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Surgery for Gastroesophageal Reflux Disease:

Esophageal Impedance to Progress?

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In the era that preceded the availability of proton pump inhibitors (PPIs) for the treatment of gastroesophageal reflux disease (GERD), physicians debated about which component of refluxed gastric juice was most harmful - acid, bile salts, or other noxious gastric substances. Those debates largely ceased in the 1990s when numerous studies showed that reflux esophagitis, no matter how severe, healed in the large majority of cases when gastric acid secretion was blocked by PPIs.[1] Today, medical therapy for GERD focuses almost exclusively on the control of gastric acid production with antisecretory medications like PPIs. Despite their great success in healing reflux esophagitis, however, PPIs fail to completely eliminate symptoms attributed to GERD in up to 40% of patients.[2] Furthermore, there have been a recent spate of publications warning of the potential dangers of chronic PPI therapy such as increased risk for pneumonias, *C. difficile* colitis and hip fractures.[3] Clearly, the medical treatment of GERD is far from ideal.

The primary thrust of modern medical therapy for GERD is not to control reflux, but rather to render the refluxed material innocuous by reducing its acidity. In contrast, surgical anti-reflux therapy is designed to eliminate gastroesophageal reflux by performing a fundoplication. Proponents of fundoplication have argued that the chronic reflux of non-acidic gastric material is not innocuous, even though it might not cause reflux esophagitis.[4] Non-acidic reflux can cause symptoms and, in theory, could even contribute to carcinogenesis. The prospect of surgical therapy as a permanent cure for GERD that eliminates complications and obviates the expense, inconvenience and side effects of life-long medical therapy certainly is appealing. Unfortunately, surgery also has substantial risks, and there are few high-quality, long-term studies that have compared directly the safety and efficacy of modern medical and surgical therapies for GERD.

In this issue of *Clinical Gastroenterology and Hepatology*, Lundell et al. report the long-term results of a multicenter, prospective, randomized trial of medical and surgical therapies for GERD.[5] The trial, which began in 1991, randomly assigned 310 Scandinavian patients who had GERD symptoms and erosive esophagitis to receive treatment either with omeprazole or with open antireflux surgery. The follow-up study included 71 (46%) of the original 155 patients in the omeprazole group and 53 (34%) of the original 155 patients in the surgery group. Up to 12 years after randomization, the proportion of patients in continuous remission was found to be significantly higher in the surgical group (53%) than in the medical group (40% if

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the analysis was limited to patients receiving a fixed dose of omeprazole 20 mg daily, 45% if the analysis included patients for whom the omeprazole dose was increased up to 60 mg daily). During the 12-year follow-up, 36% of patients who had a fundoplication subsequently were treated with PPIs, whereas 14% of the patients randomized to the medical group subsequently had a fundoplication. There were no significant differences between the groups in the frequency of GERD complications, but new symptoms of dysphagia, flatulence, and inability to belch or vomit were significantly more common in the surgical group. Nevertheless, there were no significant differences in quality of life scores between the two treatment groups.

This study documents a small, but statistically significant advantage for antireflux surgery in the long-term control of GERD symptoms. Despite this advantage, I find it difficult to fathom why a typical GERD patient would opt for a potentially hazardous operation to fix a problem managed almost as well by a reasonably safe medication. Patients who choose fundoplication because of concerns about chronic medication usage should note that fundoplication did not eliminate the use of PPIs in more than one-third of patients in this study. In addition, a substantial minority of patients developed new symptoms as a result of the operation. Although I strongly suspect that fear of esophageal cancer motivates some GERD patients to opt for antireflux surgery, high-quality studies have not shown a significant cancer-preventive effect for that operation.[6] Indeed, the only patient who developed an esophageal cancer during the 12-year follow-up of this study was in the surgical group.

What I find most distressing about the results of this study is how poorly both the medical and surgical therapies performed in the long-term treatment of GERD. Despite the great efficacy of PPIs and fundoplication for the short-term healing of reflux esophagitis, for the long term this study documents the return of symptoms or endoscopic signs attributed to GERD in approximately one-half of patients treated medically or surgically. Clearly, both forms of therapy leave much to be desired.

