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ORIGINAL CONTRIBUTIONS

Reproducibility of Multichannel Intraluminal Electrical Impedance Monitoring of Gastroesophageal Reflux

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OBJECTIVE: Esophageal impedance measurement is a novel method for gastroesophageal reflux monitoring. Reproducibility is an important aspect of every biomedical test. The aim of this study was therefore to asses the reproducibility of gastroesophageal reflux monitoring using impedance measurements.

METHODS: Impedance and pH signals were recorded in 20 healthy volunteers during 90-min postprandial periods on two separate days. Hourly rates of gas, liquid, and mixed gas-liquid reflux episodes were measured in each recording period as well as percentage of time with pH < 4 and rate of acid reflux episodes. As a quantitative description of inter- and intraindividual variation for each variable, the mean percentage of covariation (100 $\times$ SD/mean: %COV) was calculated. As a second measure for reproducibility, Kendall's coefficients of concordance (W values) were calculated.

RESULTS: For all variables, interindividual %COV was at least 50% higher than intraindividual %COV. Statistically significant concordances were found for gas reflux ($W = 0.81$, $p = 0.04$) and mixed reflux ($W = 0.85$, $p = 0.03$) while concordance for liquid reflux tended to be significant ($W = 0.75$, $p = 0.08$). This was comparable to the reproducibility of the number of acid reflux episodes and percentage of time with pH < 4 ($W = 0.78$, $p = 0.05$ and $W = 0.88$, $p = 0.02$, respectively).

CONCLUSION: Postprandial gastroesophageal reflux data assessed with impedance monitoring are as reproducible as assessed with pH monitoring.

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INTRODUCTION

Patients with symptoms of heartburn and regurgitation often suffer from reflux of acidic gastric contents into the esophagus. This can be shown with a pH study. However, there is evidence that reflux symptoms may also occur in association with nonacid reflux (1). Furthermore, a subset of patients with reflux disease experiences no relief after effective acid suppression. It has been suggested that reflux of nonacid substances such as pepsin and bile acids may play a role in the genesis of reflux symptoms (2). Furthermore, it has been shown that nonacid components of the refluxate also play a role in the genesis of Barrett's epithelium (3).

Multichannel intraluminal electrical impedance monitoring makes it possible to detect nonacid liquid and gas flow through the esophagus (4). Recent studies have shown that combined pH and impedance monitoring provide additional information compared to pH measurements alone (5–7). The fact that impedance monitoring can also detect gas transport through the esophagus makes it a useful tool to study air swallowing and excessive belching as well (8).

Currently, pH monitoring is a generally accepted test for the quantification of gastroesophageal reflux, and various studies have shown that reproducibility of pH monitoring is good (9–15). The aim of this study was to investigate the reproducibility of esophageal electrical impedance monitoring and to compare this with the reproducibility of acid reflux measurements.

MATERIALS AND METHODS

Patients

Twenty healthy volunteers (14 males and 6 females: mean age 28 yr, range 19–46 yr) underwent two separate recordings of esophageal impedance and pH within an interval of 1–2 wk. Patients were free of any gastrointestinal symptoms and were not taking any medication. Informed written consent was obtained before the start of the study and the protocol was approved by the medical ethics committee of the University Medical Center, Utrecht.

Study Protocol

After an overnight fast a routine esophageal manometry was performed to determine the distance from the nostrils to the lower esophageal sphincter (LES). Thereafter, the impedance and the pH catheters were introduced transnasally and positioned based on the manometric findings (see below). A standardized meal was offered consisting of one hamburger

(McDonald's Quarter Pounder), 20 g of fresh onions, 44 g of potato chips, and 475 ml of orange juice (in total 967 kcal). This meal was used to provoke reflux in a previous study of our group (16). The meal had to be finished in 30 min. After the meal, impedance and pH signals were recorded for 90 min. Patients remained seated for the duration of the study.

