Normal values and regional differences in oesophageal impedance-pH metrics

a consensus analysis of impedance-pH studies from around the world

Sifrim, Daniel; Roman, Sabine; Savarino, Edoardo; Bor, Serhat; Bredenoord, Albert J; Castell, Donald; Cicala, Michele; de Bortoli, Nicola; Frazzoni, Marzio; Gonlachanvit, Sutep; Iwakiri, Katsuhiko; Kawamura, Osamu; Krarup, Anne; Lee, Yeong Yeh; Soon Ngiu, Chai; Ndebia, Eugene; Patcharatraku, Tanisa; Pauwels, Ans; Pérez de la Serna, Julio; Ramos, Rosa; Remes-Troche, Jose Maria; Ribolsi, Mentore; Sammon, Alastair; Simren, Magnus; Tack, Jan; Tutuian, Radu; Valdovinos, Miguel; Xiao, Yinglian; Zerbib, Frank; Gyawali, C Prakash

Published in:
Gut

DOI (link to publication from Publisher):
10.1136/gutjnl-2020-322627

Publication date:
2021

Document Version
Accepted author manuscript, peer reviewed version

June 10, 2020

NORMAL VALUES AND REGIONAL DIFFERENCES IN ESOPHAGEAL IMPEDANCE-pH METRICS: A CONSENSUS ANALYSIS OF IMPEDANCE-pH STUDIES FROM AROUND THE WORLD

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Abstract word count: 260; manuscript word count: 3378 words

Short title: Normative impedance-pH values

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Conflict of interest

Daniel Sifrim receives research grants from Reckitt Benckiser UK, Jinshan Technology China and Alfa Sigma, Italy. C.

Sabine Roman: consulting Medtronic, research support Diversatek Healthcare, Medtronic;

Edoardo Savarino: Lecture Fee: Medtronic, Takeda, Janssen, MSD, Abbvie, Malesci;

Consulting: Medtronic, Takeda, Janssen, MSD, Reckitt Bencikser, Sofar, Unifarco, SILA, Oftagest

C. Prakash Gyawali consults for Medtronic, Diversatek, Ironwood, IsoThrive and Quintiles.

Author contributions:

Acknowledgement: we would like to thank Dr Kornilia Nikaki, Mrs Shirley Sonmez, Dr Etsuro Yazaki, Dr Akinari Sawada and Dr Yoshimasha Hoshikawa for their help in the organization of the multicenter collaboration and initial checking and sorting of the impedance pH studies received from international centers.

Author roles: DS: study concept, data collection, organization of Wingate consensus meetings, consensus analysis, drafting and finalization of manuscript; SR study concept, discussion of diagnostic criteria, consensus analysis, critical review of manuscript; ES: study concept, discussion of diagnostic criteria, consensus analysis, critical review of manuscript; CPG: study concept, discussion of diagnostic criteria, consensus analysis, finalization of manuscript.

Abstract (260 words)

Background: Limitations of existing impedance-pH thresholds include small sample size of normative studies, inclusion of artefactual pH drops and incorrect identification of impedance reflux events. We aimed to obtain a new set of impedance-pH thresholds based on expert consensus analysis of tracings from a large number of healthy subjects.

Methods: Of 541 de-identified studies performed worldwide using two different systems (Diversatek, USA, and Laborie, Netherlands), 150 tracings with esophageal diagnoses, behavioural disorders and study-related artefacts were excluded. The remainder studies were each manually analysed by two reviewers working together either in-person or through video-conference, consisting of editing of meals and pH drops, identification of impedance reflux events and post reflux swallow-induced peristaltic wave (PSPW) using strict pre-established criteria, and measurement of distal mean nocturnal baseline impedance (MNBI).

Results: Consensus analysis was performed in 391 tracings (mean age 32.7 years, range 18-71, 54.2% female). Normative thresholds were significantly different between Diversatek and Laborie (total AET: 2.8 and 5%, reflux episodes: 55 and 78, MNBI at 3 cm: 1400 and 1500 ohms, at 5 cm: 1400 and 1800 ohms respectively). Males had higher acid exposure, more reflux episodes and lower MNBI. Significant regional differences were identified, including higher PSPW scores in Western countries, and higher MNBI in Asia using Diversatek, and higher acid exposure in the Netherlands, higher MNBI in Asia and South Africa, and lower MNBI in Turkey using Laborie.

