaxation of the lower esophageal sphincter, are being investigated. Psychotherapy, used in other functional disorders, is a possible alternative method, although there are no controlled studies demonstrating its efficacy in FH.

Eosinophilic esophagitis

The Eosinophilic Esophagitis (EoE) is a chronic inflammatory disease, defined as a primary clinical-histological alteration of the esophagus. It presents association of the following three characteristics: esophageal and/or upper gastrointestinal symptoms; biopsy of the esophageal mucosa containing 15 or more eosinophils/field; and exclusion of GERD, suggested by normal esophageal pH monitoring or failure to respond to high doses of PPI[36].

EoE has a low prevalence of 0.02% in the general population and 1% in patients with Refractory GERD[37]. In adults, it usually occurs in young males and the most common symptoms are intermittent dysphagia, food impaction and heartburn. Allergic conditions (rhinitis, rhinosinusitis, asthma, dermatitis) and hypersensitivity to environmental, food or drug allergens may be associated.

Upper endoscopy may show normal esophagus or a large spectrum of abnormalities: granular mucosa, feline esophagus or esophageal trachealization, white exudates which represent eosinophilic microabscesses, longitudinal furrows, and even extensive stenoses. Endoscopic biopsies should be performed, even in cases of normal esophagus, in the mid and distal segments. In order to rule out eosinophilic gastroenteritis, gastric and duodenal biopsies are also recommended.

Dietary orientation for EoE in adults is controversial. The treatment consists of avoiding inhalation of aeroallergens, and pharmacological therapy. The PPI is recommended prior to initiating specific medications for EoE in order to differentiate the diagnosis between GERD and EoE[38]. Topical corticosteroid is the first-line drug: fluticasone 880 at 1760 μg/day, orally, divided into two to four daily doses, for six to eight weeks. Other options are viscous solution of budesonide, oral systemic corticosteroid (prednisone or methylprednisolone) and montelukast.

Lymphocytic esophagitis

Lymphocytic esophagitis (LyE) is a new clinicopathologic condition, histologically defined as peripapillary intraepithelial lymphocytosis with spongiosis (intercellular edema) of the esophagus, with no or few granulocytes (neutrophils and eosinophils) [39-41]. This entity is rare, but the prevalence is increasing, and the natural history is still undetermined, although it seems to have a benign chronic course.

The reported symptoms of LyE are heartburn, chest pain, nausea and abdominal pain, but dysphagia is the most frequent symptom. Esophageal perforation was reported in two cases in the literature, thought to be secondary to this entity. Risk factors for LyE are old age, female gender and smoking history. LyE has potential clinical associations with GERD, pediatric inflammatory bowel disease and esophageal motility disorders.

Upper endoscopy may demonstrate normal aspect of the esophagus or esophageal changes such as nodularities, linear furrows, whitish exudates, webs, rings and stenosis. These features are similar to those seen in eosinophilic esophagitis. Endoscopic biopsies, mainly obtained from the middle esophagus, are needed to make the diagnosis. Histologically, the most commonly used cut-off level of the increased number of intraepithelial lymphocytes (IEL) is ≥20 IEL/high power field (HPF), but this is still controversial, since it varies from ≥10 IEL/HPF to ≥50 IEL/HPF in the literature[39-41].

Empirical therapies use PPI and topical corticosteroids. Esophageal endoscopic dilation can be used to treat symptoms, mainly dysphagia, due to decreased esophageal diameter in webs, rings or stenoses.

Drug-induced esophagitis

Drug-induced esophagitis (DIE) is the esophageal mucosal injury caused directly by the tablet taken orally and impacts the esophagus. The incidence of DIE is estimated to be 3.9 per 100,000 population per year. The main drugs involved are antibiotics (clindamycin, doxycycline, tetracycline), ascorbic acid, bisphosphonates (alendronate), ferrous sulfate, nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, naproxen), potassium chloride, quinidine and theophylline[42,43].

The pathophysiology involved is that the swallowed drug adheres to the inner wall of the esophagus and causes direct damage. For example, the alendronate is highly hygroscopic (absorbs water), clindamycin, doxycycline and tetracycline have low pH, and potassium chloride is hyperosmotic. These drug features provide local irritation and may cause esophageal damage[43].

Patients often present with odynophagia, retrosternal pain, chest pain, dysphagia, heartburn, vomiting and hematemesis[43]. Risk factors for DIE are older age, female gender, large tablets, decreased saliva production, altered esophageal motility and swallowing the tablet with little or no water, while lying down or right before sleep.

The endoscopic study of the esophagus can demonstrate erythema in 83% of cases, erosions in 58%, ulcers in 26% (hemorrhagic ulcers in 18% and "kissing type" ulcers in 8%) and stenoses in 8%. These lesions are mainly found in the middle third of the esophagus, which is the most common site of impaction of tablets, in 75.6% of cases, due to extrinsic compression of the esophagus by the aortic arch or the left atrium[43,44].

