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Normal values of esophageal 24-hour impedance-pH ambulatory in an Argentine cohort of healthy volunteers

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ABSTRACT – Background – There are no data of reference values on 24-hour multichannel intraluminal impedance and pH (pH-MII) monitoring in Argentinian populations. **Objective** – Our aim was to obtain the normal values of pH-MII variables among healthy asymptomatic volunteers in a metropolitan Health Care Center of Argentina, and to compare them with data already published from other regions around the world. **Methods –** A cross-sectional study was undertaken in a tertiary referral center in Buenos Aires. We enrolled healthy subjects and asked them to undergo esophageal pH-MII 24hours monitoring. pH-MII variables were recorded and described. **Results –** Median reflux events was 20.5 (25–75%, 95%) interquartile range: (14–46, 50) and proximal reflux episodes was 2.5 (0–10, 11). Sixty percent were acid reflux episodes: 12 (5–29, 38), representing a relatively low value when compared to those reported in European, American and Chinese populations. **Conclusion –** Our study shows the first reference of normal values of gastroesophageal reflux in an Argentinian population. We found a total number of reflux events and a total number of proximal reflux events lower than what was reported until this date by other authors.

Keywords – Normal values; esophagus; 24-hour impedance-pH ambulatory.

INTRODUCTION

Montreal consensus establishes that gastroesophageal reflux disease (GERD) is present when gastric content reflux produces bothersome symptoms and/or complications in the esophagus or respiratory tract[1].

GERD, which is a prevalent condition, may not only lead to an impairment in the quality of life, but it can also predispose to the development of Barrett's esophagus, a preneoplasic entity that can be present in up to 15% of GERD patients[2,3]. Barrett's esophagus with high-grade dysplasia has been related to an incidence rate of esophageal adenocarcinoma of 7%, whereas its association with low-grade dysplasia has shown an incidence rate of 0.7%[4].

Twenty-four-hour impedance- pH (MII-pH) testing is considered to be the best diagnostic tool for GERD, it is considered to be the gold standard when considering those GERD patients without erosive disease on upper endoscopy or among those patients with refractory GERD. This diagnostic tool can measure the number of reflux episodes as well as the chemical characteristics of reflux content, whether it is proximal or distal reflux and its association with symptoms.

Olmos et al.[5] published the only Argentinian epidemiological study assessing the prevalence of GERD based on symptoms and endoscopic findings. Accordingly, studies from the United States and Europe have shown that GERD prevalence can vary from 10 to 20% among adults[6,7].

To our knowledge, there is a lack of studies assessing the values esophageal impedance-pH among asymptomatic subjects from South America. This type of information becomes relevant when defining which values should be taken as abnormal – historically, in our region the normal values from European studies have been taken as a formal guide when analyzing MII-pH[8,9]. It could be hypothesized that the normal values of the aforementioned studies may vary from region to region, a phenomenon related to dietary factors among others. However, recently published studies showed similar MII values among asymptomatic Chinese[10] and South-African[11] subjects when compared to the ones from Europe or North America.

Our aim was to obtain the value of MII variables among healthy asymptomatic volunteers, and to compare them with data already published from other parts of the world.

METHODS

Design and study population

A cross-sectional study was undertaken between January 2014 and February 2015 at the Gastroenterology Department of the "Hospital de Alta Complejidad en Red – El Cruce" located at the metropolitan area of Florencio Varela, Buenos Aires, Argentina. Healthy volunteers were asked to participate. After signing informed consent, standard extensive questionnaire was administered in order to rule out GERD symptoms[12]. Subjects would be excluded if they exhibited at least one of the following features:

- Symptoms of typical (pyrosis, regurgitation) or atypical (chronic cough, chest pain, asthma aerofagia) GERD.
- History of previous gastrointestinal surgeries – excluding appendectomy.

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- Use of proton pump inhibitors or prokinetics.
- Smokers (more than 40 cigarettes per day).
- History of neurologic diseases, hypothyroidism, diabetes mellitus, Chagas disease, inflammatory bowel disease.
- Alcohol consumption (more than 40 gr per day).

The study was conducted following Declaration of Helsinki (2013) recommendations; it was reviewed and approved by our local Ethics Committee. Study participation was always voluntary.

Study procedures

Healthy volunteers who fulfilled inclusion criteria were asked to assist to our institution with an 8-hour fasting before pH-metry with impedance test. There were advised to follow their regular diet during the lenght of the study.

A high-resolution esophageal manometry was initially performed in each subject to rule out esophageal motor disorders and to accurately locate lower esophageal sphincter. A local anaesthetic was used (lidocaine), and pH-metry+impedance catheter was placed transnasally with the distal sensor located 5 cm above the proximal border of the lower esophageal sphincter.

