

EDITORIAL

Dilated Intercellular Spaces: Extending the Reach of the Endoscope

Two manuscripts in this issue utilize quantitative methods to analyze the association between gastroesophageal reflux disease (GERD) and dilated intercellular spaces (DIS) evident on transmission electron microscopy of the esophageal epithelium. One study of 20 patients found that, irrespective of whether or not a pH study was positive, all GERD patients who had responded to proton pump inhibitors therapy had intercellular space measurements that were at least twice normal. The other study demonstrated that DIS resolved with effective GERD therapy in essentially every instance. Both studies suggest that DIS are an objective structural marker of endoscopy-negative reflux disease.

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Along with the seemingly ubiquitous application of proton pump inhibitors (PPIs), the therapeutic frontier in gastroesophageal reflux disease (GERD) has shifted. The resolution of esophagitis, an elusive therapeutic target a mere 15 years ago, has become passé with emphasis now being focused on an even more elusive target; symptom resolution, in particular, heartburn. Along with this shift, the utility of endoscopy as a diagnostic tool in GERD is eroding. Rarely embarked upon as an initial evaluation, endoscopy is now generally reserved for the evaluation of patients with failed or imperfect symptomatic response to PPI therapy. Although eminently pragmatic, the problem with that approach is that endoscopy then becomes quite insensitive in diagnosing GERD. The minimal lesions detected by endoscopy (mucosal breaks in the Los Angeles classification scheme of esophagitis) are relatively easily resolved by PPIs. Thus, even if they had been present prior to PPI therapy, mucosal breaks will have healed by the time of endoscopy. Hence, the appeal of a more sensitive histopathological marker of reflux injury. A prime candidate for this role is the finding of DIS in the squamous epithelium, the subject of two manuscripts in this issue of the journal (1, 2).

The acid-sensitive nociceptor model of GERD holds that heartburn is elicited by chemo-stimulation of intraepithelial nerve endings located either within or immediately beneath the stratified squamous epithelium of the esophageal mucosa. Noxious refluxate gains access to and stimulates these nerve endings as a consequence of increased permeability of the esophageal epithelium that is, in itself, a consequence of acid/pepsin injury to that epithelium. Physiological studies have quantified this increased epithelial permeability using Ussing chamber studies of rabbit esophageal epithelium and epithelial potential difference measurements in humans. Several key observations have emanated from those investigations: (i) luminal exposure to acid and pepsin reduces

the transepithelial electrical resistance of esophageal mucosa without producing gross epithelial erosions (3), (ii) reduced transepithelial resistance is associated with increased epithelial permeability to large molecules (potentially including 6 kd epidermal growth factor which could then gain access to and initiate replication in the basal cell layer of the epithelium) (3), (iii) that some endoscopy-negative GERD patients with reduced esophageal epithelial resistance demonstrate normalization of that epithelial resistance after PPI therapy (4), and (iv) that the morphometric marker of increased epithelial permeability is of DIS on transmission electron microscopy studies of esophageal epithelial biopsy specimens (5). Until now, the missing pieces in this puzzle have been whether or not the DIS marker by itself is a sensitive and specific marker of endoscopy-negative reflux disease and whether or not its resolution correlates with treatment responsiveness. Studies published in this issue of the journal by Cicala *et al* and Calabrese *et al* shed substantial light on these issues.

Both the Calabrese study (1) and the Caviglia study (2) utilize quantitative methods to analyze the association between GERD and DIS of the esophageal epithelium. In the Caviglia study, 20 patients with endoscopy-negative reflux disease and 7 asymptomatic controls were studied; 9 reflux patients had abnormal esophageal acid exposure by pH monitoring and 11 had normal acid exposure values. Endoscopy-negative reflux disease was defined by the presence of typical GERD symptoms (heartburn and regurgitation) for at least 6 months that was responsive to PPI treatment. They found that, irrespective of the pH data, all GERD patients had intercellular space measurements that were at least twice normal leading to the conclusion that DIS is an objective structural marker of endoscopy-negative reflux disease. The Calabrese study analyzed the responsiveness of the DIS lesion to PPI therapy in a group of 38 symptomatic patients; 22 with endoscopy-negative disease, and 16 with esophagitis. All endoscopy-negative patients had quantitatively abnormal esophageal acid exposure on pH monitoring. All patients were initially found to have DIS (2.5× normal on average) with no significant difference between the endoscopy

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negative and esophagitis patients. After 3 months of therapy with 40 mg of omeprazole daily, 92% of patients showed complete recovery of the DIS and resolution of heartburn. Of the three nonresponders, two responded to an additional 3 months of PPI therapy with both DIS recovery and heartburn resolution while one patient failed to respond in either domain. The authors conclude that recovery of DIS was accompanied by heartburn resolution in all cases.

