Journal of Visualized Experiments

Simultaneous laryngopharyngeal and conventional esophageal pH monitoring

--Manuscript Draft--

Article Type:	Invited Methods Article - JoVE Produced Video
Manuscript Number:	JoVE61641R2
Full Title:	Simultaneous laryngopharyngeal and conventional esophageal pH monitoring
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Additional Information:	
Question	**Response**
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TITLE:

Simultaneous laryngopharyngeal and conventional esophageal pH monitoring

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KEYWORDS:

Gastroesophageal reflux disease, GERD, laryngopharyngeal reflux, LPR, pH monitoring, esophageal pH monitoring, oropharyngeal pH monitoring, pH metry, gastrointestinal function testing

SUMMARY:

Laryngopharyngeal pH monitoring has been specifically designed to measure acid exposure above the upper esophageal sphincter and complements diagnostic evaluation in patients that present with mainly extraesophageal reflux symptoms. Patients with suspected laryngopharyngeal reflux (LPR) were evaluated using distal esophageal and laryngopharyngeal pH testing simultaneously.

ABSTRACT:

In addition to typical reflux symptoms, many patients with gastroesophageal reflux disease (GERD) present with extraesophageal symptoms such as cough, hoarseness or asthma, which can be caused by laryngopharyngeal reflux (LPR). Due to their multifactorial origin, those symptoms can be a great diagnostic and therapeutic challenge. Esophageal pH-monitoring is commonly used to determine abnormal esophageal acid exposure and confirm the diagnosis of GERD. However, for better evaluation of acid exposure above the upper esophageal sphincter, a new laryngopharyngeal pH measurement system is now available and may lead to more reliable results in patients with predominantly extraesophageal symptoms. This article aims to present a standardized protocol for simultaneous pH measurement using esophageal and laryngopharyngeal pH probes in order to obtain acid exposure scores from both measurements.

INTRODUCTION:

Gastroesophageal reflux disease (GERD) is one of the most common benign diseases affecting up to 20% of people in western countries[1]. In addition to typical symptoms such as heartburn or regurgitation, some patients may suffer from atypical symptoms such as cough, hoarseness, or asthma[2,3]. Despite the agreement that chronic cough, chronic laryngitis, and asthma can have a reflux related origin and are significantly associated with laryngopharyngeal reflux (LPR), the exact pathomechanism still remains unclear. As these symptoms are usually part of a multifactorial process, they depict a great diagnostic and therapeutic challenge[4].

Distal esophageal pH monitoring 5 cm above the lower esophageal sphincter is commonly used to determine abnormal esophageal acid exposure in patients with suspected GERD[2]. In an attempt to use the same technique, proximal conventional pH monitoring was introduced in the late 1990s as a diagnostic device to measure abnormal acid exposure at the upper esophageal sphincter (UES) as the probe is placed at or slightly above the UES. However, this method does not always provide valid and accurate results as the probe is not designed for an oropharyngeal environment leading to the measurement of invalid artifacts such as pseudoreflux events caused by drying out of the probe[5,6].

Lately, laryngopharyngeal pH monitoring was introduced as a new diagnostic device specifically designed to measure acid exposure in the oropharynx, as the probe is placed above the UES slightly lateral to the uvula (**Figure 1**). Since previous research has shown it to have a positive predictive value of 80% for a successful outcome after antireflux surgery in patients with primarily atypical symptoms, this new tool has been a valuable addition to the diagnostic pathway in selected patients. Its tear drop sensor is equipped with an antimony technology that detects liquid and aerosolized acid and does not need direct mucosal contact to measure valid results. In addition, the sensor can, in contrast to proximal pH monitoring, resist drying out which may lead to more reliable results[7,8].

Current literature on the correlation of concomitant conventional esophageal and laryngopharyngeal pH measurement is sparse. Previous studies either included only a small number of patients or did not perform both measurements simultaneously[9-11]. We recently published data on the correlation between both pH measurements in a large cohort of 101 patients with suspected GERD. We concluded that laryngopharyngeal and esophageal pH measurement do not necessarily need to correspond due to the existence of a variety of different reflux scenarios[12]. We furthermore developed a human reflux model with patients following esophagectomy and reconstruction with a gastric interposition showing 100% correlation between both pH monitoring methods in volume-refluxers[13].

Here, we aim to provide instructions for simultaneous pH measurement using distal esophageal and laryngopharyngeal pH monitoring. In addition, guidance on analysis of composite acid exposure scores and correlation between results obtained by both methods is given. We furthermore present the newest data of a large patient cohort evaluated using simultaneous esophageal and laryngopharyngeal pH monitoring.

PROTOCOL:

The following study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty of the University of Cologne.

NOTE: Ensure that the patient arrives NPO for the following gastrointestinal function testing. Perform a high-resolution manometry to determine the exact location of the lower esophageal sphincter (LES) and to rule out esophageal dysmotility disorders such as achalasia. The patient should be off antisecretory medication for at least 7 days prior to ensure a valid pH measurement.