Most patients have a benign course within a few days, responding well to the suspension of the harmful medication and administer PPI to prevent any GER from worsening the lesions[42,43]. Sucralfate may be useful for protection of the esophageal mucosa. Provide orientations to the patient to prevent further tablet impaction, such as taking the tablet in the orthostatic position, followed by a glass of water and not lying down for at least one hour after taking the tablet[11, 42].

Other causes

Other causes to be investigated are esophageal or gastric cancer, esophageal motor disorders (achalasia, diffuse spasm), infectious esophagitis due to bacteria, viruses or fungi (Candida albicans, cytomegalovirus, herpes simplex and others), caustic esophagitis, actinic esophagitis, esophageal stenosis, gastroparesis, esophagitis due to dermatological diseases (acquired bullosa epidermolysis, pemphigus vulgaris, cicatricial pemphigoid, and lichen planus), bile reflux, and Zollinger-Elisson syndrome. The treatment is specific to each of these causes.

CONCLUSION

Symptoms and other possible manifestations of GERD are heartburn, regurgitation, dysphagia, non-cardiac chest pain, chronic cough, chronic laryngitis, asthma and dental erosions. Refractory GERD was defined, by the majority of researchers, as the condition that presents a missing or partial response, after twice-daily PPI treatment. We describe a review of the current literature of the causes and treatment of PPI unresponsive symptoms. Initially, the management of PPI refractoriness consists in correcting low adherence to PPI therapy, adjusting the PPI dosage, and reinforcing the recommendations on lifestyle modification.

In the persistence of the symptoms, other causes of Refractory GERD should be investigated by clinical parameters, upper digestive endoscopy, esophageal manometry and ambulatory reflux monitoring (esophageal pH monitoring or esophageal impedance-pH monitoring).

Several causes of refractoriness to PPI therapy may be due to the true Refractory GERD or even other non-reflux diseases, which can generate symptoms similar to GERD. The diagnosis and treatment is specific to each cause.

Author contribution

The author contributed to this paper with conception and design of the study, bibliographic review, data analysis, manuscript elaboration, revision and final approval of the manuscript.

Azzam RS. Sintomas persistentes ao tratamento com inibidor da bomba de prótons são devidos à doença do refluxo gastroesofágico refratária ou decorrentes de outras afecções? Arq Gastroenterol. 2018;55(Suppl 1):85-91.

RESUMO – **Contexto** – A doença do refluxo gastroesofágico (DRGE) é a condição clínica que se desenvolve quando o refluxo do conteúdo gástrico provoca sintomas incômodos e/ou complicações. O relaxamento transitório do esfíncter inferior do esôfago é o principal mecanismo fisiopatológico da DRGE. Os sintomas e complicações podem estar relacionados ao refluxo do conteúdo gástrico para o esôfago, cavidade oral, laringe e/ou pulmão. Os sintomas e outras possíveis manifestações da DRGE são pirose, regurgitação, disfagia, dor torácica não-cardíaca, tosse crônica, laringite crônica, asma e erosões dentárias. O inibidor da bomba de prótons (IBP) é o medicamento de primeira escolha e o mais comumente utilizado para o tratamento da DRGE. A definição mais difundida de DRGE Refratária é a condição clínica que apresenta sintomas com resposta parcial ou ausente ao tratamento com IBP duas vezes ao dia. A persistência dos sintomas ocorre em 25% a 42% dos pacientes que utilizam IBP uma vez ao dia e em 10% a 20% dos que utilizam IBP duas vezes ao dia. **Objetivo** – O objetivo é apresentar uma revisão da literatura atual, salientando as causas, aspectos diagnósticos e abordagem terapêutica dos casos com sintomas suspeitos de refluxo e não responsivos ao IBP. **Conclusão** – Inicialmente, o manejo da refratariedade ao IBP consiste em corrigir a baixa aderência à terapia com IBP, ajustar a dosagem do IBP e reforçar as recomendações sobre modificação do estilo de vida, evitando alimentos e atividades que desencadeiem os sintomas. O IBP diminui o número de episódios de refluxo ácido, no entanto o número de refluxos "não-ácidos" aumenta e o paciente continua apresentando refluxo apesar do IBP. Desta forma, é possível reduzir consideravelmente a ocorrência de sintomas, especialmente aqueles dependentes da acidez do material refluído. A resposta à terapia com IBP pode ser avaliada através de parâmetros clínicos, endoscópicos e de monitorização do refluxo. Na persistência dos sintomas, outras causas de DRGE Refratária devem ser suspeitadas. Em seguida, deve ser iniciada a investigação diagnóstica, que é apoiada por parâmetros clínicos e exames complementares, como endoscopia digestiva alta, manometria esofágica e monitorização ambulatorial do refluxo (pHmetria esofágica ou impedancio-pHmetria esofágica). As causas de refratariedade à terapia com IBP podem ser devidas à DRGE Refratária verdadeira ou mesmo a outras doenças não relacionadas ao refluxo, que podem gerar sintomas semelhantes à DRGE. Existem várias causas de refratariedade ao IBP, como uso inadequado da droga (falta de aderência do paciente à terapia com IBP, dosagem inadequada de IBP), refluxo ácido residual devido à supressão ácida inadequada, escape ácido noturno, refluxo "não-ácido", metabolismo rápido do IBP, esvaziamento gástrico lento e diagnóstico equivocado de DRGE. Este representa uma causa frequente de insucesso do tratamento clínico e neste caso, o problema não é o tratamento, mas sim o diagnóstico. As causas de diagnóstico equivocado da DRGE são pirose funcional, acalásia, megaesôfago, esofagite eosinofílica, outros tipos de esofagite e outras causas. O diagnóstico e o tratamento são específicos para cada uma dessas causas de refratariedade ao tratamento clínico com IBP.