One of the paradoxes of therapeutic trials targeting patients with endoscopy-negative reflux disease is that the demonstrated therapeutic response to PPIs is less impressive than is the response in an esophagitis population when gauged by the resolution of the esophagitis. Several potential explanations have been offered to explain this, one of which is patient heterogeneity. The crux of that argument is that heartburn is a nonspecific symptom potentially arising from chemostimulation, mechano-stimulation, or even hyperalgesia (6). As such it can be a manifestation of a number of disorders in addition to GERD. While some of those conditions such as achalasia or eosinophilic esophagitis are readily detected by other investigations, hyperalgesia and even more so, "functional heartburn", are often diagnosed only after an arduous path involving a multitude of investigations and trialed therapies. Clearly, there is a need for better diagnostic methods in this arena and a broader study of DIS may well shed light on the area. The studies of Calabrese and Civiglia reported herein are very helpful in this regard. However, it is important to also recognize the limitations of these studies. These were carefully selected patient; in one study they all had quantitatively abnormal esophageal acid exposure and in the other they all had demonstrated responsiveness to PPI therapy. Hence, one could argue that these patients all belong to the endoscopy-negative population that physiologically behaves identically to an esophagitis population but is simply beyond the detection sensitivity of the endoscope (7). It would be of great interest to extend this analysis to a broader, less selected, group of heartburn patients. Are DIS found in the acid sensitive esophagus or esophageal hyperalgesia? Are DIS found in "functional heartburn" or is that entirely a CNS mediated phenomenon?

The potential applicability of DIS to clinical trials in GERD is appealing. After all, the limited sensitivity of endoscopy and the reproducibility/tolerability issues with esophageal pH monitoring are well recognized. If DIS truly correlates with pathological reflux-induced heartburn, then the finding of DIS might very well define an appropriate population for

enrollment in clinical trials of GERD treatments. Furthermore, the resolution of DIS might serve as a rational therapeutic endpoint for such studies. Such criteria would add a degree of objectivity to studies that are otherwise mired in the complexity of symptom severity quantification and quality of life assessment; both difficult endpoints due to notorious variability among subjects. Indeed, an objective marker of GERD with enhanced sensitivity has great appeal; the description of DIS as a marker of reflux injury and healing may well have extended the reach of the endoscope into the ultrastructure domain.

*Peter J. Kahrilas, M.D.
Department of Medicine
Northwestern University's Feinberg
School of Medicine*

REFERENCES

1. Calabrese C, Bortolotti M, Fabbri A, et al. Reversibility of GERD ultrastructural alterations and relief of symptoms after omeprazole treatment. *Am J Gastroenterol* 2005; in press.
2. Caviglia R, Ribolsi M, Maggiano N, et al. Dilated intercellular spaces of esophageal epithelium in non erosive reflux disease patients with physiological acid exposure. *Am J Gastroenterol* 2005;100:543-548.
3. Tobey NA, Hosseini SS, Argote CM, et al. Dilated intercellular spaces and shunt permeability in nonerosive acid-damaged esophageal epithelium. *Am J Gastroenterol* 2003;99:13-22.
4. Carlsson R, Fändriks L, Jönsson C, et al. Is the esophageal squamous epithelial barrier function impaired in patients with gastroesophageal reflux disease? *Scand J Gastroenterol* 1999;5:454-8.
5. Tobey NA, Carson JL, Alkiek RA, et al. Dilated intercellular spaces: A morphological feature of acid reflux-damaged human esophageal epithelium. *Gastroenterology* 1996;111:1200-5.
6. Kahrilas PJ. Clinical vignette: Refractory heartburn. *Gastroenterology* 2003;124:1941-5.
7. Kahrilas PJ. Diagnosis of symptomatic GERD. *Am J Gastroenterol* 2003;98(suppl 1):S15-S23.

Reprint requests and correspondence: Peter J. Kahrilas, M.D., Northwestern University, Feinberg School of Medicine, Division of Gastroenterology, Department of Medicine, 676 N. St. Clair Street, Suite 1400, Chicago, Illinois 60611.

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