During the length of the study, subjects would have to register in a diary times of food ingestion, as well as body position changes. They were asked to avoid chewing gum and predominantely-acid food or beverages. After 24 hours, subjects would return and the catheters were removed. Diaries were delivered by the subjects and their data were reviewed by the investigators.

Equipment

- High-resolution manometer – Sandhill Scientific, Insight G3, Denver, CO, USA.
- Twenty-four-hour impedance-pH monitor – Sandhill Scientific ZAI-S61C01E.

Catheters with impedance channels at 3; 5; 7; 9; 15 and 17 cm from distal tip. The system includes a portable device and catheters with an antimonium pH electrode located 5 cm above their distal tip and 8 pairs of electrodes at 2; 4; 6; 8; 10; 14; 16; 18 cm above lower esophageal sphincter. Impedance amplificators release a voltage equivalent to 1–2 kHz, and their flux depend on changes of intraluminal impedance – pH sensors were calibrated using four and seven buffers and reference sensor was placed on the anterior chest wall of the patient. Tests results were analyzed by two esophageal motility fellows with advanced training and an expert in esophageal motility. In case of disagreement, the expert's criteria prevailed. Sandhill Scientific software BioVIEW, version 5.7.00 was used and the following variables were retrieved and analyzed per subject:

- Percentage of total time with pH <4 (acid exposure time - AET).
- Number of reflux episodes: total, distal and proximal.
- Acid, weakly acid reflux episodes, mixed and liquid.
- Daytime and nocturnal reflux episodes.
- Mean time of bolus transit and mean time of acid clearance.

Subjects who showed one of the following were excluded from the study:

- Pathologic values (AET>7%).
- Catheter migration.
- Technical artifacts during impedance-pH recording.

Definitions

- Distal reflux: a retrograde fall of at least 50% from basal impedance value in the last two channels. Chemical characteristics of reflux were defined according to expert consensus[13] criteria from Porto, 2002.
  - Acid reflux: pH decreases below four (which is equivalent to >12 mEq HCl/L) or occurring when the esophageal pH is already <4.
  - Superimposed acid reflux: reflux episode occurring while pH is still below four before acid clearance occurs.
  - Weakly acid reflux: a reflux episode with the esophageal pH of 4–6.5.
  - Non-acid reflux: pH increases over seven or remains above seven during reflux episode (0 mEq/L of HCl/L).
  - Bolus clearance: volume clearance of a single reflux episode.
  - Chemical clearance: acid clearance of a single reflux episode.

Statistical analysis

Stata software was used for this purpose (v11.1, Statacorp, College Station, TX, USA). Categorical variables were described as percentages and numerical variables as median with their 25–75% interquartile range; additionally, 95% quartile was described. Mean with its standard deviation was eventually used according to the fashion used in previously published studies assessing normal values. For the comparison of categorical variables, Fisher test was used. For the comparison of numerical variables, Student *t* test or Mann Whitney test were accordingly used. A *P* value of less than 0.05 was considered as statistically significant.

RESULTS

Thirty healthy subjects were consecutively enrolled [12 men, mean age 33 (range 19–59) years]. After impedance-pH test, six were excluded: two because of abnormal findings (AET>50%), one due to catheter migration and two dues to technical artifacts. (FIGURE 1).

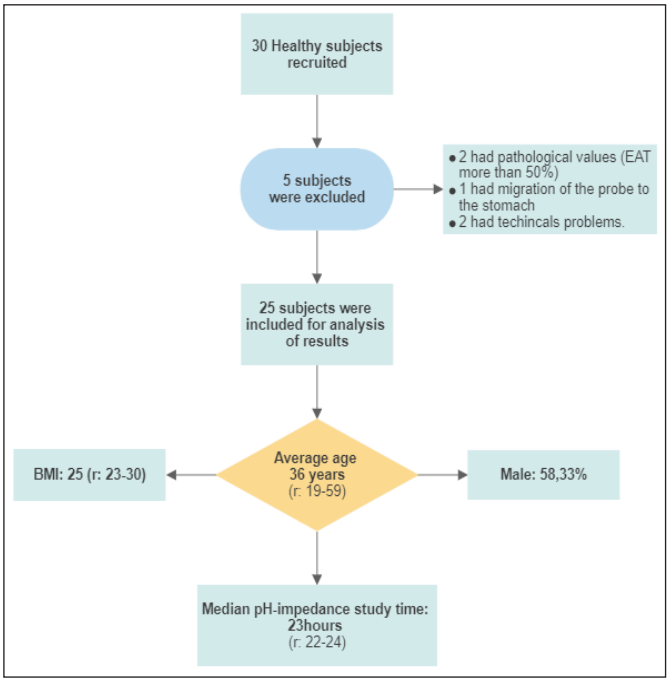

FIGURE 1. Healthy subjects enrolment flowchart.