DESCRITORES – Refluxo gastroesofágico. Inibidor da bomba de prótons. Doença do refluxo gastroesofágico refratária. Sintomas refratários.

REFERENCES

1. Vakil van N, Zanten S, Kahrilas P, Dent J, Jones R, Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900-20.
2. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013;108:308-28.
3. Dent, J, El-Serag, HB, Wallander, MA, et al. Epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut. 2005;54:710-17.
4. Stanghellini, V. Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in the general population: Results from the domestic/international gastroenterology surveillance study (DIGEST). Scand J Gastroenterol Suppl. 1999;231:29-37.
5. Nasi A. Doença do refluxo gastroesofágico refratária. In: Quilici FA, Galvão-Alves J, Chebli JMF, Mattos AA, Abrahão Jr LJ, editors. Desafios terapêuticos na prática do gastroenterologista. São Paulo: Manole; 2017. p.1-6.
6. Chiba N, De Gara CJ, Wilkinson JM, Hunt RH. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology. 1997;112:1798-810.
7. Scarpignato C, Pelosini I, Di Mario F. Acid suppression therapy: where do we go from here? Dig Dis. 2006;24:11-46.
8. Nasi A, Moraes- Filho JPP, Cecconello I. Doença do refluxo gastroesofágico: revisão ampliada. Arq Gastroenterol. 2006;43:334-41.
9. Dellon ES, Shaheen NJ. Persistent reflux symptoms in the proton pump inhibitor era: the changing face of gastroesophageal reflux disease. Gastroenterology. 2010;139:7-13.
10. Hershcovici T, Fass R. An algorithm for diagnosis and treatment of refractory GERD. Best Pract Res ClinGastroenterol. 2010;24:923-36.
11. Richter J. How to manage refractory GERD. Nat Clin Pract Gastroenterol Hepatol. 2007;4:658-64.