1. Setting up the esophageal pH monitoring system

1.1 Insert batteries into the esophageal monitoring system.

1.2 Connect the esophageal pH catheter to the device.

1.3. Start the device. Make sure date and time is accurate. Select **Start study**.

1.4 Calibrate the catheter in solutions with pH 4 and 7 and rinse the probe in water. Set the probe aside for insertion.

2. Setting up laryngopharyngeal pH monitoring system by first formatting the SD card with patient's data.

2.1 Insert the SD card into the computer and open the software for laryngopharyngeal pH monitoring (e.g., DataView 4). Add a new patient by clicking on **New** and typing in all details about the patient. Click **Save** to save the data to the SD card. Eject the SD card and insert it into the recorder.

2.2 Insert batteries into the transmitter using the supplied screwdriver to remove the cover of the transmitter case and install a new CR1632 lithium coin battery.

2.3 Insert two AA batteries into the recorder.

2.4 Turn the recorder on. Use the up/down keys to select **Setup**. Press any round key to select the **Setup** mode. Modify the time and date if needed by using the up/down keys to change the digits and any round key to select the respective value. If time and date is correct, select **Yes** and continue.

2.5 Select **No** when the Recorder asks "Tst PSG Adapter?".

2.6 Select **Study** in the main menu.

2.7 The transmitter is now detected automatically. Confirm that the correct transmitter is detected and press any round key for confirmation. The transmitter displays the serial number that is paired with the recorder.

2.8 Attach the probe to the transmitter.

NOTE: When connected to the transmitter, the red light-emitting diode (LED) at the probe tip will flash once per second. The LED stops flashing after four hours to conserve battery life.

2.9 Select **Hydrate** for the calibration process. Hydrate the probe with the provided clear water solution by placing the probe tip in the clear water solution and agitating briefly. Press any round key to start the hydration process.

NOTE: The Recorder will display “Hydrating” and will count down from “300 seconds” to zero or will transition to 15 seconds countdown when the recorder detects that the probe is hydrated. Set the probe aside for insertion.

3. Placing the esophageal pH catheter first

3.1 Ensure that the patient is sitting upright, looks straight and swallows periodically. Provide a small glass of water with a straw to assist swallowing.

3.2 Ask the patient which side of their nose is clearer and easier to breathe through.

3.3 Apply a topical gel that contains a local anesthetic to the probe shaft for ease of insertion.

3.4 Insert the Probe through the patient’s nose, straight in and not up. A measuring scale on the probe shaft helps to determine the correct position.

NOTE: The correct position is 5 cm above the LES as previously determined by high resolution manometry.

4. Securing the esophageal pH catheter

4.1 Secure the probe as closely to the nares as possible to ensure that it does not move during the study using surgical tape.

4.2 Attach the probe to the cheek, near the nose.

4.3 Loop the probe over the ear and use tape to affix the probe to the neck, behind and below the ear.

5. Placing the laryngopharyngeal pH catheter

5.1 Ensure that the patient is sitting upright, looks straight and swallows periodically.

5.2 Apply a topical gel that contains a local anesthetic to the distal end of the probe shaft for ease of insertion.

Caution: DO NOT apply topical gel to the probe tip where the sensor is located.

5.3 Insert the probe through the patient's opposite nostril of the esophageal catheter, straight posteriorly and not up.

NOTE: The round probe tip will help it curve around and through the velopharyngeal port into the oropharynx. The distance from the patient's nares to the oropharynx can often be estimated by using the distance from the nares to the earlobe.

5.4 Confirm that the red light is clearly visible, lateral to or slightly below the uvula. Use a tongue depressor for clear visibility if needed.

NOTE: If the patient's gag reflex is triggered, retract the probe to a higher position in the oropharynx.

6. Securing the probe and transmitter

6.1 Secure the probe as closely to the nares as possible to ensure that it does not move during the study using surgical tape.

6.2 Attach the probe to the cheek, near the nose.

6.3 Loop the probe over the ear and use tape to affix the probe to the neck, behind and below the ear.

6.4 Attach the transmitter to the patient's clothing with the clip-on transmitter carrying case.

7. Ensuring that simultaneous pH measurements are performed

7.1 Make sure the internal clocks of both pH measurement devices are synchronized. Manually adjust the times if needed.

7.2 Start esophageal and laryngopharyngeal pH studies concurrently. Select a 24-hour study for the laryngopharyngeal pH measuring device.

8. Patient diary and instructions

8.1 Ask the patient to fill out a detailed diary that includes mealtimes, exact time of supine periods and symptoms they experience during the time of the study.

8.2 Provide the following instructions for the 24-hour measurement period to the patient to ensure a successful data recording:
Three mealtimes on day 1 of the study, one mealtime on day 2 of the study.
No supine periods before 9pm.
Eat, drink, and behave as usual (daily activities can be done)

Caution: Devices are NOT waterproof.

9. Removing the esophageal and laryngopharyngeal probe after the 24-hour study period is completed

9.1 Concurrently end the study on both devices.

9.1.1 End the esophageal pH study by pressing the two buttons located in the middle simultaneously until "upload later" appears on the display.

9.1.2 End the laryngopharyngeal pH study by simultaneously pressing the cough, ESC and heartburn button until "complete" appears on the display.

9.2 Remove tape and gently pull out both catheters.

10. Interpreting the results obtained by the esophageal pH study

10.1 Connect the device to a computer. Open the software used for analyzing results obtained from the esophageal pH measuring device and upload the patient's study.