Impedance and pH Monitoring

For impedance monitoring a 7-channel impedance catheter was used (Aachen University of Technology, FEMU, Aachen, Germany). This catheter (outer diameter 2.3 mm) enabled recording from seven segments, each recording segment being 2-cm long. The recording segments were located at 0–2, 2–4, 4–6, 8–10, 10–12, 14–16, and 17–19 above the upper border of the manometrically localized LES. Impedance signals were stored in a digital system (Aachen University of Technology, FEMU, Aachen, Germany) using a sample frequency of 1000 Hz. Intraluminal pH monitoring was performed with a glass pH electrode (Ingold A.G., Urdorf, Switzerland) and data were stored in a digital datalogger (Orion, MMS, Enschede, the Netherlands) using a sampling frequency of 2 Hz. The pH glass catheter was positioned 5 cm above the upper border of the LES. Using a cable that connected the pH datalogger with the impedance datalogger the pH signals were stored on both dataloggers enabling synchronization.

Data Analysis

Previously established criteria were used to identify swallows, gas reflux, liquid reflux, and mixed gas-liquid reflux (5, 17, 18). Furthermore, using the pH tracings, liquid reflux, mixed gas-liquid reflux, and gas reflux were classified as acidic or nonacidic, using a threshold of pH < 4. Percentage of time with pH < 4 was also assessed. Analysis was performed manually by two physicians with experience in this area; disagreement was solved by consensus. These observers were blinded to the outcome of the other measurement.

"Air swallows" were defined as swallows in which the liquid bolus, identifiable by a decrease in impedance, was preceded by an increase in impedance of at least 1,000 Ω above baseline. A threshold of 1,000 Ω was chosen because this was found to be well above the amplitude of baseline noise. The number of regular swallows as well as the number of "air swallows" were counted.

Evaluation of Reproducibility

Standard deviations (SD) and percentage coefficient of variation (100 × SD/mean: %COV) were calculated for impedance and pH data. The mean %COV of the 20 values of the first measurement and the mean %COV of the 20 values of the second measurement were calculated. An overall mean %COV was derived as a measure of interindividual variation. Furthermore, the mean %COV of the first and the second measurement in the 20 volunteers was calculated. This value, calculated from the values of the 20 individuals, was used as a measure of intraindividual reproducibility (19).

As a second measure for reproducibility, Kendall's coefficients of concordance (W value) were calculated using the mean values for the named variables from individual

Table 1. Intraindividual and Interindividual Reproducibility of Measurements of Mixed Gas-Liquid Reflux (Rates/h)

	Day		Intraindividual		
Volunteer	1	2	Mean	SD	%COV
1	1.30	4.20	2.75	2.05	74.57
2	7.10	10.80	8.95	2.62	29.23
3	7.90	4.60	6.25	2.33	37.34
4	6.00	3.80	4.90	1.56	31.75
5	1.30	2.00	1.65	0.49	30.00
6	2.00	2.00	2.00	0.00	0.00
7	2.60	3.30	2.95	0.49	16.78
8	3.30	1.30	2.30	1.41	61.49
9	6.70	4.50	5.60	1.56	27.78
10	7.30	5.30	6.30	1.41	22.45
11	6.50	6.00	6.25	0.35	5.66
12	0.00	0.00	0.00	0.00	0.00
13	2.70	4.00	3.35	0.92	27.44
14	3.30	3.30	3.30	0.00	0.00
15	5.30	5.50	5.40	0.14	2.62
16	3.40	1.30	2.35	1.48	63.19
17	4.00	6.00	5.00	1.41	28.28
18	4.70	4.90	4.80	0.14	2.95
19	2.60	2.60	2.60	0.00	0.00
20	3.30	4.00	3.65	0.49	13.56
Interindividual					
Mean	4.07	3.97	4.02	0.94	23.75
SD	2.26	2.31	2.10		
%COV	55.69	58.13	52.24		

SD = standard deviation; %COV = percentage of covariance. The mean SD and mean %COV for the two columns (day 1 and day 2) constitute an index of interindividual variation, whereas the equivalent values for the 20 individual rows are an index of intraindividual variation.

