Reflux Monitoring: On or Off Therapy?

Michael F. Vaezi, MD, PhD, MSc(Epi)[1]

Am J Gastroenterol 2011;106:183–185; doi:10.1038/ajg.2010.318

The role of esophageal pH (or impedance) monitoring in diagnosing gastroesophageal reflux disease (GERD) has evolved over the years. In the era of empiric therapy with potent acid-suppressive agents such as proton pump inhibitors (PPIs), esophageal reflux monitoring is often reserved for patients with PPI-refractory symptoms (1,2). Given the complexity of patient presentations, technological advancement, and emerging data in the field of GERD, two essential questions need to be addressed: (i) What are the indications for esophageal pH testing in patients suspected to have GERD? (ii) If patients do not respond to aggressive acid suppression, what is the likelihood that they still have reflux; and should the testing be performed at baseline (i.e., off therapy), or is it more important to know whether there is continued reflux despite therapy (i.e., on therapy)?

Indications for esophageal pH or impedance monitoring (Table 1)

An empiric trial with a PPI is the recommended initial approach in all patients initially suspected to have GERD-related symptoms (1). Empiric PPI therapy has a high sensitivity although variable specificity in diagnosing GERD (3). A positive response to an empiric PPI trial is presumed to suggest GERD as the cause of patients' symptoms. In this setting there is no indication for pH or impedance monitoring unless the patient is unwilling to continue with therapy for cost or compliance reasons or is having adverse side effects despite clinical benefit. These scenarios may necessitate surgical fundoplication as the alternative therapy for GERD in the PPI-responsive group, the rationale being to make sure that patients have objective documentation of the disease for which they will undergo an intervention. Prior symptomatic response to PPI trial is of critical importance for this indication. Additionally, patients who have undergone surgical or endoscopic therapy but continue to have symptoms of reflux after surgical intervention should also undergo esophageal testing in order to determine whether their symptoms are secondary to reflux and to help prevent unnecessary therapy with medications such as PPIs or H_2 blockers. In this setting it is intuitive that the test should be performed off PPI therapy. The goal of pH testing in this group, who were already determined to have reflux before their surgical intervention, is to evaluate for failed or dysfunctional wrap.

Adequacy of acid control in those with complicated GERD, such as Barrett's esophagus, is a less commonly used indication for pH monitoring, in which case, by indication, it would need to be performed on therapy. However, in the majority of patients with Barrett's esophagus, symptomatic, not pH, control is the clinical marker used by physicians. pH or impedance monitoring is also recommended in patients who are refractory to empiric PPI therapy. In fact, this is now the most common indication for performance of esophageal reflux monitoring. It is in this group that the role of pH or impedance monitoring is controversial. Which test should be performed (impedance or pH monitoring), and should it be performed off or on PPI therapy?

Reflux monitoring then and now

The original role of pH testing when it was first introduced was to define the presence of reflux in symptomatic patients with normal upper endoscopy. Patients with classic symptoms of reflux, such as heartburn and regurgitation, with normal endoscopy underwent 24-hour ambulatory pH testing to show whether their symptoms were due to abnormal esophageal acid exposure before implementation of therapy. This was in the era of less optimal acid-suppressive therapy, such as H_2-receptor antagonists, necessitating the added physiologic confirmation of GERD. However, over time and with the advent of more aggressive acid suppression with PPIs, there has been dilution in the specificity of pH testing for GERD. In patients with normal esophageal acid exposure but a close relationship between the reflux events and their symptom report, symptom indexes such as the symptom index (SI) or symptom association probability (SAP) were added to the pH analysis to help in the diagnosis of GERD (4,5). These measures were preached upon and overzealously adopted by many experts in the field despite the lack of outcome studies to validate their clinical use.