10.2 Manually type in the patient's data and the information obtained by the patient's diary, such as mealtimes, upright and supine periods and symptoms experienced during the study period. Delete any button presses that might have accidentally been performed by the patient during the study period.

10.3 Exclude mealtimes from the data analysis.

10.4 On the report, look at important parameters and thresholds provided to determine an abnormal esophageal acid exposure such as the composite score, the total % pH below baseline (upright and supine) and total number of events.

10.5 Calculate a composite score (DeMeester score) for the study period using % time pH < 4 total, upright and supine, total number of events, number of events lasting longer than 5 minutes and the duration of the longest event[14]. Make sure the report shows the composite score.

NOTE: A DeMeester score > 14.72 displays an abnormal esophageal acid exposure.

11. Interpreting results obtained by laryngopharyngeal pH monitoring

11.1 Insert the SD card into the computer and open the software used for analyzation of results obtained by the laryngopharyngeal pH measuring system. To upload the study, click on **Retrieve**.

11.2 Manually add the information obtained by the patient's diary, such as mealtimes, upright and supine periods and symptoms experienced during the study period. Left click on the graph and drag and highlight the area on which you want to add the event and chose the respective event. Delete any button presses that might have accidentally been performed by the patient during the study period.

11.3 Exclude mealtimes from the data analysis.

11.4. Click on **Report** to see a graph displaying acid exposure in the oropharynx during the study period, including supine period, symptoms and mealtimes as well as a study summary.

11.5 On the report, look at important parameters and thresholds to determine an abnormal oropharyngeal acid exposure such as the composite score, the total % pH below baseline (pH < 5.5 upright and pH < 5 supine) and total number of events.

11.6. Calculate a composite score (RYAN Score) for both the upright and supine period using the % time pH below 5.5 upright and 5 supine, total number of events and the duration of the longest event[8]. Make sure, a composite score for the upright and supine period is shown in the report.

NOTE: A RYAN Score of > 9.4 upright and > 6.8 supine shows a severely abnormal oropharyngeal acid exposure.

REPRESENTATIVE RESULTS:

A total of 181 patients were evaluated using the previously described standardized protocol. Results of the first 101 patients have been previously published[12]. The following data depicts an extension of the previously published cohort, however, evaluated using the new software for analyzation of results obtained by laryngopharyngeal pH testing[15]. Demographic data is depicted in **Table 1**. All patients presented with atypical symptoms including chronic cough, hoarseness, sore throat, or pharyngeal burning. In addition, most patients suffered from typical GERD symptoms such as heartburn, regurgitation, or dysphagia.

A normal oropharyngeal acid exposure obtained by laryngopharyngeal pH testing was defined as a RYAN Score < 9.4 upright and/or < 6.8 supine. A normal esophageal pH test result was defined as a DeMeester Score of < 14.72. Detailed data on results obtained by both pH measurements is depicted in **Table 2**. Of patients with a normal laryngopharyngeal test result, 58 patients (55.2%) also showed a corresponding normal esophageal pH test with a mean DeMeester Score of 5.3 (range 0.3 – 14.1).

Abnormal oropharyngeal acid exposure was more frequently seen in a upright position, with 72

patients showing an abnormal RYAN Score upright compared to 9 patients in a supine position, p value < 0.0001. Correlation with abnormal distal esophageal acid exposure was shown in 49 patients (64.5%) with a mean DeMeester score of 64.7 (range 15.5 – 285.4).

Overall, correlation between esophageal pH monitoring and laryngopharyngeal pH monitoring, defined as both tests showing corresponding abnormal or normal results, was seen in 107 patients (59%).

Abnormal oropharyngeal acid exposure was seen in 76 patients. A non-corresponding, normal distal esophageal acid exposure was seen in 27 of those patients (35.5%). Interestingly, 11 patients with an abnormal oropharyngeal acid exposure but a normal esophageal test result showed reflux associated mucosal changes during upper gastrointestinal endoscopy. A normal oropharyngeal test result was found in 105 patients. A non-corresponding, abnormal distal esophageal acid exposure was seen in 47 of those patients (44.8%). Reflux associated mucosal changes were found in 25 patients with an abnormal esophageal acid exposure and a normal oropharyngeal test result.

Twenty-six patients underwent laparoscopic antireflux surgery after simultaneous pH measurement. Abnormal oropharyngeal acid exposure was shown in 16 patients (61.5%) with a mean RYAN score upright of 59.9 (range 4.3 – 153.9). Correlation with an abnormal distal esophageal acid exposure was seen in 13 patients with a mean DeMeester Score of 90.4 (range 20.4 – 283.5). Correlation of an abnormal laryngopharyngeal pH test results with abnormal esophageal acid exposure increased to 81.2% in surgical candidates.

FIGURE AND TABLE LEGENDS:

Table 1: Demographic information, symptoms, and surgical therapy. Detailed demographic information and symptom distribution of our study cohort as total number of patients and percentage from study cohort is shown. Cough, hoarseness and globus sensation were summarized under atypical symptoms. In addition, this figure shows how many patients underwent surgical therapy for treatment of GERD and which method was chosen.

