Non-acid Reflux: What to Do When You Don't Feel the Burn

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Combined pH-impedance monitoring, in contrast to catheter-based or wireless pH monitoring, detects esophageal reflux episodes independent of pH, thus facilitating testing without discontinuation of antisecretory therapy (proton pump inhibitor, PPI). Specifically, guidelines recommend pH-impedance monitoring while taking PPI for symptomatic patients with prior confirmatory evidence of GERD (proven GERD) such as advanced esophagitis, biopsy-confirmed Barrett's esophagus, peptic stricture, or positive ambulatory reflux monitoring [1, 2], in order to help determine whether so-called non-acid reflux is responsible for persisting symptoms. When pH-impedance testing is performed while taking PPI, the majority of reflux episodes become weakly acidic or weakly alkaline (pH > 4.0), loosely termed non-acidic reflux [3]. In this context, pH-impedance monitoring is more sensitive than pH monitoring alone in the detection of reflux episodes, both acidic and non-acidic [4].

In contrast to distal esophageal acid exposure time (AET) as calculated from pH monitoring, abnormal thresholds for the total numbers of reflux episodes detected with pH-impedance monitoring are not well defined, nor consistently predictive of symptomatic outcomes with medical or surgical antireflux therapy [5, 6]. Although not specifically addressing non-acidic reflux episodes alone, the Lyon Consensus proposes that > 80 total reflux episodes/24 h may be considered abnormal, < 40 reflux episodes/24 h physiologic, and intermediate values inconclusive [7], albeit with low Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence and limited clinical outcome data [2]. These thresholds have only recently been

validated in a randomized, controlled study utilizing magnetic sphincter augmentation (MSA) versus twice daily PPI in regurgitation-predominant GERD. A threshold of > 80 reflux episodes was predictive of symptomatic improvement with MSA, whereas a threshold of < 35 episodes post-therapy predicted both symptom improvement and satisfaction with therapy [8]. Nevertheless, guidance with regard to definitions and thresholds for the numbers of reflux episodes, or how to manage patients with increased numbers of reflux episodes, remains limited in the literature.

In this context, the study by Reddy et al. in this issue of *Digestive Diseases and Sciences* evaluates real-life provider management patterns in patients with increased non-acid reflux, defined as > 80 reflux episodes with physiologic AET (< 4%) as determined by pH-impedance monitoring performed while taking antisecretory therapy [9]. Of 43 patients managed almost exclusively by gastroenterologists over a three-year period at the University of Michigan, no additional intervention was the most common approach (found in almost half their cohort), potentially reflective of the lack of management guidance in the literature. When recommended, interventions varied greatly and included baclofen, surgical evaluation for hernia repair and/or fundoplication, neuromodulators, antacid therapies, prokinetics, and lifestyle changes. Interventions were more likely with positive reflux-symptom association (RSA) using symptom index or symptom association probability, which was present in nearly two-thirds (28/43) of the cohort. 79% of these patients with positive RSA had recommended changes in management, compared with 29% of those without RSA.

The authors use the term “non-acid reflux” to define all reflux episodes identified in their on-PPI pH-impedance cohort. Two points of caution regarding interpretation: automated reflux episode detection is inaccurate, with significant overcall especially of non-acidic reflux episodes [10]. Even experts disagree on what constitutes a reflux episode as measured with pH-impedance monitoring [11, 12]. Further, even with testing performed while taking PPI, some proportion of the reflux episodes are acidic. This distinction is relevant clinically, as RSA with acidic reflux events

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(acid hypersensitivity) while taking PPI therapy can predict suboptimal symptomatic outcomes from escalation of antireflux therapy, guiding management toward pain modulators [13]. RSA with all impedance-detected reflux episodes, both acidic and non-acidic (reflux hypersensitivity), might suggest refractory GERD if the primary symptom is regurgitation [4, 6], whereas if the primary symptoms are heartburn or chest pain, a functional syndrome is more likely [14]. An important caveat is the rumination syndrome, which can also manifest as regurgitation, and needs to be diagnosed based on regurgitation patterns as seen with pH-impedance monitoring in conjunction with a compatible clinical history [15]. Additionally, other supportive evidence, such as a hiatus hernia, can sway diagnosis toward GERD [13], with potential to benefit from antireflux surgery [16, 17].

Given the presence of reflux esophagitis (9/39), Barrett's esophagus (8/39), and hiatus hernias (20/43) among the Reddy et al. cohort, some proportion likely had true GERD. On the other hand, others likely had symptom generation from visceral hypersensitivity, overlapping with GERD. Therefore, since several phenotypes can coexist within RSA categories, appropriate management requires personalized care and precision recommendations specific to the clinical setting for each patient, taking into consideration the initial symptoms, data from ancillary tests, and results of treatment trials.

Returning to the issue of increased numbers of non-acidic reflux episodes, this study by Reddy et al. demonstrates the wide variability of real-life practice patterns in the setting of physiologic AET. This study also highlights how the decision-making process needs to start *prior* to performing pH-impedance monitoring, as all patients should have proven GERD when the study is performed while taking PPI therapy. Thus, pH-impedance monitoring on therapy should represent a fork in the road—one management direction if certain characteristics are fulfilled, and other different approaches if not, forming the foundation of personalized care. While the current study was not designed to evaluate therapeutic outcomes and does not provide evidence for proven GERD prompting reflux monitoring while taking PPI therapy, the varied management decisions implemented suggest that the experienced gastroenterologists at the University of Michigan were indeed personalizing care for their patients as best they could, taking clinical characteristics and results from ancillary tests that were not formally presented in the study into consideration. Nevertheless, their findings illustrate the need for further study of the definition and significance of elevated numbers of reflux episodes in clinical practice, with assessment of standardized outcomes, reflux monitoring data on and off PPI therapy, and comparisons of therapeutic approaches.

In summary, advances in esophageal diagnostics such as combined pH-impedance monitoring come with a

responsibility to provide guidance on how to interpret and utilize the data acquired in order to further the clinical care of our patients. Although combined pH-impedance monitoring enables the detection of reflux episodes independent of acidity, for performance of testing on PPI therapy, and for potential augmentation of the yield of RSA, the present study stresses the need for clinicians to understand how to use this added information in order to improve patient management.

Compliance with Ethical Standards

Conflict of interest CPG discloses consulting and speakers' bureau relationships with Medtronic, Diversatek, Ironwood, Isothrive, and Quintiles. AH and AP do not declare any pertinent conflicts.

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