An additional layer of complexity was introduced with the indiscriminate inclusion of symptoms less likely associated with GERD, such as chronic cough, globus, sore or burning throat, chest pain, and hoarseness, as GERD-related (6). Epidemiologic data and prevalence studies, and not outcome data, suggested association between these extraesophageal symptoms and GERD, which then increased referral of patients with these chronic symptoms to gastroenterologists' offices. Finally, introduction of a more sensitive reflux monitor, impedance–pH

[1]Department of Gastroenterology and Hepatology and Center for Swallowing and Esophageal Disorders, Vanderbilt University Medical Center, Nashville, Tennessee, USA. **Correspondence**: Michael F. Vaezi, MD, PhD, MSC(Epi), Department of Gastroenterology and Hepatology, Vanderbilt University Medical Center, 1660 TVC, Nashville, Tennessee 37232, USA. E-mail: michael.vaezi@vanderbilt.edu

monitoring, allowed detection of reflux of any constituency (liquid or gas) and pH (acid, weakly acid, or non-acid) (7). As expected, prevalence studies soon followed suggesting a relationship between weakly acid or non-acid reflux and residual symptoms in patients suspected to have GERD (8–10). However, no outcome data have proven this relationship. Thus, over time, since the initial uses of pH monitoring, there has been an erosion of the specificity of reflux detection as sensitivity has increased, with minimal outcome data to help clarify the generated confusion.

It is important to recognize and accept that the use of empiric therapy with PPIs has changed the role of esophageal reflux testing. The most important value of pH or impedance monitoring is no longer in defining the presence of GERD but rather in its exclusion—especially as esophageal reflux monitoring is now most commonly used in those with symptoms "refractory" to PPI therapy, who most likely do not have the disease for which they are being tested. What defines refractory symptoms in GERD is different in the United States compared with European countries. In the latter, poor response to once-daily PPI therapy is considered refractory, whereas in the former, patients are considered refractory after partial or incomplete response to twice-daily PPI therapy. I favor saving any esophageal reflux testing until after the patient has had at least two months of twice-daily PPI therapy, reserving diagnostic testing (pH and/or impedance monitoring) for those with poor response to aggressive acid suppression. At this juncture, the decision to proceed with esophageal pH or impedance testing off or on PPI therapy would then depend on pretest likelihood and diagnostic value in each scenario.

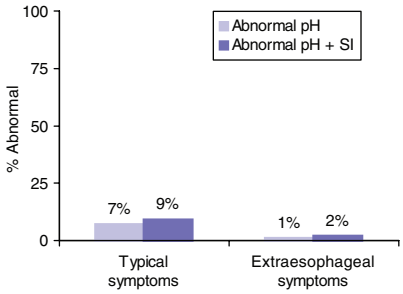

Figure 1. Prevalence of abnormal pH or abnormal pH + SI (symptom index) in patients with typical reflux and in those with extraesophageal symptoms on twice-daily proton pump inhibitor therapy. Note the low prevalence in both groups whether or not SI is utilized in addition to pH parameters.

Likelihood of reflux in PPI-refractory patients on or off PPI therapy

It is agreed that ambulatory pH testing in PPI-refractory symptomatic patients is most likely to be normal if performed on therapy (11) (**Figure 1**). Only 1% of patients with extraesophageal and 7% of those with typical reflux symptoms had abnormal distal esophageal acid exposure when they were tested on twice-daily PPI therapy. Addition of SI did not dramatically change these values: 2% and 9%, respectively (**Figure 1**). Impedance monitoring testing on twice-daily therapy increases the likelihood of abnormality to only 37%, on the basis of a study in a large group of PPI-refractory patients (9). Thus, on therapy, esophageal testing with impedance or pH is most likely to be normal—63% or 99%, respectively—suggesting that GERD is not the cause of patients' persistent symptoms. In this setting, a search for non-GERD causes should be initiated. The criticism of this approach is that we will not know whether the patient has reflux at baseline. The counterargument to this criticism would be that knowledge of baseline reflux status in this group of patients does not help answer why they continue to have symptoms while on twice-daily PPI therapy.

Advocates of off-therapy testing argue that normal esophageal reflux parameters at baseline would exclude the likelihood that the patients' symptoms are reflux-related. However, a recent study suggests that the majority (72%) of patients refractory to twice-daily PPI therapy would actually have abnormal esophageal acid exposure if tested off PPI therapy (12). In this case, off-therapy testing only confirms GERD but does not explain the persistence of symptoms while on therapy. However, should future studies suggest that, in a subgroup of patients, pH testing off therapy is more likely to be normal, then off-therapy testing may be more useful. Additionally, a more recent study suggested that using SAP off therapy resulted in higher "yield" than on-therapy testing, 50% vs. 37%, respectively, advocating for off-therapy testing in this group of patients (13). However, higher SAP values off PPI therapy again do not explain the reason for poor response to PPI therapy in this group of patients. This further highlights the inappropriateness of SAP as a secondary marker for reflux-related symptoms. Recent studies have questioned the clinical utility of SI or SAP, especially in patients with refractory symptoms suggesting poor test performance (14). SI and SAP measures depend highly on the number of reflux events and the value of percent time pH <4; thus, it is not surprising that SI and SAP values might be higher off therapy (with a higher likelihood of reflux events) than on PPI therapy.