Table 2: Results obtained by laryngopharyngeal and esophageal pH testing (n = 181). A summary of results obtained by laryngopharyngeal and esophageal pH testing is shown. A normal laryngopharyngeal pH test was defined as a RYAN score < 9.4 upright and < 6.8 supine. A normal esophageal pH test was defined as a DeMeester score < 14.72. The total number of patients with respective results, the percentage from the study cohort, mean scores and ranges of RYAN or DeMeester scores are displayed.

Figure 1: Laryngopharyngeal pH testing system. This figure shows the laryngopharyngeal pH monitoring system, consisting of a recorder and a transmitter with an attached measuring probe. In addition, the calibration vials as well as the water vial for the hydration process are shown.

DISCUSSION:

Esophageal pH monitoring is commonly used to confirm the diagnosis of GERD in patients with

typical reflux symptoms. However, many patients present, in addition to typical reflux symptoms, with atypical reflux symptoms such as cough or hoarseness most likely related to LPR. Current guidelines suggest an empiric trial with PPIs to proof a reflux related origin of those symptoms and a standardized objective measurement is lacking[2]. Laryngopharyngeal pH testing, due to its location above the upper esophageal sphincter, provides a new objective diagnostic method to measure abnormal oropharyngeal acid exposure and may lead to more reliable results in those patients.

Previous studies tried to analyze the correlation between laryngopharyngeal and esophageal pH monitoring[9-11]. However, those studies did not establish a standardized protocol, included only a small number of patients ($n \leq 36$) or did not perform both measurements simultaneously. Hence, a valid correlation between both techniques could not be found. Weitzendorfer et al. recently published a larger series of 70 patients, that underwent simultaneous esophageal and laryngopharyngeal pH testing in addition to a thorough assessment of symptoms, quality of life and saliva sampling[16]. The authors state that no correlation between a positive oropharyngeal acid exposure and any other objective or subjective test result could be established. Wilhelm et al. previously tried to establish a reliable reference group for the validation of laryngopharyngeal pH monitoring in patients after total gastrectomy[10]. Unfortunately, only a small number of patients (n=10) was included in the study and since upright and supine periods were not entered correctly, no valid results could be obtained. In addition, no esophageal pH monitoring was performed to investigate the correlation between both methods, or the origin of positive laryngopharyngeal test results. We recently published data on the correlation between simultaneous laryngopharyngeal and esophageal pH measurement of 101 patients with suspected GERD and extraesophageal symptoms and showed that results of both measurements do not necessarily need to correspond[12]. Due to different thresholds, different probe location and pathophysiology, comparison of both methods can be challenging and misleading. We believe that more than one reflux scenario exists, and esophageal and laryngopharyngeal pH monitoring rather complement each other leading to a better evaluation of this challenging patient cohort. We agree with previous studies, that as of now, laryngopharyngeal pH monitoring alone is not suitable as a screening device for GERD or LPR and further studies are needed to clarify the origin of non-correlating test results. However, our previous study has shown that this standardized protocol presents as a great addition to the diagnostic pathway of this challenging patient cohort especially for surgical decision making. Furthermore, we developed a human reflux model with patients following esophagectomy and reconstruction with a gastric interposition. Those patients often suffer from severe reflux symptoms postoperatively and present with no reflux barrier and a limited esophageal motility, concepts that are important contributors to the pathophysiology of GERD. We used this cohort as a control group to further validate our standardized protocol. Final numbers are unpublished, but early work showed 100% correlation between both pH monitoring methods in this volume-reflux model[13].

In addition, previous studies did not consider that some reflux episodes may not reach the oropharynx leading to a discrepancy that can, however, be physiologically explained. In addition, different thresholds for laryngopharyngeal and esophageal pH lead to a different calculation of composite acid exposure scores for both pH monitoring methods. Whereas a pH of < 5.5 upright

or < 5.0 supine is considered abnormal in the oropharynx a pH of < 4 is abnormal for the distal esophagus[8,14]. Therefore, a reflux episode with a pH of 5 is considered normal in the distal esophagus but measured as an abnormal reflux episode in the oropharynx. Furthermore, a DeMeester Score of > 14.72 shows abnormal esophageal acid exposure and a negative score states that the patient has no pathological reflux[17]. However, only severe oropharyngeal reflux leads to an abnormal RYAN Score of > 9.4 upright and > 6.8 supine. A patient with mild or moderate abnormal oropharyngeal acid exposure might still have a normal RYAN Score.

This standardized protocol ensures simultaneous performance of esophageal and laryngopharyngeal pH measurement. Both measurements are started concurrently, and internal clocks are synchronized to ensure a truly simultaneous measurement. In addition, patients are asked to maintain a detailed diary throughout the measurement for mealtimes, symptoms, upright and recumbent phases. Diary entries are then entered manually for both devices, ensuring the right timing and accuracy. Moreover, this ensures that the same lifestyle and day-to-day changes are displayed in both measurements.