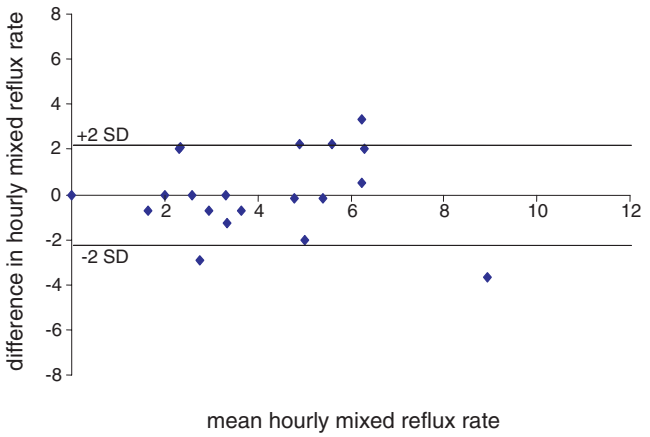

Figure 1. Reproducibility of mixed reflux rate (Bland-Altman plot).

recordings and tested for significance. An error probability of $p \leq 0.05$ was considered statistically significant. Throughout the manuscript data are presented as mean ± SEM.

Assessment of reproducibility was facilitated by presenting data in Bland-Altman plots. In these plots the difference between the first and second measurement is plotted against the mean value of the two measurements, which makes it possible to graphically compare these two values. When the difference between measurements on the first day and the second day is small, data points are scattered closely to the x-axis. Symmetrical scattering around the x-axis indicates that there is no trend toward a difference of the measurements of the second day compared to the measurements of the first day and the difference between the two measurements occurs in a random fashion.

RESULTS

As shown in Table 1 the mean rate at which mixed gas-liquid reflux episodes occurred was 4.0/h. As illustrated the variation between different patients was much larger than the variation occurring within the same patient (Fig. 1). Scattering of the data points occurs close to the x-axis in a rather symmetrical way.

As shown in Table 2 similar findings were made for the other reflux parameters, for swallowing rate, and for air swallowing. For virtually all parameters, the interindividual %COV was considerably higher than the intraindividual %COV. Concordance between the measurements was substantial for all parameters with Kendall's W values varying between 0.75 and 0.90 (Table 2). Statistically significant concordance was reached for hourly rate of gas reflux episodes, mixed reflux episodes, acid reflux episodes, swallowing, air swallowing, and percentage of time with pH below 4. For three parameters the reproducibility was borderline significant: hourly rate of liquid reflux episodes, mixed acid reflux episodes, and liquid acid reflux episodes. The hourly rate of these three types of events was rather low, as can be seen in Table 2.

Figures 2–5 show Bland-Altman plots for hourly rates of liquid reflux episodes, gas reflux episodes, swallows, and air swallows. In these figures data points are closely scattered around the x-axis, indicating a relatively small difference between the two measurements as compared to the mean of the two measurements. Furthermore, the scattering around the x-axis is symmetrical, indicating that the values of the second measurement are randomly distributed around the mean of the two measurements and that no upward or downward trend exists.

DISCUSSION

Previous studies showed that pH monitoring is a fairly reproducible method for detection of gastroesophageal reflux (9–15). In a study by Wiener *et al.*, in which a cutoff value of 4% of the time with pH < 4 was used for the diagnosis of gastroesophageal reflux disease (GERD), reproducibility for this diagnosis was 80% (15). Most studies that investigated reproducibility of the percentage of time with pH < 4, reported a higher reproducibility.

We studied reproducibility of impedance monitoring for the detection of gastroesophageal reflux. As shown in Table 2, %COV is much larger between patients than it is within patients. Furthermore, testing for concordance using Kendall's W test showed that the concordance between the two measurements of gas and mixed reflux was statistically significant, while concordance between the two measurements of liquid reflux tended to be statistically significant.