Table 1. Indications for esophageal pH monitoring

1.	Documentation of abnormal esophageal acid exposure in endoscopy-negative patients considered for endoscopic or surgical antireflux procedures
2.	Patients who have undergone endoscopic or surgical reflux therapy who continue to have symptoms of gastroesophageal reflux disease (GERD)
3.	Assessment of adequacy of acid control in patients with complicated GERD, such as Barrett's esophagus
4.	Evaluation of PPI-refractory patients (most common indication)

Conclusions and what to do

Until we have better outcome data, given the effectiveness of empiric therapy, I recommend using patients' response to aggressive acid-suppressive therapy as the guide to whether or not GERD might be playing a role in their symptom complex. Complete lack of response to twice-daily

PPI therapy should sound clinical alarms about the causal association between reflux and patients' complaints. The objective of further testing with pH or impedance monitoring should be to exclude reflux, which can most likely be done (63% or 99% of tests, respectively) if the test is performed on PPI therapy. Knowledge of baseline esophageal reflux parameters in this group, especially using secondary unproven markers such as SI and SAP, results only in additional tests to prove what is already established by patients' lack of response to aggressive PPI therapy. Let's not forget that the value of testing with esophageal pH or impedance monitoring in patients refractory to twice-daily PPI therapy is not in identifying reflux as the cause of patients' persistent symptoms. Rather, it is to document that GERD is not the cause, and a search for non-GERD causes should next be pursued.

CONFLICT OF INTEREST

Guarantor of the article: Michael F. Vaezi, MD, PhD, MSc(Epi).

Financial support: None.
Potential competing interests: None.

REFERENCES

1. Kahrilas PJ, Shaheen NJ, Vaezi MF. American Gastroenterological Association Institute technical review on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1392–413.e5.
2. Hirano I, Richter JE. ACG practice guidelines: esophageal reflux testing. Am J Gastroenterol 2007;102:668–85.
3. Numans ME, Lau J, de Wit NJ *et al.* Short-term treatment with proton-pump inhibitors as a test for gastroesophageal reflux disease: a meta-analysis of diagnostic test characteristics. Ann Intern Med 2004;140:518–27.
4. Wiener GJ, Richter JE, Copper JB *et al.* The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. Am J Gastroenterol 1988;83:358–61.
5. Weusten BL, Roelofs JM, Akkermans LM *et al.* The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. Gastroenterology 1994;107:1741–5.
6. Vakil N, van Zanten SV, Kahrilas P *et al.* The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900–20.
7. Shay S. Esophageal impedance monitoring: the ups and downs of a new test. Am J Gastroenterol 2004;99:1020–2.
8. Vela MF, Camacho-Lobato L, Srinivasan R *et al.* Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology 2001;120:1599–606.
9. Mainie I, Tutuian R, Shay S *et al.* Acid and nonacid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398–402.
10. Sifrim D, Holloway R, Silny J *et al.* Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24-hour pH-impedance recordings. Gastroenterology 2001;120:1588–98.
11. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol 2005;100:283–9.
12. Pritchett JM, Aslam M, Slaughter JC *et al.* Efficacy of esophageal impedance/pH monitoring in patients with refractory gastroesophageal reflux disease, on and off therapy. Clin Gastroenterol Hepatol 2009;7:743–8.
13. Hemmink GJ, Bredenoord AJ, Weusten BL *et al.* Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? Am J Gastroenterol 2008;103:2446–53.
14. Slaughter JC, Goutte M, Vaezi MF. Neither SI or SAP are reliable tools for assessing symptoms and reflux events [abstr]. Gastroenterology 2010;138(Suppl 1):S487.