Conclusion: Normal values for impedance pH monitoring has both regional and system related differences, indicating that clinical interpretation needs to use normal thresholds valid for the system utilized and world region.

Key words: impedance-pH monitoring; acid exposure time; post reflux swallow-induced peristaltic wave; reflux episodes

Introduction

Ambulatory impedance-pH monitoring is well established in the investigation of esophageal symptoms suspicious of gastroesophageal reflux disease (GERD) [1, 2], and may be of particular value where symptoms persist or do not improve with empiric GERD treatment trials or GERD management, or where the diagnosis of GERD is inconclusive[2]. Although normal values are available for commonly used impedance-pH parameters[3-11], their global application has limitations, stemming from use of small healthy volunteer cohorts from one or two countries for normative data. Further, significant technical limitations in analysis exist, such as inclusion of pH drops from meals/artefacts and inconsistent rules for identification of impedance reflux events, leading to large inter-reviewer variability[10, 12-18]. Several measurement systems are utilized for impedance-pH monitoring worldwide. Despite regional differences in prevalence of GERD phenotypes, symptomatic profiles and GERD complications [19], the same impedance-pH threshold values are used to define normality by these measurement systems[2-4, 9]. It remains unclear if measurements obtained using different systems or across world regions are comparable, especially since automated analysis provided by impedance-pH systems suffers from significant overcall of reflux episodes[20-22]

Accurate identification and quantification of acid and non-acid reflux episodes on impedance-pH monitoring is important for precise calculation of esophageal acid exposure time (AET), for reflux-symptom association (RSA) analysis, and for evaluation of clearance mechanisms such as the post-reflux swallow induced peristaltic wave (PSPW). Both reflux episodes and PSPW need to be reliably identified and recorded, for correct calculation of the PSPW index. Baseline impedance from impedance-pH monitoring can provide a measure of esophageal mucosal integrity. Baseline impedance during the nocturnal supine period has been shown to be higher in healthy subjects and patients with functional heartburn and lower in patients with reflux disease[23-25].

We hypothesized that use of strict analysis rules, taking into account system and regional differences, would provide strong and reliable normative data that augments the clinical usefulness of impedance-pH monitoring. We **aimed** to obtain a new set of normal values for impedance-pH monitoring based on consensus analysis of impedance pH tracings obtained using different hardware/software systems from a large worldwide cohort of healthy asymptomatic subjects.

Methods

Subjects

A total of 541 impedance-pH tracings from healthy asymptomatic subjects from Africa, Asia, Europe, North America, and South America were de-identified "on site", encrypted and uploaded into a secure web based storage system (Tresorit, USA) by the International Working Group; these were downloaded into a database at the Wingate Institute, London UK. Exclusion criteria consisted of thoracic or digestive foregut surgery (except appendectomy), alcohol consumption >40 g/d, use of medications that alter intra-gastric acidity or esophageal motility, as well as history of diabetes mellitus, neurologic disorders or other chronic gastrointestinal disease. All tracings were initially checked, and excluded if they had technical artefacts, marked esophageal symptoms or anti-reflux medication intake. During the subsequent analysis process, tracings were excluded if they fulfilled criteria for behavioral disorders (aerophagia, supragastric belching and rumination), low MNBI in all impedance channels suspicious for eosinophilic esophagitis (EoE), and hiatal hernia larger than 2 cm (in those with available HRM). The international contributors confirmed that included subjects had no reflux symptoms based on validated GERD questionnaires; most subjects did not have previous endoscopy or biopsy, and these were not required nor evaluated as part of this study. Since the present study consisted of *post hoc* analysis of previously collected de-identified pH-impedance data with no links to the original study subjects, Institutional Review Board approval was not deemed necessary.

Ambulatory Impedance-pH tracings

After at least 6 hours of fasting, the impedance-pH catheter was placed trans-nasally with one pH electrode positioned 5 cm proximal to the lower esophageal sphincter (LES), and six impedance channels with their mid-point located 3, 5, 7, 9,15, and 17 cm proximal to the

LES. During the recording period, subjects were encouraged to continue with their usual daily activities and meals. Meal times and recumbent periods were recorded. A similar test protocol (with variations in start time and meals) was followed by all international contributors of impedance-pH tracings.

