

# Combined pH-Metry/Impedance Monitoring Increases the Diagnostic Yield in Patients with Atypical Gastroesophageal Reflux Symptoms

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## Key Words

Impedance · GERD · Atypical symptoms · Globus · Hoarseness · pH-metry

## Abstract

**Background:** Globus sensations, hoarseness and chronic cough are suggested to be atypical manifestations of Gastroesophageal Reflux Disease (GERD). The aim of the study was to investigate whether combined pH-metry and multi-channel intraluminal impedance monitoring increases the diagnostic yield. **Methods:** 41 patients with atypical GERD symptoms were included in the study. Globus sensation was the dominant symptom in 23 patients (56.1%). The remaining 18 patients (43.9%) complained mainly about hoarseness or chronic cough. All patients were examined by endoscopy, dual-channel pH-metry and impedance monitoring off-therapy with proton pump inhibitors (PPI). Diagnostic yield of the respective method was determined. **Results:** A total of 26 patients (63.4%) had pathological findings in any method. The highest diagnostic yield was achieved by combined 24-h pH-metry/impedance measurement (61.0%), followed by solely impedance measurement (48.8%), distal pH-metry (29.3%), endoscopy (22.8%) and proximal pH-metry (17.1%). All patients with a positive PPI-test and 25% of patients (5/20) with a negative PPI-test had a pathological result in pH-metry/impedance. **Conclusion:** Multichannel intraluminal

impedance monitoring increases the diagnostic yield for objective detection of atypical manifestation of GERD. Combined 24-h pH-metry/impedance measurement has the best diagnostic yield for detection of gastroesophageal reflux and has therefore the potential to represent a new diagnostic gold standard.

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## Introduction

Gastroesophageal Reflux Disease (GERD) has a high prevalence and an increasing incidence [1, 2]. Apart from typical symptoms – heartburn and acid regurgitation – atypical or extraesophageal symptoms like chronic cough, globus sensations in the throat and hoarseness are often discussed to be caused by pathological reflux of gastric content into the esophagus [3].

The significance of diagnosis and treatment of atypical manifestations of GERD is still a matter of debate [4–6]. Empirical treatment with proton pump inhibitors (PPI) in the double standard dose and response of symptoms is often the first option of diagnosis. However, patients with atypical GERD symptoms usually have a decreased response to probatory PPI-therapy [7]. In addition, placebo respond rates up to 50% are reported [8, 9]. Therefore, it has been suggested that proximal reflux

needs to be objectively identified before treatment. Measurement of proximal esophageal acid exposure time by means of dual-channel pH-monitoring seemed to be an appropriate diagnostic tool and was accounted as the gold standard [10, 11]. However, recent pH-studies do not confirm a causal role of proximal reflux [12, 13].

A new diagnostic approach for atypical GERD symptoms is represented by 24-h multichannel intraluminal impedance (MII) measurement in combination with pH-monitoring. It offers the possibility to determine the quantity and quality of non-acidic and weakly acidic reflux episodes apart from acidic reflux events by exact determination of exposure time and proximal extent of the refluxed bolus [14]. Recently, it has been reported that MII identifies all types of persistent reflux symptoms despite PPI-therapy and the importance of non-acidic and acidic reflux events in patients with atypical symptoms is of clinical relevance [15]. Data on this new method are still sparse and so far MII has not been compared with dual pH-metry in patients with atypical reflux symptoms 'off-PPI'.

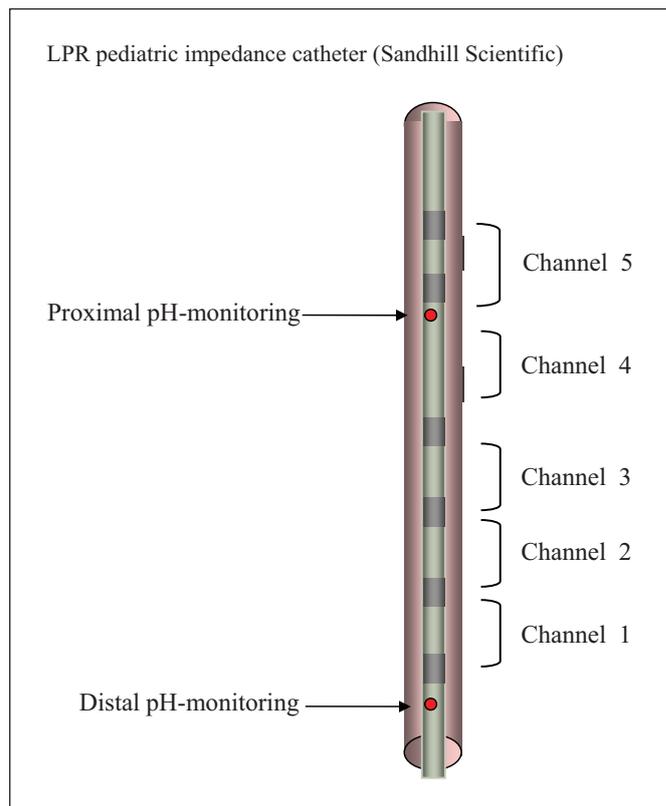
Therefore, the aim of the present study was to evaluate the diagnostic benefit of MII in addition to dual-channel pH-metry and endoscopy in patients 'off-PPI' for at least 14 days. All patients investigated in the present study had predominantly atypical GERD symptoms of either chronic cough, hoarseness or globus sensations.