Overall, 84% of included subjects reported consumption of "mate" (Illex paraguarensis) on a regular basis. The periods of mate were manually excluding, since they had pH drop. Tolerance to pH-metry was acceptable. Consequently, 25 subjects were finally included for analysis. Demographic features are shown in TABLE 1. Median time of study was 23 hours (25–75% IQR, 22–24 hours).

TABLE 1. Demographic data of included subjects.

Age[a] (years)	36 (19–59)
Gender (% M)	58.33
Occupation (% employees)	66.66
Body mass index[b]	25 (23–30)

[a]Results described as median and range. [b]Results described as median and 25–75% interquartile range.

Overall, 632 reflux episodes were registered among included subjects, with a mean of 22.15 reflux episodes per subject.

Supine-position total reflux episodes (95% quartile) was five of these, four were acid reflux episodes.

Median number of reflux events according to impedance testing was 20.5 (median 25–75%, 95%) interquartile range: (14–46, 50). Sixty percent were acid reflux episodes: 12 (5–29, 38); 37% were non-acid: 5, 5 (1–17, 30) and 3% were weakly-acid reflux episodes (TABLE 2).

TABLE 2. Type of reflux episodes in 24 hour-time among included subjects.

	Total reflux episodes	Acid reflux episodes	Weakly-acid reflux episodes
Total median (25th,75th) 95th	20.5 (14–46) – 50	12 (5–29) –38	5.5 (1–17) – 30
Erect	19 (14–35) – 50	11.5 (6–24) – 38	5 (2.5–12) – 25
Supine	2 (0–3) – 5	0 (0–1) – 4	0.5 (0–2) – 4

Results described as median and 25–75% interquartile range-95%.

Median proximal reflux episodes were 2.5 (0–10, 11) which represented 16% of the total number of reflux episodes. Esophageal volume clearance time was shorter than chemical esophageal clearance time: 18.5 versus 91 seconds, respectively (TABLE 3).

TABLE 3. Clearance time according to body position variation. Reflux proximal extension.

	Bolus clearance time	Reflux proximal extension
Total (median 25th, 75th, 95th)	18.5 (12–29) – 58	3 (1–5.5) –10
Erect (median 25th, 75th, 95th)	22 (13–35.5) – 99	0 (0–3) – 14
Supine (median 25th, 75th, 95th)	10.5 (0–42) – 107	0 (0–1) – 5

According to body position, reflux events on supine position were 53; 37% were proximal and 49% were acid. Acid clearance time was shorter in erect position (2758 vs 1735 seconds). TABLE 4 describes the acid reflux variables according to impedance.

TABLE 4. Acid reflux variables according to impedance.

	% of acid exposure time	Acid clearance time	Number of acids reflux events
Total (median 25th, 75th, 95th)	1 (0.2–3.4) – 5.5	91 (47–184) – 382	12 (5–29) – 38
Erect (median 25th, 75th, 95th)	1.7 (0.2–5.3) – 10.3	85 (47–169) – 382	11.5 (6–24) – 38
Supine (median 25th, 75th, 95th)	0 (0–0.9) – 2.3	0 (0–161) – 285	0 (0–1) – 4

Women showed a slightly increased number of reflux episodes (median 3.25 vs 2.44, P=0.08); however, men showed a greater but non-significant proportion of acid reflux episodes (1 vs 0.68, P=0.1).

Subjects with less than 47 years of age showed a greater number of total reflux episodes (mean 29.66 vs 18.57, P=0.04).

TABLE 5 describes the results of pH and impedance variables found among included subjects.

TABLE 5. pH and impedance variables among included subjects.

% of time with pH<4 (AET)	1 (0.2–3.4) – 5.5
% of time with pH<4 erect	1.7 (0.2–5.3) – 10.3
% of time with pH<4 supine	0 (0–0.9) – 2.3
DeMeester score	3.45 (1.2–10.7) – 14.7
Total number of reflux episodes	20.5 (14–46) – 50
Total number of acid reflux episodes	12 (5–29) – 38
Total number of non-acid reflux episodes	5.5 (1–17) – 30
Total number of proximal reflux episodes	2.5 (0–10) –11
Total number of proximal acid reflux episodes	1.5 (0–4) – 11
Total number of superimposed acid reflux episodes	0 (0–0) – 2
Bolus clearance time	18.5 (9–46) – 57
Bolus clearance time, erect	19.5 (9–45) – 63
Bolus clearance time, supine	9 (0–51) – 78
Mean acid clearance time total	91 (47–184) – 382
Mean acid clearance time, erect	85 (47–169) – 382
Mean acid clearance time, supine	0 (0–161) – 285
Nocturnal reflux, 1st quarter	0 (0–1) – 3
Nocturnal reflux, 2–4th quarter	0 (0–0) – 2

Results described as median, 25–75% interquartile range, 95% quartile. AET: acid exposure time.