Impedance-pH analysis

All tracings were analyzed by SR, DS, CPG and ES, each with experience in reviewing >300 impedance-pH studies annually. The reviewers first convened at the Wingate Institute in London in July 2018, where interpretation paradigms were discussed at length, and rules for standardized identification of reflux episodes and PSPW were developed (Table 1) taking available literature and the reviewers' experience into consideration. At a second Wingate Institute meeting in July 2019, the consensus analysis process was initiated with each tracing analysed by two reviewers working together, and with rotating combinations of reviewers. Thereafter, the same methodology was used through video-conference to complete consensus analysis of all tracings. Reviewers initially applied automated analysis, followed by manual review of each identified reflux episode and PSPW for accuracy, with 2-reviewer consensus for each retained episode.

The analysis process consisted of editing of pH drops (to exclude artefacts and meal/drink induced pH drops), identification of impedance reflux events and PSPW using strict pre-established criteria (Table 1), and measurement of distal MNBI using a recently reported simplified method[26]. After manual editing, the following parameters were considered for normative data: total, upright and supine AET, number of reflux events (total, acid and non-acid), PSPW index and MNBI at 3 and 5 cm above the LES.

Statistical analysis

Data are expressed as median and percentile values (5th, 25th, 75th, and 95th percentiles). Depending on normality of distribution, we used either paired Student's t-test or Mann-Whitney test for paired comparison. Likewise, we used one way ANOVA with Tukey test or Kruskal-Wallis followed by Dunn's test as appropriate. Upper limit of normal was defined as the 95th percentile of normal values. For PSPW index and MNBI thresholds, we used the 5th and 25th percentile values. $P \leq .05$ was considered statistically significant.

Results

Subjects

After exclusion of 150 tracings (Figure 1), consensus analysis was performed in tracings from 391 healthy asymptomatic subjects studied using two different systems: Diversatek (Boulder, Colorado, US, previously Sandhill Scientific, n=265) and Laborie (Enschede, Netherlands, previously Medical Measurement Systems n=126). The worldwide composition of the included impedance-pH studies was as follows: Argentina (n:16), Belgium (n:16), China (n:64), Italy (n:56), Japan (n:7), Malaysia (n:28), Mexico (n:20), The Netherlands (n:21), South Africa (n:56), Sweden (n:10), Thailand (n:9), Turkey (n:30), United Kingdom (n:44), United States (N:14).

The mean age of included subjects was 32.7 years (range 18-71 years), distributed as follows: 130 subjects between 18 and 24 years, 153 between 25 and 39 years, and 108 between 40 and 71 years. There were 212 females (54.2%) and 179 males. Compared to females, males had significantly higher total acid exposure, higher number of reflux episodes and lower MNBI at 3 cm above the LES (Table 2). There was no significant impact or linear correlation between age and levels of total acid exposure ($r^2 = 0.001$, Figure 2). In contrast, older subjects had lower MNBI in the distal esophagus (Table 2).

Impedance pH studies using different measurement systems

Normal values for Diversatek (n: 265) and Laborie systems (n: 126) are displayed in Table 3 and Figure 3. When all studies performed worldwide with these 2 systems were compared, we found higher total AET, number of reflux episodes and MNBI at 5 cm above LES with Laborie compared to Diversatek. To assess whether such variation could be due to regional differences, we compared data obtained by both systems within the same world regions i.e. Asian countries and Western countries. This analysis confirmed that Laborie

system measures higher esophageal AET and MNBI values in both Western countries and Asia. (Table 3).

Regional differences in Impedance pH parameters

We observed significant regional differences in normative data when comparing normal values between Western countries, Asia, South America, South Africa and Turkey (Figure 4). Using the Diversatek system, we observed significantly higher esophageal AET in South America compared to other western countries and Asia. The PSPW index was significantly higher in Western countries, while the MNBI in the distal esophagus was significantly higher in Asia. Likewise, using the Laborie system, we observed significantly higher AET in the Netherlands, higher distal esophageal MNBI in Asia and South Africa, and particularly low MNBI in Turkey (Figure 4).