## Patients and Methods

### Patients

Patients were illegible for inclusion if they have had a malignant disease, were younger than 18, older than 80 years, unwilling to participate, unable to provide informed consent, or suffered from any condition that contraindicates a safe placement of the impedance catheter such as strictures in the esophagus, pharynx or nose. We also excluded patients with an intake of PPI within the last 2 weeks prior inclusion. All included 41 patients suffered from predominant symptoms suspicious for an extraesophageal manifestation of GERD and were investigated in our outpatient clinic between July 2005 and February 2006. 21 patients were males, 20 were of female gender. The mean age was  $54.2 \pm 15.6$  years, mean BMI was  $24.4 \pm 4.2$ . Predominant symptoms were globus sensation in 23 patients (56.1%), hoarseness in 7 patients (17.1%) and chronic cough in 11 patients (26.8%). 39 of the 41 patients (95.1%) were examined by an ENT-specialist or pulmonologist before study inclusion. Among those, 23/39 (59.0%) patients revealed pathological findings (signs of laryngitis or obstruction as determined by pulmonary function test).

40/41 patients were treated with PPIs in at least standard dosage for at least 4 weeks before examinations were performed in accordance with our protocol. Among those, 20/40 (50%) had a positive PPI-test (i.e. improvement of symptoms was noted).



**Fig. 1.** LPR pediatric impedance catheter (Sandhill Scientific). Multiple impedance channels at 6.0, 8.0, 10.2, 12.2, 18.0 and 19.7 cm; distal pH antimon probe at 5 cm, proximal at 17.5 cm from z-line.

### pH-Metry and Impedance Recording

Combined pH-metry/MII monitoring was performed after withdrawing acid suppressive therapy for at least 14 days. Dual-channel pH-metry/MII was recorded with an impedance catheter (Tecnomatix No: ZPI S62C18E; Sandhill Scientific, Colo., USA). Six impedance-electrodes are placed on defined spots on this catheter (6.0, 8.0, 10.2, 12.2, 18.0 and 19.7 cm) to determine the direction and exact localization of the reflux. Furthermore, 2 pH-antimon probes are located in the distal and proximal end of the catheter (fig. 1). The distal antimon probe was placed 5 cm above the manometrically predefined lower esophagus sphincter. For pH-measurement in the proximal esophagus, the second antimon probe was placed 17.5 cm proximal to the lower sphincter. Data were recorded for at least 22 h, uploaded on a personal computer and analysed by using a commercially available software system (BioView, Sandhill Scientific). Gastroesophageal reflux events detected by impedance changes were defined on the basis of previous studies [16–18]. Acidic reflux episodes in the proximal or distal esophagus were counted if the pH fell below 4; all episodes were counted as non-acidic when the pH was above 4. The refluxed gastric content was characterized concerning its composition (gas, fluid or mixed). MII was considered pathological when more than 73 fluid and/or mixed reflux episodes appeared in the

esophagus during 22–24 h or the bolus exposition of gastric contents in the esophagus was more than 2.1% during daytime. pH-Metry of the distal esophagus was considered as pathological when the percentage of time pH below 4 was more than 4%. Proximal pH-metry was considered pathological when the percentage of time pH below 4 was more than 1%. The patients had the possibility to indicate 3 predominant symptoms in the course of the measurement, which was correlated with pathological findings in combined dual-channel pH-metry and intraluminal impedance monitoring. The symptom index was regarded positive if an event was marked within 5 min after the onset of a reflux episode and defined as negative when a documented reflux event occurred without any perceived aggravation of persistent symptoms.