TABLE 6 describes the gastroesophageal reflux comparison to similar studies expressed by Ndebia et al. and adapted with Argentina values comparison.

TABLE 6. Gastroesophageal reflux comparison to similar studies (Ndebia et al. Adapted with Argentina values).

	South Africa	Europe	China	USA	Argentina
All reflux	49 (29.65) – 97	44 (25.58) – 75	40 (31.53) – 75	30 (18.45) – 73	20.5 (14–46) – 50
Acid reflux	15 (5.31) – 55	22 (10.35) – 50	22 (7.36) – 54	18 (7.31) – 55	12 (5–29) – 38
Weakly acid reflux	17 (9.28) – 55	11 (5.18) – 33	16 (10.24) – 40	9 (6.15) – 26	5.5 (1–17) – 30
Weakly-alkaline reflux	8 (4.13) – 36	3 (1.7) – 15	0 (0.1) – 4	0 (0.0) – 1	0 (0–1) – 13

Results described as median, 25–75% interquartile range, 95% percentile.

DISCUSSION

Impedance-pH monitoring is considered the most accurate diagnostic tool for the detection of reflux events; noticeably, there are no references on normal values published so far in Argentina. We have documented the values of impedance-pH among healthy subjects without GERD.

So far, normal values were taken from the experiences published in North America and Western Europe, but our populations differ in terms of dietary habits in Argentina, dinner time is usually at a later time and a Mediterranean type of diet is usually followed; this elements could have a significant impact on what is considered as a normal pattern of reflux events.

Noticeably, median reflux events were 20.5, a relatively low value when compared to those reported in European, American and Chinese populations. Our study shows a total number of reflux events and a total number of proximal reflux events that are lower than reported until this date by other authors. We hypothesize that many variables may have influenced these findings: dinner times, genetic susceptibility and issues regarding age, gender, geographical distribution of the participants and the size of the population studied.

Recently, Sifrim et al.[14] published the first consensus of impedance-pH normal values around the world, in which we participated, with 391 tracings analyzed and the median reflux events number anlyzed with Diversatek pH-MII System (Inc.) was 21 (95% interquartile range: 10–34, 55). Comparatively, these mentioned values are closer to our results (20.5 (14–46) –50). Another possible cause of different results could be pH-monitoring and analyzing systems used around the world (e.g. Diversatek Inc. or Laborie Corp.). Concerning the low number of proximal events, it could be due to the fact that asymptomatic healthy volunteers do not usually present high volume reflux events, which is the most likely element to reach the proximal esophagus[15]. Age influence on reflux patterns is still a matter of debate. Some authors have suggested a positive association between age and reflux patterns[16], while others did not observe any influence of it[17]. We found a possible influence of age on the number of total reflux episodes in our cohort, but only 16 patients were younger than 47 years old so we cannot rule out the possibility of the presence of type 2 error in the analysis. On the other hand, another regional differences concluded in this important work[14], was the difference between the baseline level of impedance results. This levels, were elevated in some regions such as Asia, and low in others. Since this parameter is related to the mucosa integrity and that depends on microscopic intraluminal factors, it could be modified by the ultrastructural genetics of the esophageal mucosa, and related to the geographic region.

Regarding AET, the 95% percentile was 5.5%, which is in accordance to the Lyon consensus[18] statement that considers an AET over 6% as definitively abnormal. Our finding enforces the concept that normal AET values should have a cutoff of 6%.

DeMeester score values published 30 years ago may not be applicable nowadays because of the changes experienced not only in terms of life expectancy, but also in terms of qualitative and quantitative changes in dietary habits and modifications in body mass index.

Cutoff values for weakly-acid reflux events was seven, which could explain the relatively low prevalence of such events in our population[13]. Although considered to be infrequent, weakly-acid reflux events may represent actual acid reflux events that are easily neutralized by saliva clearance or esophageal clearance. Our findings showed that proximal reflux events represented 16% of total reflux events, whereas among Chinese subjects they represented a proportion near 26%[19]; 22% among Belgian subjects included in the study by Zerbib et al.[20] or 6% in a South African study[10]. Clinical relevance of proximal reflux is far from clear; its association with extra-esophageal reflux symptoms has been questioned. On the other hand, Cicala et al.[21] showed that both erosive reflux disease as well as non-erosive reflux disease patients had a significantly higher number of proximal reflux events when compared to subjects without GERD.