We recommend that patients are off antisecretory medication for at least 7 days prior to this standardized protocol to ensure a valid pH measurement. Both, laryngopharyngeal and esophageal pH monitoring, show the highest sensitivity and specificity when performed off PPIs. If the patient cannot pause this medication due to an unbearable symptom load or other reasons, the same protocol may still be performed. However, instead of the DeMeester and the RYAN score, the graphic presentation of the data as well as impedance can be helpful tools to interpret the test results. Furthermore, this protocol includes a hand-written diary. However, instead of a detailed written diary, patients could also use button presses on both devices to record their symptoms and supine periods. Our clinical experience has shown, that keeping a written diary is easier for most patients and less error prone. In addition, both pH measurements can be performed separately if needed, however, no correlation of results can be obtained in that case. We usually place the esophageal probe first, as shown in the video manual. It does not matter from a scientific standpoint which probe is placed first, but the esophageal probe is usually more difficult to place making it easier for the patient to start with the most uncomfortable part of the study and having both nostrils to choose from. If the probe curls or does not seem to be able to pass down to the lower esophagus, changing the patient's head position and overall posture may help. Often times, using the other nostril may lead to a successful placement of the probe. If the red light of the laryngopharyngeal measurement probe stops blinking, before the probe has been successfully placed, the battery of the transmitter can be reinstalled to make it blink again.

Critical steps of the protocol include the exact determination of the LES, ensuring a correct placement of the esophageal pH probe 5 cm above the LES and correct placement of the oropharyngeal pH probe lateral to or slightly below the uvula. Only if both probes are placed correctly, a valid correlation between results can be obtained. In addition, securing the probes to maintain exact position is most important and challenging. Especially heavy make-up, facial hair and hot days can complicate securing the probe. Furthermore, ensuring that the patients keeps a detailed and honest diary with exact times is crucial to later correlate supine periods, symptoms, and mealtimes with measured reflux episodes. Overall, all patients in our cohort

tolerated both pH probes.

Limitations of the method lay especially in the location of the probes. Esophageal pH monitoring has shown to present reliable results determining abnormal acid exposure in patients with GERD[14]. However, due to its location 5 cm above the LES, an evaluation of acid exposure in the oropharynx cannot be performed. We typically use a long probe impedance pH monitoring system at our institution to not only measure distal esophageal pH but in addition, bolus movement and non-acid reflux events. Particularly, impedance has shown to increase the sensitivity of the measurement in patients with atypical symptoms[18]. The protocol, however, can also be used for a regular distal esophageal pH monitoring system. Wireless distal esophageal pH monitoring can also be used instead of a conventional measuring system. Laryngopharyngeal pH testing provides a validated measurement of acid exposure above the upper esophageal sphincter, measuring liquid and vaporized acid, however, does not measure reflux episodes that do not reach the oropharynx[8]. Furthermore, day-to-day lifestyle changes challenge a 24-hour pH measurement as the patient can have a normal test result for the measured time period, however, complain of reflux symptoms on another days, that has not been measured. The laryngopharyngeal pH monitoring system provides an option for a 48-hour study period which may lead to more reliable results. In addition, a new software for evaluation of results obtained by laryngopharyngeal pH monitoring was released recently. A study comparing both software versions showed that results obtained by either software cannot be compared to each other[15]. Results from this study were evaluated using the new and improved software version, however, retrospective comparison of data may be limited by the use of different software versions.

Future studies need to address if laryngopharyngeal pH monitoring can be used as screening tool for LPR and if this new technique is able to predict a successful surgical outcome in patients with mainly atypical reflux symptoms. However, the use of the protocol ensures a comprehensive evaluation of acid exposure in this challenging patient cohort is maintained and provides guidance on complementary laryngopharyngeal and esophageal pH monitoring.

ACKNOWLEDGMENTS:
The authors would like to thank Restech for providing an educational grant.

DISCLOSURES:
Dolores Müller received an educational grant from Restech. All other authors have nothing to disclose.