Table 2. Reproducibility of Swallow and Reflux Parameters

		Intraindividual		Interindividual			
	Mean	SD	%COV	SD	%COV	Kendall's W	*p*-Value
Number of mixed reflux episodes/h	4.02	0.94	23.75	2.10	52.24	0.85	0.03
Number of liquid reflux episodes/h	1.47	0.87	59.01	1.30	88.30	0.75	0.08
Number of gas reflux episodes/h	2.74	0.92	56.15	2.34	85.65	0.81	0.04
Number of swallows/h	64.15	7.66	13.04	24.66	38.44	0.90	0.02
Number of air swallows/h	22.50	6.07	28.80	11.31	50.30	0.84	0.03
Number of mixed acid reflux episodes/h	2.85	1.20	51.37	1.97	69.27	0.78	0.06
Number of liquid acid reflux episodes/h	1.35	0.99	50.02	1.73	127.79	0.77	0.06
Number of episodes pH < 4	3.52	1.00	36.37	2.23	64.57	0.78	0.05
% time pH < 4	6.12	2.45	54.77	7.98	129.98	0.88	0.02

SD = standard deviation; %COV = percentage of covariance.

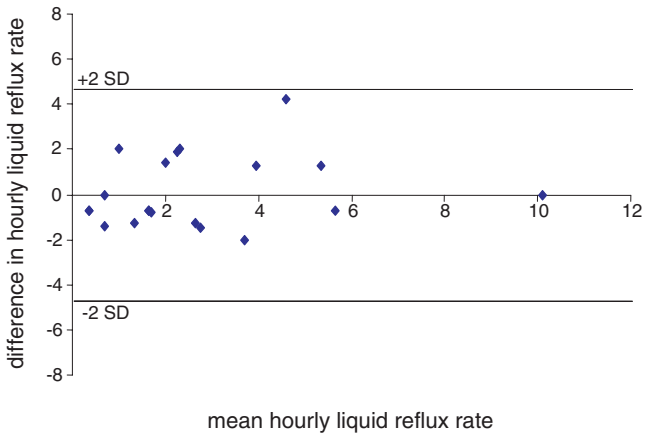

Figure 2. Reproducibility of liquid reflux rate (Bland-Altman plot).

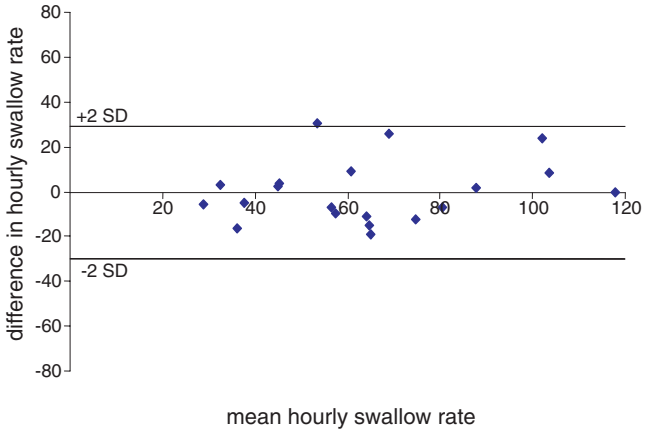

Figure 4. Reproducibility of swallow rate (Bland-Altman plot).

Results from our pH studies confirmed those obtained in previous reports, and both percentage of time with pH < 4 and hourly rate of reflux episodes were found to be reproducible. Reproducibility of the rate of liquid reflux, mixed gas-liquid acid reflux, and liquid gas-liquid acid reflux episodes were borderline significant. This is most likely due to a type 2 error, resulting from the rather low rate of (acid) reflux episodes in these healthy volunteers as well as to the relatively short recording time (90 min). Others have shown that reproducibility increases with the length of the study, showing much higher intraindividual concordance in 24-h measurements than in 3-h measurements (10). Since in our 90 min study standardized meals and position were used, the reproducibility found may theoretically differ from the reproducibility of 24-h ambulatory impedance monitoring.

Reproducibility of a biomedical test is determined not only by patient-related factors, but also by technical factors. Differences in catheter position, data acquisition, and data analysis can influence the results of impedance monitoring. The degree of reproducibility is only acceptable when variations caused by technical factors are rather small. The fact that we found a good reproducibility of gastroesophageal reflux testing with intraluminal impedance monitoring can be considered as an important validation of this technique. Apart from reflux parameters, swallowing rate and air swallowing rate as determined with intraluminal impedance were also found to be reproducible in healthy volunteers. The frequencies found in this study were well within the reported range (20).