#### Endoscopy

Esophagogastroduodenoscopy (EGD) was performed after withdrawing acid suppressive therapy for at least 14 days. Examinations were performed after an overnight fast using standard endoscopes (Olympus GIF 140 or GIF 160). Absence or presence of refluxesophagitis was noted. Classification of refluxesophagitis was graduated in accordance to the Savary-Miller or Los Angeles Classification.

#### Statistics

Data are shown in a descriptive manner. Differences between symptom clusters (globus vs. hoarseness/chronic cough) were analyzed by  $\chi^2$ /Fisher's exact test or Mann-Whitney U test, where appropriate. A  $p < 0.001$  was regarded as statistically significant after adjustment with the Bonferroni method. For all calculations SPSS for Windows 14.0 software package (SPSS, Chicago, Ill., USA) was used.

## Results

A pathological finding of gastroesophageal reflux was found in 26/41 patients (63.4%) if at least one pathological result was present in either endoscopy, distal pH-metry, proximal pH-metry or MII.

Table 1 summarizes the diagnostic yield obtained with the respective methods. Proximal acidic reflux did not occur as a single phenomenon in any of the patients. None of the patients investigated had refluxesophagitis higher than grade Ib according to the Savary-Miller or Grade B according to the Los Angeles Classification. There was only one patient who had reflux esophagitis determined by endoscopy but no pathological finding in pH-metry and/or impedance recording. Four patients (9.8%) had exclusively positive pH-metry and 7 patients (17.1%) had a pathological impedance measurement without further pathological findings.

When data were analyzed for potential differences between patients with globus vs. hoarseness/chronic cough, no differences were observed ( $\chi^2$ / Fisher's exact test: all  $p > 0.4$ ). Pathological reflux was detected by any of the methods applied in 14/23 (60.9%) patients with predominantly globus and in 12/18 (66.7%) patients with predominantly hoarseness/chronic cough ( $p = 0.794$ ).

**Table 1.** Frequency of a pathological result (diagnostic yield) of the respective methods as applied (see Methods)

	Patients	Percentage
Endoscopy	11/41	22.8
Proximal pH-metry	7/41	17.1
Distal pH-metry	12/41	29.3
Impedance measurement	20/41	48.8
Combined pH-metry/impedance	25/41	61.0

Patients often showed pathologic findings in more than one method.

**Table 2.** Results of MII measurement comparing patients with globus ( $n = 23$ ) and those complaining about chronic cough or hoarseness ( $n = 18$ )

	Globus, median (min–max)	Cough/hoarseness, median (min–max)	p (Mann-Whitney U test)
Gas-reflux events	22 (5–73)	25.5 (5–58)	0.351
Liquid-reflux events	21 (4–74)	36.5 (12–173)	0.013
Mixed-reflux events	25 (0–52)	33 (4–83)	0.503
Acid-reflux events	38 (0–82)	44.5 (2–157)	0.312
Non acid events	27 (12–74)	39 (11–92)	0.916
Distal acid reflux time	2.2% (0–8.4)	2.2% (1–13.2)	0.599
Bolus reflux time	1.6% (0.3–4.1)	2.0% (0.8–9.6)	0.057
Total reflux events	78 (22–134)	79 (11–92)	0.118
Symptom index negative	67 (22–131)	76 (50–237)	0.659

Table 2 shows results of the impedance measurement comparing patients with globus and patients with cough and hoarseness. Data are stratified for characteristics of reflux events, time of occurrence and association with symptoms. As demonstrated, except for number of liquid refluxes there were no significant differences with respect to the type of symptoms experienced. Reflux occurred in most cases at daytime. Pathological events were rarely perceived by the patients in form of an aggravation of chronic symptoms (positive symptom index).

All patients with a previously positive PPI-test also had pathological findings in combined distal pH-metry/MII. On the other hand, there were 5 of the 20 patients (25%) with a previously negative PPI-test who had a pathological pH-metry/MII.

Comparing patients with pathological findings from the ENT-specialist or pulmonologist and patients with normal results in pulmonological or laryngoscopic examination, there was no difference detectable in the outcome of any of the applied methods.

## Discussion

The superiority of combined MII/pH-metry compared with pH-metry in the diagnosis of GERD is already proven. However, data which have been published are based on patients with typical GERD symptoms or on patients which were monitored under acid suppressive therapy [14, 15, 27]. To the best of our knowledge, this is the first study to investigate patients 'off-PPI' with atypical GERD symptoms by means of combined dual-channel pH-metry/MII and endoscopy. Whether MII improves the diagnostic value on gastroesophageal reflux disease management in patients 'off-PPI' is discussed controversially and data on this topic are still sparse [19, 20].