12. Fass R, Gasiorowska A. Refractory GERD: what is it? Curr Gastroenterol Rep. 2008;10:252-7.
13. Becker V, Bajbouj M, Waller K e cols. Clinical trial: persistent gastro-oesophageal reflux symptoms despite standard therapy with proton pump inhibitors – a follow-up study of intraluminal-impedance guided therapy. Aliment Pharmacol Ther. 2007;26:1355-60.
14. Hillman L, Yadlapati R, Thuluvath AJ, Berendsen MA, Pandolfino JE. A review of medical therapy for proton pump inhibitor nonresponsive gastroesophageal reflux disease. Dis Esophagus. 2017;30:1-15.
15. Ahlawat SK, Mohi-Ud-Din R, Williams DC, Maher KA, Benjamin SB. A prospective study of gastric acid analysis and esophageal acid exposure in patients with gastroesophageal reflux refractory to medical therapy. Dig Dis Sci. 2005;50:2019-24.
16. Weijenborg PW, Cremonini F, Smout AJPM; Bredenoord AJ. PPI therapy is equally effective in well-defined non-erosive reflux disease and in reflux esophagitis: a meta-analysis. Neurolgastroenterol Motil. 2012;24:747-50.
17. Becher A, El-Serag H. Systematic review: the association between symptomatic response to proton pump inhibitors and health-related quality of life in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2011;34:618-27.
18. Dal-Paz K, Moraes-Filho JP, Navarro-Rodriguez T, Eisig JN, Barbuti R, Quigley EM. Low levels of adherence with proton pump inhibitor therapy contribute to therapeutic failure in gastroesophageal reflux disease. Dis Esophagus. 2012;25:107-13.
19. Barrison AF, Jarboe LA, Weinberg BM, Nimmagadda K, Sullivan LM, Wolfe MM. Patterns of proton pump inhibitor use in clinical practice. Am J Med. 2001;111:469-73.
20. Freire CCF, Dal-Paz K, Azzam RS et al. Análise da prescrição ambulatorial de omeprazol no Hospital das Clínicas da USP. GED Gastroenterol Endosc Dig. 2012;31(Supl.1):342-3.
21. Martinez SD, Malagon IB, Garewal HS, Cui H, Fass R. Non-erosive reflux disease (NERD) - acid reflux and symptom patterns. Aliment Pharmacol Ther. 2003;17:537-45.
22. Kuo B, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. Am J Gastroenterol. 1996;91:1532-8.
23. Bautista JM, Wong WM, Pulliam G, Esquivel RF, Fass R. The value of ambulatory 24 hr esophageal pH monitoring in clinical practice in patients who were referred with persistent gastroesophageal reflux disease (GERD)-related symptoms while on standard dose anti-reflux medications. Dig Dis Sci. 2005;50:1909-15.
24. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol. 2005;100:283-9. Comment in: Am J Gastroenterol 2005;100:1893-4; author reply 1894.
25. Karamanolis G, Vanuytsel T, Sifrim D, Bisschops R, Arts J, Caenepeel P, et al. Yield of 24-hour esophageal pH and bilitec monitoring in patients with persisting symptoms on PPI therapy. Dig Dis Sci. 2008;53:2387-93.
26. Hemmink GJ, Bredenoord AJ, Weusten BL, Monkelbaan JF, Timmer R, Smout AJ. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? Am J Gastroenterol. 2008;103:2446-53.
27. Sifrim D, Holloway R, Silny J et al. Acid, nonacid and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology. 2001;120:1588-98.
28. Tutuian R, Castell DO. Use of multichannel intraluminal impedance to document proximal esophageal and pharyngeal nonacid reflux episodes. Am J Med. 2003;115:119S-123S.
29. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther. 2003;17:243-51.
30. Koek GH, Sifrim D, Lerut T, Janssens J, Tack J. Effect of the GABA(B) agonist baclofen in patients with symptoms and duodeno-gastrooesophageal reflux refractory to proton pump inhibitors. Gut. 2003;52:1397-402.
31. Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. Pharmacogenomics. 2011;12:873-88.
32. Ishizaki T, Horai Y. Review article: cytochrome P450 and the metabolism of proton pump inhibitors - emphasis on rabeprazole. Aliment Pharmacol Ther. 1999;13(Suppl 3):27-36.
33. Troncon LEA. Motilidade gástrica: fisiopatologia e métodos de estudo. REPM. 2008;2:14-25.
34. Galmiche JP, Clouse RE, Bálint A, Cook IJ, Kahrilas PJ, Paterson WG, Smout AJPM. Functional esophageal disorders. Gastroenterology. 2006;130:1459-65.
35. Aziz Q, Fass R, Gyawali CP, Miwa H, Pandolfino JE, Zerbib F. Functional esophageal disorders. Gastroenterology. 2016;150:1368-79.
36. Furuta GT, Liacouras CA, Collins MH et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. Gastroenterology. 2007;133:1342-63.
37. Sá CC, Kishi HS, Silva-Werneck AL, et al. Eosinophilic esophagitis in patients with typical gastroesophageal reflux disease symptoms refractory to proton pump inhibitor. Clinics (Sao Paulo) 2011;66:557-61.
38. Azzam RS, Vecchia VD, Castro AP, Navarro-Rodriguez T. Esofagite eosinofílica e DRGE. In: Galvão-Alves J, editor. Edições monotemáticas FBG - doença do refluxo gastroesofágico. São Paulo: Federação Brasileira de Gastroenterologia; 2011. p.57-85.
39. Jideh B, Keegan A, Weltman M. Lymphocytic esophagitis: report of three cases and review of the literature. World J Clin Cases. 2016;4:413-8.
40. Rouphael C, Gordon IO, Thota PN. Lymphocytic esophagitis: still an enigma a decade later. World J Gastroenterol, 2017;23:949-56.
41. Rubio CA, Sjödahl K, Lagergren J. Lymphocytic esophagitis: a histologic subset of chronic esophagitis. Am J Clin Pathol. 2006;125:432-7.
42. Mason SJ, O'Meara TF. Drug-induced esophagitis. J Clin Gastroenterol. 1981;3:115-20.
43. Zografos GN, Georgiadou D, Thomas D, Kaltsas G, Digalakis M. Drug-induced esophagitis. Dis Esophagus. 2009;22:633-7.
44. Abid S, Mumtaz K, Jafri W, Hamid S, Abbas Z, Shah HA, Khan AH. Pill induced esophageal injury: endoscopic features and clinical outcomes. Endoscopy. 2005;37:740-4.

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