Included subjects did not follow any restraints in terms of diet during the study. Even though some local dietary habits that could have an impact in reflux events, such as mate consumption or late dinner times, we did not find an apparently increased number of acid reflux events when compared to previously published studies. Lyon consensus proposes that >80 reflux episodes in 24 hours is abnormal, whereas less than 40 is within physiological range. Intermediate values are inconclusive. Nevertheless, it becomes more relevant the association between reflux episodes and the occurrence of symptoms in each subject. The number of reflux events in our study seems to be relatively lower than what has been published so far.

An Argentinean study carried out by Olmos et al.[5] in which we participated, included 397 GERD patients who underwent upper endoscopy; prevalence of esophagitis in this cohort of patients was 35%. The clinical features significantly associated with erosive lesions were nocturnal symptoms [OR 2.55 1.55–4.18)] and a body mass index over 25 kg/m^2 [OR 1.91 (1.03–3.55)]. These findings are in concordance with previously published evidence. However, a lower number of reflux episodes could potentially be associated in the relatively lower prevalence of esophageal adenocarcinoma that is witnessed in Argentina and/or Latin-America as well as the discrepancies observed in terms of it distribution according to age and gender[22,23]. Evidence supporting this hypothesis is needed.

An often-neglected aspect of studies such as ours is the median time of acid clearance the time that takes for pH to increase over four after an acid reflux episode. This is a phenomenon that is related to several mechanisms, like esophageal peristaltic movements as well as pH and volume of reflux content. In our study, median clearance time was 91 seconds, which was four times longer

than bolus clearance time (18.5 seconds). This indicates that reflux content is cleared first and then acid residue becomes cleared which depends on secondary peristalsis as well as saliva buffering. The automatic analysis of these parameters is very weak. It depends on the accurate identification of reflux episodes and the accurate identification of start and end of reflux. In general, the software's are very bad for this and it is very time consuming to do it manually.

Limitations should be mentioned. First of all, our sample may not be representative of the whole Argentinean population. In addition, the size of study population is relatively scarce so it turns out to be a weakness of this study to be taken into account. There are several difficulties to achieve a greater number of population sample such as the lack of interest of healthy subjects to enroll, lack of economics resources to carry out the studies or many technical difficulties to correctly analyze the tracings (e.g., tracings excluded because of wrong catheter placement). Maybe for that reason, there are several recognized publications about "impedance-pH normal values" from different regions around the world with relatively scarse sample size population too[8,9].

To our knowledge, this is the first study to assess MII-pH values among non-GERD patients in Argentina. This type of studies is of utmost importance to define normal values and cutoffs of the different variables that are measured in these types of diagnostic tools, which are essential in the management of certain GERD patients.

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Authors' contribution

Ramos RI: planning and conducting the study, collecting and interpreting data, drafting the manuscript. Cernadas G: interpreting data and drafting the manuscript. Curvale C: interpreting data and drafting the manuscript. Matano R: drafting the manuscript.

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RESUMO – Contexto – Não há dados de valores de referência sobre o monitoramento de impedância intraluminal multicanal 24 horas e monitoramento de pH (pH-MII) em populações argentinas. **Objetivo** – O objetivo foi obter os valores normais das variáveis pH-MII entre voluntários assintomáticos saudáveis em um centro metropolitano de saúde da Argentina, e compará-los com dados já publicados de outras regiões do mundo. **Métodos –** Estudo transversal foi realizado em um centro de referência terciário em Buenos Aires. Foram recrutados indivíduos saudáveis para se submeterem ao monitoramento esofágico pH-MII 24 horas. As variáveis pH-MII foram registradas e descritas. **Resultados –** A média de eventos de refluxo foi de 20,5 (25–75%, 95%) entre os episódios interquartis: (14–46, 50) e os episódios de refluxo proximal foram de 2,5 (0–10, 11). Sessenta por cento foram episódios de refluxo ácido: 12 (5–29, 38), representando um valor relativamente baixo quando comparado com os relatados em populações europeias, americanas e chinesas. **Conclusão –** Nosso estudo mostra a primeira referência de valores normais de refluxo gastroesofágico em uma população argentina. Encontramos um número total de eventos de refluxo e um número total de eventos de refluxo proximal menor do que o relatado até esta data por outros autores.

Palavras-chave – Valores normais; esôfago; impedância-pHmetria de 24 horas.

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