According to our data, 63.4% of patients suffering from globus, hoarseness and/or chronic cough had a pathological finding in any of the applied methods (endoscopy, dual-channel pH-metry and impedance recording). However, combined distal pH-metry/impedance measurement had the highest diagnostic yield with 61.0% in comparison to endoscopy or dual-channel pH-metry where only around a quarter of all patients revealed pathological findings. These data suggest that impedance recording should be included in the diagnostic work-up of patients with atypical GERD.

It might be argued that it is not necessary to do examinations in patients with symptoms suggestive for atypical manifestations of GERD since a trial of PPI is

enough for establishing a diagnosis by symptomatic response after therapy. The fact that all patients who felt a symptom relief after the intake of PPI had a pathological combined dual-channel pH-metry/MII allows us to assume that GERD patients with chronic/persistent symptoms were mostly identified by combined dual-channel pH-metry/MII. However, there were also 5 among the 20 patients with a negative PPI-test who had a definite pathological finding in pH-metry/MII. Therefore, 25% would have been regarded as not suffering from GERD despite detection of pathological gastroesophageal reflux. These patients might be medicated with a higher dose rate PPI or treated with long-term medication (e.g. for at least 3 months).

Data of the present study show that 36.6% of the patients had no pathological finding in any performed method. The suspected atypical manifestation of GERD might therefore be questioned in these cases. Taking into account the costs associated with a probatory PPI-therapy and the questionable therapeutic benefit, one might therefore argue that PPI-therapy is not useful in all patients with a negative pH/impedance measurement. Of course, there might be individual cases with an unambiguous symptom index or borderline results who benefit from PPI-therapy. Further placebo-controlled studies appear helpful to further investigate such patients. Up to this timepoint, exclusively combined pH/impedance monitoring seems to have the potential to lead to a more accurate confirmation of GERD as a cause of atypical symptoms.

Dual-channel pH-metry has been regarded as the most appropriate method for objective measurement of atypical GERD before MII was integrated into the clinical work flow. However, in some clinical trials dual pH-metry could not predict the severity of patients' symptoms [12]. In addition, there is a lack of consensus for reference values for proximal esophageal measurements [6, 21]. Some have suggested that proximal acidic reflux is mostly a pathological event [11], whereas others found proximal reflux in a considerable percentage even in healthy volunteers [21]. In our study, 24-h monitoring of pH in the proximal esophagus did not provide any additive information and may be regarded of little value. This has also been stated by others [12, 22, 23]. Another shortcoming of pH-metry is the fact that this method can only detect acidic reflux but not non- or weakly acidic reflux episodes; furthermore, it has to be stated that dual-channel pH-metry may also be inaccurate due to the difficult placement of the proximal pH sensor in patients with shortened esophagi [28].

Apart from functional determination of reflux events, some clinicians regard laryngoscopy as a useful adjunct. Defects of the thin epithelium of the larynx caused by refluxed acidic or other gastric contents can be detected [24]. The major con to this technique is, however, the prevalence of similar laryngoscopically detected pathological findings in healthy volunteers [25]. Patients investigated in our study had no different outcome in any of the applied methods, no matter if they had a pathological finding in laryngoscopy. This approves the already suspected limited value of laryngoscopy for the establishment of the diagnosis of GERD and the therapeutic benefit from PPI [7].

All these considerations demonstrate that the diagnostic approach to patients with a clinical suspicion of an atypical manifestation of GERD has so far been insufficient. According to our data these limitations might be resolved by MII monitoring. MII had by far the highest diagnostic yield. Indirect evidence for the usefulness of MII detecting reflux events comes from another recently published retrospective study showing a positive outcome in treating patients with fundoplication who had

persistent GERD symptoms despite PPI-therapy but a pathological symptom index in MII [26]. Nevertheless, assessment of symptom index appears to be difficult particularly in patients with atypical GERD. Here, the symptom index cannot be appreciated similar to patients with typical symptoms like heartburn or regurgitation. Atypical reflux symptoms (such as hoarseness or globus) usually persist continuously. Hence, it is somewhat problematic for those patients to mark an atypical reflux event at a single timepoint.

Further studies have to prove if patients with chronic symptoms suspicious for an atypical manifestation of GERD and objectified pathological findings in combined MII/pH-metry will respond to PPI-therapy or surgery for augmentation of the antireflux barrier in comparison to those who are treated empirically without any objectified pathological finding. Up to this timepoint, combined 24-h pH-metry of the distal esophagus and MII measurement should be regarded as an important part in the diagnostic work-up in patients with symptoms suggestive for atypical manifestation of GERD.

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