The reproducibility of reflux monitoring using esophageal impedance measurement was found to be comparable to the reproducibility of reflux testing with pH monitoring. This indicates that esophageal impedance monitoring can be an important new tool for studying and diagnosing GERD (10). The additional value of impedance measurements in conjugation with pH monitoring explains the increasing use of this technique. A recent publication of normal values and the consensus report concerning terminology have opened doors to more widespread clinical application (21, 22). Furthermore, the reproducibility of impedance measurements indicates that this technique might be suitable for investigation of the effects of new drugs and other treatment modalities on the occurrence of gastroesophageal reflux. However, one should take into account that, although intraindividual variations are

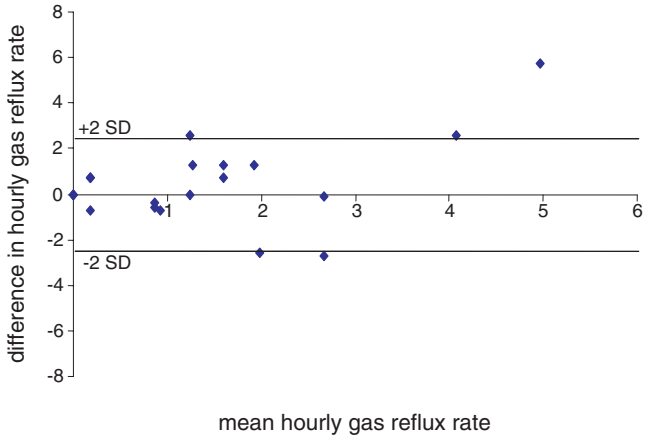

Figure 3. Reproducibility of gas reflux rate (Bland-Altman plot).

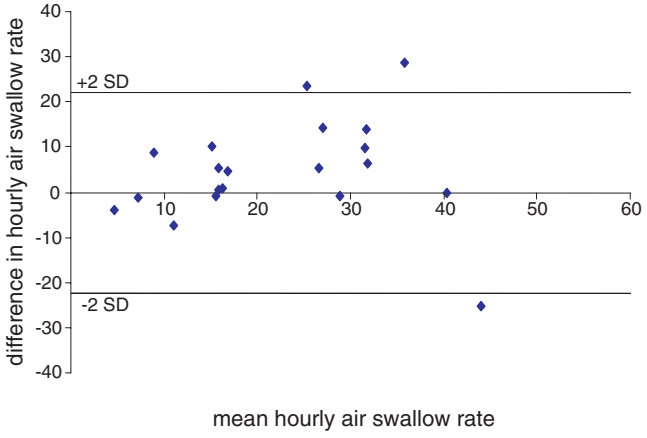

Figure 5. Reproducibility of air swallow rate (Bland-Altman plot).

small compared to interindividual variations, a normal day-to-day variance within patients does occur and that this may limit the statistical power of studies with small sample sizes. In ambulatory studies physiological intraindividual variation could be larger than the variations found in this study, since in our setting patients were studied in the same position and used the same standardized meal during each of the two measurements.

The Porto consensus report introduced a new nomenclature for reflux monitoring (22). In this nomenclature, definitions of reflux are based on the combined use of pH and impedance monitoring. Reflux is thus divided in acid reflux (fall of pH below 4), superimposed reflux (when pH is already below 4), weakly acidic reflux (when pH is between 4 and 7), and weakly alkaline reflux (pH above 7). Reproducibility of these four types of reflux depends on the combination of pH and impedance monitoring techniques. The aim of this study was to investigate reproducibility of impedance monitoring alone and therefore we did not investigate reproducibility of these four parameters.

In conclusion, we showed that intraluminal impedance measurement is a reproducible method for studying (air) swallowing, liquid reflux, gas reflux, and mixed gas-liquid reflux. The reproducibility of measurement of these reflux events is comparable to the reproducibility of acid reflux measurement by means of pH monitoring.

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