Normative values for physiologic gastroesophageal reflux

Esophageal acid exposure

The 95th percentile of total esophageal AET for asymptomatic subjects was 2.8% for Diversatek studies and 5% for Laborie studies (Figure 3A). Although we found significant regional and system related differences (Figure 4A), these data suggest that subjects with AET below these thresholds fall into a physiologic AET range.

Total number of reflux episodes

The 95th percentile of total number of reflux events for asymptomatic subjects was 55 for Diversatek studies and 78 for Laborie studies (Figure 3B). There was very important system and regional variability. However, the data suggest that asymptomatic subjects (studied with Diversatek) with less than 55 reflux episodes/ 24h have physiologic reflux. Likewise, when studied using Laborie, physiologic reflux is identified when <78 reflux episodes/ 24h.

PSPW index

Although the median values for PSPW index was around 50% with both systems in most regions, healthy asymptomatic subjects showed a very large variability in PSPW index with a significant number of subjects with scores below 50% (i.e. between 40-10%). The 5th percentile for PSPW index was 15 using Diversatek and 19 with Laborie (Figure 3B). This data is relevant for the use of PSPW index cut-off value for clinical purposes (conclusive diagnosis of GERD and prediction of outcomes), and suggests that PSPW cannot be used as a single parameter to define GERD but has to be used together with other features.

MNBI in the distal esophagus

Important system and regional differences were identified that need consideration in definition of the MNBI normative threshold, and in evaluation of esophageal mucosal integrity. In Asia and South Africa, the 5th percentile for MNBI was around 1800-2100 ohms. In contrast, in Western countries the 5th percentile was around 1500 ohms, and even lower in Turkey (1200 ohms) (Figure 4C). Interestingly, using the Diversatek system, the median MNBI at 5 cm above the LES was lower than that at 3 cm, but the 5th percentile was not different, therefore the lower cutoff would be the same (Figure 3C). With Laborie system, there were no significant differences between MNBI measured at 3 and 5 cm above the LES.

Discussion

This study was undertaken to overcome drawbacks in existing normal values for impedance-pH monitoring metrics, which were derived from small normative studies from typically one or two countries, along with technical limitations from inclusion of pH drops due to meals/artefacts, and identification of impedance reflux events using inconsistent rules. To overcome known inter-rater variability[15-17], interpretation paradigms were discussed at length before consensus analysis, rules for standardized identification of reflux episodes and PSPW were agreed upon *a priori*, and each included reflux episode was agreed upon by two reviewers during the consensus analysis. This methodology has been successfully used in the past to overcome inter-rater variability[5, 13, 20], and adds to the validity of our work. In addition to a new set of normal values for impedance-pH metrics, we report both regional and system related differences in normative thresholds. We conclude from our findings that clinical impedance-pH interpretation needs to utilize thresholds valid for the specific system and the world region where the test is performed.

As part of the GERD consensus discussions that culminated in the Lyon Consensus[2, 27], an international group of investigators were requested to contribute tracings from healthy asymptomatic controls utilized for their research or clinical studies. As many as 27.7% tracings had to be excluded for various reasons (Figure 1), with all exclusions thoroughly discussed and applied by consensus. While technical problems with hardware, software or the tracing itself were the reason for many of the exclusions (64, 11.8% of the total), confounding diagnoses (evidence for reflux disease, large hiatus hernia, eosinophilic esophagitis, behavioural disorders including aerophagia, supragastric belching and rumination syndrome) accounted for a significant proportion (86, 15.9%), indicating that healthy control cohorts from even established motility centers can include disorders that would not be considered part of health.

These findings highlight the need for careful selection of future asymptomatic controls for normative studies and comparison cohorts.

In contrast to previous impedance-pH normative data (95th percentile threshold of 5.3-6.3% for total AET and 2.1-6.8% for supine AET) [4, 5, 9], we report significantly lower thresholds of normal physiologic reflux (2.8-5% for total AET, and 1.9-4% for supine AET). We attribute this difference to careful editing of meal periods, and elimination of artefactual upright and supine pH drops. Our data for numbers of reflux episodes using Diversatek studies (95th percentile of 55/24 h) corresponds to previous studies by Zerbib et al.[5] and Savarino et al [28] (53-58 episodes/24 h), but is clearly lower than the 73 episodes/24h initially reported by Shay et al.[9] The experience gained from impedance reflux recognition over the years, the more strict criteria applied, and consensus analysis can explain this difference. While higher number of reflux episodes were detected using the Laborie system, there is no previous normative data for comparison using this system. Difference in number of reflux episodes between Diversatek and Laborie are less likely to be due to system differences but possibly due to country or regional effect.