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Figure

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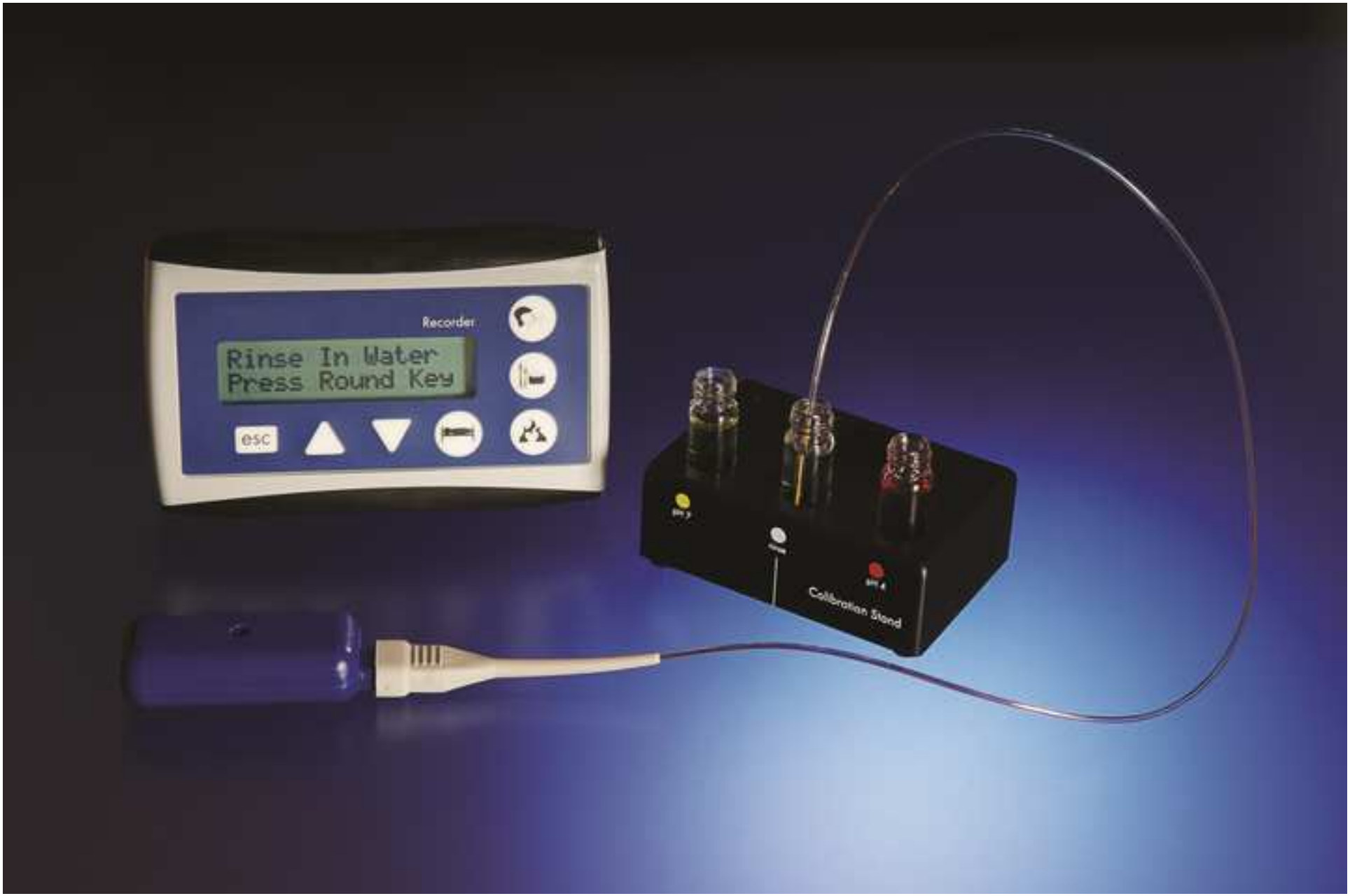

Table 1

	N	%
Total patients	181	100
Females	110	60.8
Age (mean; range), years	52	22 – 86
BMI (mean; range), kg/m2	25.2	18.4 - 46.8
Atypical reflux symptoms	181	100
Regurgitation	116	64.1
Heartburn	127	70.2
Dysphagia	80	44.2
Surgical Therapy		
Nissen	15	8.3
Toupet	4	2.2
LINX	4	2.2
Endostim	2	1.1

Table 2

	laryngopharyngeal pH testing					esop
		RYAN upright		RYAN supine		
	n (%)	*mean*	*range*	*mean*	*range*	*n (%)*
normal	105 (58)	1.12	0 - 8.41	0.33	0 - 6.43	85 (47)
abnormal	76 (42)	52.8	0 - 228.9	2.92	0 - 48.41	96 (53)

›hageal pH testing

	DeMeester
mean	*range*
6.31	0.3 - 14.2
59.53	14.8 - 285.4

Name of Material/ Equipment	Company	Catalog Number	Comments/Description
AA Battery	-	-	-
Calibration Solutions pH 4 and 7	Medtronic		part of the Digitrapper Reflux Testing
CR 1632 Lithium coin cell battery	-	-	-
Digitrapper pH & Impedance catheter	Medtronic		
Digitrapper Recorder	Medtronic		
Gelicain	PUREN		topical gel
Hydration vials with clear water	Respiratory Technology Corporation		part of the Restech Dx pH system
Leukoplast	BSN medical GmbH		surgical tape
Restech Dx pH probe	Respiratory Technology Corporation		part of the Restech Dx pH system
Restech Recorder	Respiratory Technology Corporation		part of the Restech Dx pH system
Restech Transmitter	Respiratory Technology Corporation		part of the Restech Dx pH system
Screwdriver	Respiratory Technology Corporation		part of the Restech Dx pH system
SD Card plus Adapter	Respiratory Technology Corporation		part of the Restech Dx pH system
tongue depressor	NOBAMED		wooden

system

Rebuttal Letter

Dear Editor and Reviewers,

Thank you very much for your feedback and thorough review.

We would like to answer all comments in detail and describe other changes to the previous version of our manuscript. All changes to the manuscript were done using MS Word "track changes".

Review Editor

Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammatical errors.

Thank you for your comment. We thoroughly proofread the manuscript and consulted a native speaker to ensure that there are no spelling or grammatical errors.

Avoid the phrase "video manual" in the title.

Thank you for your comment. We changed the title accordingly.

Textual Overlap: Significant portions show significant overlap with previously published work. Please re-write the text on lines 72-78, to avoid this overlap.

Thank you for your comment. We re-wrote the respective paragraph in the manuscript.

Protocol Detail: Please note that your protocol will be used to generate the script for the video, and must contain everything that you would like shown in the video. Please ensure that all specific details (e.g. button clicks for software actions, numerical values for settings, etc) have been added to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

1) Please include an ethics statement before your numbered protocol steps indicating that the protocol follows the guidelines of your institutions human research ethics committee.
2) 2.4: unclear what is meant and what is to be done.
3) 3.3: what kind of gel?
4) How are RYAN and DeMeester scores calculated? Cite references.

