

ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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Use of Symptom Indices in the Management of GERD



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G&H Why have symptom indices been developed for the management of gastroesophageal reflux disease?

MFV Symptom indices, such as the symptom index (SI) and symptom association probability (SAP), were developed in order to assess the relationship between patients' reported symptoms and esophageal acid or nonacid. We treat many patients who we suspect have reflux based on their reported symptoms, such as heartburn, regurgitation, cough, and chest pain. However, in patients who do not respond to aggressive acid suppressive therapy, we utilize pH or impedance testing in order to determine the role of acid and/or nonacid reflux. It is in this setting that the SI and SAP are commonly utilized.

G&H How are the SI and SAP calculated, and how do they compare?

MFV The SI is the percentage of reflux-related symptom episodes during the study period. For example, if a patient has 10 reported symptoms and 7 of them are associated with reflux events during ambulatory pH or impedance monitoring, the SI for this patient's symptoms would be 0.7 (7/10). Typically, an SI value greater than 0.5 is considered clinically relevant. The SI has been critiqued because it does not incorporate the total number of reflux events in its calculation. A high SI value may simply be due to a patient having many reflux episodes and randomly pushing the event button once at the right time (ie, chance association).

Table 1. A 2×2 Contingency Table of Symptoms and Reflux for Calculating the Symptom Association Probability

	Symptoms	No symptoms
Reflux	S ⁺ R ⁺	S ⁻ R ⁺
No reflux	S ⁺ R ⁻	S ⁻ R ⁻

The SAP was subsequently developed in an attempt to address this limitation. SAP calculation is based on constructing a 2×2 contingency table with positive symptoms and positive reflux (S⁺ R⁺), negative symptoms and positive reflux (S⁻ R⁺), positive symptoms and negative reflux (S⁺ R⁻), and negative symptoms and negative reflux (S⁻ R⁻; Table 1). The Fisher exact test is then applied to calculate the probability that the observed association between reflux and symptoms occurred by chance.

The superiority of the SAP over the SI is based on the fact that the SAP is a simple statistical method that uses all relevant observations. The original study by Weusten and colleagues suggested that the SAP would be a better measure of association between patients' symptoms and reflux events and included the following important observations: the superiority of the SAP was solely based on its statistical nature, thus arguing for its objectivity; the study focused on correlating the findings between the SI and SAP and was not outcome-driven; and, similar to earlier studies for the SI, the group of patients who were studied had not failed proton pump inhibitor (PPI) therapy before testing and, thus, repre-

sented a group of patients different than the group for whom pH testing is currently recommended.

G&H In which reflux patients are these indices usually used?

MFV The most common indication for the use of pH or impedance-pH monitoring is patients who fail an initial empiric trial of acid suppressive therapy. In this group of partial or nonresponders to PPI therapy, many physicians advocate the use of either the SI or SAP to help identify an increased likelihood that patients' continued symptoms might be reflux-related. However, this group of patients is also the group most likely not to have reflux at all. Thus, the use of any currently available index must be guarded, and the results must be interpreted with caution.

G&H Have any studies examined the accuracy or reliability of these indices?

MFV There are limited outcome studies assessing the accuracy or reliability of any index for gastroesophageal reflux disease. The original studies were observational in nature, and subsequent studies have used the indices with the assumption that they provide useful data. However, an early study conducted by Taghavi and colleagues suggested that neither the SI nor SAP was optimal in predicting response to therapy. Using response to therapy as the outcome, the authors suggested that the positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity for the SI and SAP were not optimal (SI: PPV=73%, NPV=44%, sensitivity=80%, specificity=35%; SAP: PPV=79%, NPV=58%, sensitivity=73%, specificity=65%).

The belief that these instruments have previously been validated based on outcome-driven studies has become popular. This is not true. In fact, the original studies of the SI were conducted in patients who had chest pain, and validation was simply based on the correlation of the SI with the percentage of time that pH was less than 4. In the original study, the authors recommended the use of the SI, not in isolation, but combined with the percentage of time that pH was less than 4. Over time, these indices have become overutilized based on limited data.