Using the Diversatek system, mean baseline impedance in healthy subjects is reported to range between 2600-3400 ohms[23, 29-32], although these studies do not provide thresholds to distinguish healthy subjects from patients with GERD. A threshold of 2292 ohms has been proposed based on ROC curves to discriminate healthy subjects from symptomatic patients with reflux disease and functional heartburn, and to predict outcomes after treatment[32-34]. We report 5th percentile MNBI values around 1500 ohms at 3 and 5 cm above the LES, significantly lower than prior reports. Therefore, MNBI below 1500 ohms suggests impairment of esophageal mucosal integrity. Using the MMS system, median baseline impedance was reported to be 2827- 2259 ohms with 25th percentile values of 2127-1757 ohms [35, 36]. In our study, MNBI measured by MMS was higher, particularly at 5 cm above the LES, suggesting

that the difference might be related to methodology utilized in calculation. For our study, a recently published simplified method for MNBI analysis was used[26], that showed good correlation with the previously proposed methods [25, 30, 31].

The PSPW is a physiologic reflex that brings saliva to the distal esophagus for neutralization of the acidified mucosa[25, 34] with higher efficiency in healthy subjects than in GERD patients[37]. The PSPW index is defined as the proportion of the total number of reflux episodes associated with a PSPW, reported to be 76-80% ±13[30-32] in healthy individuals. Using ROC curves, the same authors reported that a threshold value of 61% can distinguish healthy subjects from patients with GERD, and can predict responsiveness to PPI treatment[32, 34]. In contrast, after development of consensus definitions and thorough consensus agreement on each PSPW event detected, we report high variability of PSPW index in healthy subjects; the median PSPW index was 50%, and a significant number of subjects had PSPW index below 61%. Studies assessing PSPW reported mean reflux episodes of 18-23 ± 12 /24h [30-32], much lower than published normative values[4, 5], and also lower than our findings (median 21-30 episodes, 95th percentile 55-78 episodes depending on the system). The threshold PSPW index (5th percentile) in our study was 15 for Diversatek and 19 for Laborie, with the difference from previous studies likely related to more precise identification of total reflux episodes, and perhaps to regional differences in sensitivity for PSPW triggering.

Similar to existing data, [4, 38] males had higher total AET and number of reflux episodes. Additionally, MNBI was also lower in males, suggesting either chronically higher acid exposure[35], gender-related BMI differences or genetically determined weaker esophageal mucosa. These differences were significant but small and did not affect the high and low threshold values. In contrast to previous studies [4, 38] we did not find age related differences in acid exposure and number of reflux events. Interestingly, we observed a slight but significantly

lower MNBI in subjects older than 40 years, which also might reflect chronic acid exposure. Age related differences in MNBI have only been described thus far in pediatric patients[39, 40].

We observed significant regional differences in normative data obtained with each system, which have not been previously described. These differences in AET and number/acidity of reflux episodes could be partly related to differences in diet and meal composition, as suggested by published data from Italy, China and South Africa.[6-8] Higher PSPW index in Western countries relative to Asia and South Africa could be from true differences in total number of reflux episodes or to variation in sensitivity for trigger PSPW, which in turn may be affected by the composition of the refluxate, esophageal mucosal integrity and salivary gland function. Measurements using Laborie showed higher AET, number of reflux episodes and MNBI compared to Diversatek measurements, which persisted when measurements performed by the two different systems were compared in similar world regions. While differences in AET and MNBI could relate to differences in pH electrodes, impedance electrodes, amplifiers or software algorithms utilized, differences in number of reflux episodes are likely related to regional differences, because this parameter was manually evaluated by the reviewers. All these factors may be subject to regional differences, and it is important to recognize and consider these differences when establishing normative data and threshold values in each motility laboratory.