Thank you for your comment. More specific details have been added to our protocol to ensure that viewers can successfully replicated our protocol and that the written protocol complements the video manual. 1) In addition, an ethics statement has been added. 2) The wording for step 2.4 was changed and additional instructions were provided. 3) A more detailed description of the type of gel used in steps 3.3 and 5.2 was added. 4) A more detailed description of both composite scores was provided and references with the original validation of the calculation algorithms were cited.

Protocol Numbering:
1) All steps should be lined up at the left margin with no indentations.
2) Add a one-line space between each protocol step.

Thank you for your comments. 1) All steps are now lined up at the left margin with no indentations. 2) A one-line space between each protocol step was added.

Protocol Highlight: Please highlight ~2.5 pages or less of text (which includes headings and spaces) in yellow, to identify which steps should be visualized to tell the most cohesive story of your protocol steps.
1) The highlighting must include all relevant details that are required to perform the step. For example, if step 2.5 is highlighted for filming and the details of how to perform the step are given in steps 2.5.1 and 2.5.2, then the sub-steps where the details are provided must be included in the highlighting.
2) The highlighted steps should form a cohesive narrative, that is, there must be a logical flow from one highlighted step to the next.
3) Please highlight complete sentences (not parts of sentences). Include sub-headings and spaces when calculating the final highlighted length.

Thank you for your comments. Approximately 2.5 pages of text were highlighted in the protocol to identify steps that should be visualized.

Discussion: JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form (3-6 paragraphs): 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.

Thank you for your comments. We added a paragraph to the discussion focusing in troubleshooting of the method. In addition, we added several sentences to existing paragraphs to ensure that all information is sufficiently displayed.

Figures: Avoid showing the product name in fig 1.

Thank you for your comment. The figure 1 was changed accordingly.

Figure/Table Legends: Please expand the legends to adequately describe the figures/tables. Each figure or table must have an accompanying legend including a short title, followed by a short description of each panel and/or a general description

Thank you for your comments. We expanded the legends to improve the description of our figure and two tables.

References:

1) Please make sure that your references comply with JoVE instructions for authors. Citation formatting should appear as follows: (For 6 authors or less list all authors. For more than 6 authors, list only the first author then et al.): [Lastname, F.I., LastName, F.I., LastName, F.I. Article Title. Source. Volume (Issue), FirstPage – LastPage, (YEAR).]

• If your figures and tables are original and not published previously or you have already obtained figure permissions, please ignore this comment. If you are re-using figures from a previous publication, you must obtain explicit permission to re-use the figure from the previous publisher (this can be in the form of a letter from an editor or a link to the editorial policies that allows you to re-publish the figure). Please upload the text of the re-print permission (may be copied and pasted from an email/website) as a Word document to the Editorial Manager site in the "Supplemental files (as requested by JoVE)" section. Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."

Thank you for your comments. We made sure that our references complied with JoVE instructions by using the provided template.

Reviewer #1:

Manuscript Summary:
The authors provide a pathway to show how the Restech Measurement System (Dx-pH) should be used in patients with symptoms related to GERD or LPR.
Furthermore, the authors provide some data of their series of patients and show the correlation analysis of esophageal pH monitoring and oropharyngeal pH monitoring to diagnose patients with LPR.

Major Concerns:
The manuscript is written quite ok. But I am not happy with the delivered data and the final conclusions of the authors.

The authors show us very divergent data. Fuchs et. al have published a manuscript in Diseases of Esophagus (2018), with corresponding results of MII-ph and oropharyngeal monitoring to diagnose patients with GERD.

But Wilhelm et al. have published a manuscript in 2016 in the UEG Journal, in which the authors have clearly shown, that the Restech measurement System, measures "something" (reflux) in 60% of asymptomatic gastrectomy patients.

Weitzendorfer et al. (Laryngoscope, 2020) have also shown, that there is no correlation between MII-pH and oropharyngeal monitoring with the Restech System to diagnose patients with LPR.

In the end, the authors at least state, that there is just a correlation of the results of esophageal pH monitoring and oropharyngeal pH monitoring in 59% of the patients in their series.

How can the authors state, that Restech is a reliable test, without a critical discussion of the present data in the literature?!

Thank you for your comments. We included a paragraph in our discussion, critically summarizing the current literature on the Restech device and another paragraph in results to summarize non-corresponding test results in our study cohort. As stated before, we believe, in accordance with the literature and our previous studies, that esophageal and laryngopharyngeal pH monitoring complement each other and in combination create a reliable test for GERD and LPR. We are well aware of other studies showing other data on the correlation of both devices. However, many of those studies show low scientific evidence as they included small patient cohorts(n=10-30) or measurements were not performed simultaneously. Due to day-to-day lifestyle changes, no valid statement about the correlation can nor should be made. Wilhelm et al. published that episodes measured by the Restech device are clearly not related to reflux. We agree with the authors that this is an interesting finding. However, since only 10 patients were included in the study and most did not have a valid input of supine and upright periods as evidenced in Table 1 of the respective manuscript with the abbreviation "n.a.", the calculation of the RYAN score can not be rated as being valid at any means. With that in mind, only 2 patients on Wilhelm et al.'s study cohort showed an abnormal test result and unfortunately the authors did not provide any further details about those patients. In addition, no well-established esophageal pH testing was performed to further investigate the origin of those interesting test results. Another interesting study mentioned is the study from Weitzendorfer et al. Unfortunately, we do not know which software was used to analyze results from the Restech measurement. A previous study of our group showed that results obtained by the older software DataView 3 cannot be compared to results obtained by the newer software DataView 4. We include this study in our discussion and overall, we agree that the Restech measurement device alone does not provide a reliable test or screening device for LPR patients. However, we believe that this device is a great addition to the diagnostic pathway and can be very helpful especially in surgical decision-making, and the purpose of this video manuscript is to ensure future researchers and clinicians follow the correct testing protocol established by (2010 DeMeester paper)