More recently, my colleagues and I conducted a cross-sectional study of 254 patients who had a poor response to PPI therapy. We measured the SI and SAP for each patient and determined the range of clinical values for each 2 × 2 contingency table. We next performed a robust Monte Carlo simulation to determine how varying each reflux and symptom parameter might impact the expected value of the SI or SAP. We showed that neither

the SI nor SAP was an adequate means of determining symptom association in gastroesophageal reflux disease patients due to high day-to-day variability and high likelihood values based on chance occurrence. However, we did find that the SI and SAP may be useful in the subset of patients who have high reflux events (pH <4 more than 10% of the time). This finding suggests that if a patient has moderate-to-severe reflux, the SI and SAP are more likely to be reproducible and clinically relevant. However, because most of the patients we currently evaluate fall within the mild reflux category, we do not recommend the use of either the SI or SAP to make clinical decisions, such as whether a patient should undergo surgical fundoplication.

G&H How widespread is use of the SI and SAP?

MFV The SI and SAP are commonly used in both clinical and research settings. Many studies assessing patient symptoms and physiologic reflux monitoring parameters often report one of the indices. Some physicians have suggested that patients undergo surgical fundoplication based on these indices alone, despite lack of response to aggressive acid suppressive therapy. However, I do not recommend this approach. I rely on physiologic tests, not in isolation but combined with patients' history and other test parameters. In a patient with normal findings from esophagogastroduodenoscopy (EGD) and pH and/or impedance monitoring but an abnormal SI or SAP value, I strongly recommend ignoring the latter value and relying on the former findings. However, in a patient with a moderate-to-large hiatal hernia, abnormal findings from pH and impedance monitoring, and reported symptoms of regurgitation, I am more likely to use indices and suggest fundoplication based on the test results in their totality, not in isolation.

G&H What alternative methods are available for managing gastroesophageal reflux disease?

MFV Until better indices are available, I recommend the use of physiologic testing in addition to patient-reported symptoms. It is important to ascertain which specific symptom is refractory to therapy and not assume that all gastroesophageal reflux disease symptoms are refractory. For example, a patient with reflux disease may have heartburn that improves with PPI therapy but also have continued regurgitation that is a volume phenomenon, which may require correction of the gastroesophageal barrier. A different patient who has extraesophageal symptoms, such as cough or asthma, may not have any heartburn but may complain of nighttime regurgitation, which may clue an astute physician to the likelihood of volume reflux. In

addition to these symptoms, physiologic testing with EGD and pH monitoring (while the patient is off PPI therapy) would help determine the patency of the gastroesophageal junction as well as determine the extent and severity of esophageal acid reflux. I consider the information from each of the tests a piece in the important clinical puzzle for a given patient and do not make decisions until the puzzle completes a clinical picture.

G&H Are other indices currently being developed for use in gastroesophageal reflux disease patients?

MFV Some physicians have suggested the use of complicated statistical indices in addition to the SI and SAP. However, I strongly believe that simplicity of our future testing will provide the answer to why patients continue to be symptomatic. Therefore, my colleagues and I are in the process of developing an improved method to detect reflux

based on the chronicity signature of gastroesophageal reflux disease on esophageal epithelium. This simple and minimally invasive test should help avoid unnecessary testing and prolonged treatment for patients who may not have the disease. Until then, I recommend caution in overinterpretation of the symptom indices provided by pH and/or impedance monitoring devices.

Suggested Reading

Slaughter JC, Goutte M, Rymer JA, et al. Caution about overinterpretation of symptom indexes in reflux monitoring for refractory gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2011;9:868-874.

Wiener GJ, Richter JE, Copper JB, Wu WC, Castell DO. The symptom index: a clinically important parameter of ambulatory 24-hour esophageal pH monitoring. *Am J Gastroenterol*. 1988;83:358-361.

Weusten BL, Roelofs JM, Akkermans LM, Van Berge-Henegouwen GP, Smout AJ. The symptom-association probability: an improved method for symptom analysis of 24-hour esophageal pH data. *Gastroenterology*. 1994;107:1741-1745.

Taghavi SA, Ghasedi M, Saberi-Firoozi M, et al. Symptom association probability and symptom sensitivity index: preferable but still suboptimal predictors of response to high dose omeprazole. *Gut*. 2005;54:1067-1071.