Other regional differences in reflux parameters cannot be explained easily. The higher MNBI observed in Asia and South Africa and low MNBI in Turkey were the most striking regional differences observed. Esophageal mucosal integrity is determined by complex interaction between luminal contents, intercellular adhesion mechanisms and level of microscopic inflammation.[41] It is possible that genetic mechanisms might be responsible for regional differences in microscopic ultrastructure of the esophageal mucosa, allowing for a stronger mucosal integrity. On the other hand, exposure to different meals and refluxate can

induce impairment of mucosal integrity (lower MNBI). While one would expect a decrease in baseline impedance due to luminal factors including types of refluxate, an opposite effect could also occur. Finally, although the included subjects were selected based on absence of reflux symptoms, the level of chronic microscopic inflammation was not evaluated with biopsies, and day-to-day variation in reflux exposure was not considered.

The strengths of our study lie in the global representation of the impedance-pH tracings analysed, the meticulous 2-reviewer consensus established using *a priori* criteria for reflux episode identification, and the comparisons made between impedance-pH systems across world regions. Our use of consensus analysis to obtain normative data does not mean that clinical analysis of impedance-pH tracings necessarily requires multi-reviewer consensus; rather, the use of our recommendations for identification of reflux episodes and PSPW, and our normative data may improve accuracy of impedance-pH analysis by individual clinicians. The new set of normal values described in this study should theoretically improve GERD diagnosis, identification of GERD phenotypes and prediction of outcomes after treatment, and appears to validate thresholds for physiologic AET reported in the Lyon consensus[2]. However, our study does have a few limitations, mainly related to the fact that impedance-pH studies were not prospectively planned using standardized criteria, making it impossible to control for study related or technical factors. While included subjects were asymptomatic as per the contributing site, we did not require or seek alternate confirmation (endoscopy, biopsy, manometry) of the absence of reflux disease or other confounding diagnoses. Although inter-reviewer variability in reflux episode and PSPW identification was analyzed at the outset with a sample of 20 subjects included in this study (manuscript under review), further evaluation of inter-reviewer variability was not performed for the entire study cohort. Finally, we do not have outcome data to validate the diagnostic usefulness of the new thresholds proposed based on our findings.

In summary, we report findings from the largest collection of impedance-pH studies performed in healthy asymptomatic subjects obtained from multiple countries in five continents. The most relevant parameters reported are new threshold values for esophageal AET to define physiologic reflux (i.e. 95th percentile 2.8% for Diversatek and 5% for Laborie). We report significant system-related and regional differences in most reflux parameters reported from impedance-pH monitoring, making it important for each center and motility laboratory to utilize normative data relevant to their world region and impedance-pH system used.

Table 1. The Wingate Consensus recommendations for identification of reflux episodes and PSPW

Reflux episodes	PSPW
Meal times need to be correctly identified and excluded prior to evaluation of pH-impedance events	PSPW starts within 30 seconds after impedance returns to baseline in the distal most impedance channel following a reflux episode
A reflux episode consists of a 50% drop in impedance lasting for at least 4 seconds each in distal two impedance channels with retrograde propagation	PSPW does not need to be seen in all impedance channels as long as a swallow is identified in the most proximal channel with anterograde propagation in the proximal and distal-most impedance channels
A pH drop below 4.0 concurrent with a 4 second retrograde 50% impedance drop following a belch episode is counted as a reflux episode.	An impedance drop of at least 50% below baseline needs to be present in the distal-most impedance channel
A pH drop without impedance detected reflux episode is counted as part of acid exposure time if not an artifact, but not as a reflux episode	Recovery of pH with antegrade impedance event is not mandatory but supports identification of PSPW
Automated analysis is first deployed, followed by manual confirmation/deletion of identified reflux episodes using above criteria	PSPW is best evaluated using a 2 min window, using a 3000 ohms impedance scale

Note: PSPW, post reflux swallow-induced peristaltic wave.