Reviewer #2:

Manuscript Summary:
This manuscript have a good presentation.

Major Concerns:
No

Minor Concerns:
1. The legends of the tables were not good enough. Need more informations.
2. How many patients had abnormal laryngopharyngeal reflux and normal esophageal reflux?
3. How many patients had normal layngopharyngeal reflux and abnormal esophageal reflux?

Thank you for your comments. 1. We expanded the legends to improve the description of our figure and two tables. 2./3. We added a paragraph in the results showing how many patients did not have corresponding results.

Reviewer #3:

Manuscript Summary:

This manuscript presents a step-by-step guide to conducting simultaneous esophageal and laryngopharyngeal 24-hour pH monitoring in outpatients using two separate monitoring symptoms. The authors do a good job of describing the diagnostic dilemma that clinicians face in patients with both esophageal and extra-esophageal symptoms, and why simultaneous monitoring may offer additional and valuable information in these cases. Their protocol is well written and easy to follow. The work is innovative as it highlights a way of using two separate systems simultaneously to improve the diagnostic yield for patients with a difficult problem.

Major Concerns:
None.

Minor Concerns:
- The authors include more granular detail for how to use the laryngopharyngeal pH monitoring than for the esophageal monitoring. I suspect this is because they are describing the Restech system, specifically. It may be worth mentioning that multiple different esophageal systems can be used, and/or pointing out if there are any systems the authors would not recommend using.

Thank you for your comments. We added a paragraph in our discussion addressing your comment. We usually use a long probe impedance pH monitoring system for our standardized protocol as well as the Restech device. However, a conventional pH monitoring system or a wireless distal esophageal pH monitoring system may also be used.

- The authors cite their own prior study of 101 patients in the introduction, then describe an analysis of 181 patients with the protocol described. Is the second larger group (n = 181) an extension of the first study, or a separate cohort? I think this should be clarified as I found it confusing and I'm not sure how many patients have actually been tested with this method.

Thank you for your comments. This larger cohort is an extension of the previously published dataset. Overall, 181 patients have been tested at our institution using this standardized protocol. We included a sentence to our results clarifying this.

- Several times, the authors reference their prior work in studying patients post-esophagectomy in which they observed a 100% correlation between esophageal and laryngoesophageal pH monitoring. Has this work been published? If so, it should be cited appropriately. If not, it should be described as such. In either case, I would also have appreciated a bit more explanation as to why this volume-reflux model is important to the clinical utility of the protocol that is described.

Thank you for your comments. The final results of our work have not been published yet, but are currently under peer review. However, we previously published our early experience in post-esophagectomy patients and included the citation in the manuscript as well as more information about this study.

- What should providers know about using this protocol in patients who are ON versus OFF antisecretory therapy (ie PPI)? Is the protocol still valuable in patients ON PPI? If so, how is interpretation different? This is a common issue that comes up and should be addressed in some way.

Thank you for your comments. We included information about our protocol and antisecretory therapy in the manuscript. Patients in our clinic stop PPI therapy 7 days prior to the study to ensure a valid pH measurement off PPI. Both measurements show the highest sensitivity and specificity when the patient is off antisecretory medication.

Reviewer #4:

Manuscript Summary:
Congratulations on the large test group. The simultaneous application of these two studies is difficult, the more should be appreciated the collection of this amount of data

Major Concerns:
- No conclusion
- The proposed protocol is difficult to apply in clinical practice. It is troublesome for the patient and costly

Thank you for your comments. A conclusion is present in the manuscript. However, as this manuscript will be a method paper, no scientific conclusion was made, as this was not the intention of this work.

Minor Concerns:
It seems that the simultaneous performance of tests will not help us determine the usefulness of pharyngopharyngeal pH in the diagnosis of LPR.

Thank you for your comment. We agree that there are many pros and cons to laryngopharyngeal pH testing and the current literature on the usefulness of the device is controversial. As shown in our earlier research, we have based our treatment decision on the results of the two simultaneous tests quite successfully. This standardized protocol helped us to ensure a sufficient diagnostic pathway in patients that presented with mainly atypical symptoms that may or may not be related to GERD. We believe that especially in surgical decision making and in challenging patient cohort's like these, every available diagnostic tool needs to be utilized. Future studies need to further validate laryngopharyngeal pH testing and address controversial questions raised in current literature.

We would like to thank you in advance for considering our manuscript for publication with the included changes.