Table 2. Effect of Gender and age on impedance-pH parameters

	Total acid exposure		**Total number of reflux**		**PSPW score (%)**		**MNBI 5cm (ohms)**		**MNBI 3 cm (ohms)**	
	Median (IQR)	95th	Median (IQR)	95th	Median (IQR)	5th	Median (IQR)	5th	Median (IQR)	5th
Gender										
Female	0.4 (0.1-1.2)	3.4	18(8-35)	56	50(34-64)	15	2797(2281-3495)	1480	3220(2333-3920)	1518
Male	0.9 (0.3-2) *	3.8	29(14-41) *	66	45(35-57)	15	2703(2260-3235)	1429	2843(2218-3528) *	1392
Age										
18-24	0.5(0.1-1.5)	3.4	26(11-38)	55	50(35-60)	15	2867(2322-3604)	1458	3304(2418-4044)	1490
25-40	0.6(0.1-1.6)	3.8	24(12-42)	68	48(38-61)	17	2792(2280-3428)	1630	2958(2325-3837)	1454
41-71	0.7(0.2-1.6)	3.7	19(10-33)	52	46(29-60)	15	2513(2141-3065) **	1334	2816(2076-3338) **	1381

* $p < 0.05$ vs. female
** $p < 0.05$ vs age 18-24

Table 3. Effect of System on impedance-pHmetry parameters

	Total acid exposure		**Total number of reflux**		**PSPW score (%)**		**MNBI 5cm (ohms)**		**MNBI 3 cm (ohms)**	
	Median (IQR)	95th	Median (IQR)	95th	Median (IQR)	5th	Median (IQR)	5th	Median (IQR)	5th
Total										
Diversatek	0.4(01-1.2)	2.8	21(10-34)	55	49(34-60)	15	2630(2207-3179)	1395	3001(2281-3623)	1384
Laborie	1.4(0.3-2.5)	5 *	30(12-43)	78 *	49(35-60)	19	3201(2410-4397)	1794 *	3014(2334-4098)	1542
Regions										
Asia										
Diversatek	0.3(0-1.1)	2.7	26(8-39)	61	45(29-57)	14	2942(2594-3353)	1967	3589(2790-4056)	1806
Laborie	0.6(0.2-1.5)	3.2	19(10-36)	47	39(28-55)	13	4803(3149-5113)	2397 *	3900(2804-4948)	1902*
West										
Diversatek	0.4(0.1-1.2)	2.7	21(12-35)	58	53(38-63)	15	2402(1962-2875)	1300	2830(2171-3299)	1347
Laborie	2.4(0.5-3)	7 *	39(20-46)	75 *	44(38-51)	20	3216(2647-4026)	2076*	2917(2399-3656)	2036

* $p < 0.05$ vs. diversatek

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FIGURE LEGENDS

Figure 1. Flow chart demonstrating included and excluded impedance-pH studies from two systems, Diversatek, Boulder, Colorado, and Laborie, Enschede, Netherlands. As many as 27.7% of submitted impedance-pH studies were excluded after discussion and consensus within study investigators: 15.9% had confounding diagnoses, while 11.8% had study related technical issues precluding analysis.

Figure 2. Comparison of age of subjects and total acid exposure time (AET). There was no significant impact or linear correlation between age and total AET ($r^2 = 0.001$).

Figure 3. Comparison of impedance-pH metrics between two systems, displayed using box and whisker plots. The extents of the box plots represent 25^{th}-75^{th} percentile values, and the whiskers depict 5^{th} and 95^{th} percentile values. The horizontal line within the boxes depict the median value in bold font. A. Comparison of total, upright and supine acid exposure time (AET). Values were significantly higher using Laborie compared to Diversatek. B. Comparison of numbers of total, acid and non-acid reflux episodes, and post reflux swallow induced peristaltic wave (PSPW) index. Total and upright reflux episodes were significantly higher using Laborie. C. Comparison of mean nocturnal baseline impedance (MNBI) at 3 cm and 5 cm above the lower esophageal sphincter. MNBI values were significantly higher using Laborie, compared to Diversatek, Further, 5 cm values were lower using Diversatek, but similar to 3 cm values using Laborie.

Figure 4. Comparison of impedance-pH metrics across world regions, using the two systems, Diversatek (Boulder, Colorado, USA) and Laborie (Enschede, Netherlands). The extents of the box plots represent 25^{th}-75^{th} percentile values, and the whiskers depict 5^{th} and 95^{th}

percentile values. The horizontal line within the boxes depict the median value in bold font. A. Comparison of total, upright and supine acid exposure time (AET). B. Comparison of numbers of total, acid and non-acid reflux episodes. C. Comparison of mean nocturnal baseline impedance (MNBI) at 3 and 5 cm above the lower esophageal sphincter (LES).