The study by Lundell *et al.* is a valuable contribution to our understanding of the long-term outcomes of medical and surgical therapies for GERD. Although patients in this study had open anti-reflux surgery, whereas today the procedure usually is performed laparoscopically, it is not clear that laparoscopic fundoplication is any more effective or durable than the open procedure.[7] Unless there are some fundamental improvements in the efficacy of surgical anti-reflux procedures or major new, disturbing revelations regarding the long-term risks of PPIs, it seems that there is little to be gained by performing further studies with a similar design. The major issue for physicians treating GERD today is not whether to recommend medical or surgical therapy for patients with typical symptoms and endoscopic signs of the disease. For those patients, the small potential advantage afforded by anti-reflux surgery in symptom control simply does not outweigh the risks of the operation.

A major clinical problem today, highlighted by the results of this study, is what to do for patients who have GERD symptoms that do not respond well to PPI therapy. For those patients, the fundamental question is whether their symptoms are due primarily to persistent reflux, i.e. a plumbing problem that might be corrected by an anti-reflux procedure, or to a complex visceral sensation problem that may be better addressed with behavioral therapies or neurotropic medications. With the recent availability of esophageal impedance monitoring, which can detect the reflux of both acidic and non-acidic material, there is now an excellent opportunity to perform definitive studies on the role of anti-reflux surgery for patients with “PPI-refractory” GERD.

Six mechanisms whereby GERD symptoms might persist during PPI therapy, and the clinical tests needed to establish those mechanisms are listed in Table 1. Regarding the first two mechanisms, studies involving 24-hour esophageal pH monitoring have shown that the large

majority of patients who take a PPI twice daily have normal esophageal acid exposure.[8] Exceptions to this rule include patients with long-segment Barrett's esophagus and patients with severe erosive esophagitis, for whom pathological levels of acid reflux frequently persist despite high-dose PPI therapy.[9] For the third mechanism, esophageal impedance monitoring now can establish that symptoms are associated with the reflux of non-acidic material.

Mainie *et al.* used a combination of esophageal pH and impedance monitoring to study 144 patients who had persistent GERD symptoms during antisecretory therapy, and found that 48% had a positive symptom index, suggesting a significant association between symptoms and reflux episodes.[10] In 11% of cases, the symptoms were associated with "normal" episodes of acid reflux that persisted despite PPI therapy (a condition called hypersensitive esophagus), whereas 37% of patients had symptoms that correlated significantly with episodes of non-acid reflux. This study suggests that a substantial number of patients with "PPI failure" (48%) might be helped by fundoplication. Indeed, in a follow-up study from the same group of investigators, fundoplication resulted in significant relief of symptoms for 16 of 18 patients who had PPI-resistant GERD symptoms with a positive symptom index by combined esophageal pH/impedance monitoring.[11]

For many patients with PPI-resistant GERD symptoms, antireflux surgery sometimes has been performed with the rationale that those symptoms are caused by episodes of non-acidic reflux that can be eliminated by fundoplication. Unfortunately, surgery often has been unsuccessful in this setting, a disturbing outcome that has added to internists' traditional reluctance to recommend surgical treatment for GERD. The aforementioned study by Mainie *et al.* suggests that PPI-resistant GERD symptoms are significantly associated with reflux episodes only in approximately one-half of all patients. Whereas antireflux surgery would be expected to benefit only patients with such an association, it is not surprising that surgery frequently has been unsuccessful when performed for PPI failure. If the preliminary reports on the role of impedance monitoring discussed above are valid, then even a technically flawless fundoplication performed without prior esophageal impedance monitoring in a patient with PPI-resistant GERD would have less than a 50% chance for success.

Unfortunately, in the absence of definitive studies, the role of esophageal impedance monitoring in selecting patients for antireflux surgery remains unclear. Data on the use of this test to guide patient management still must be considered preliminary. With so many patients reporting incomplete relief of GERD symptoms with PPI therapy, there is an outstanding opportunity for future research in this area. The results of those studies are anxiously awaited.

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Table 1

Potential Mechanisms for GERD Symptoms That Persist During PPI Therapy, and the Tests Needed to Establish Those Mechanisms

Potential Mechanisms	Tests Needed to Establish the Mechanism
Abnormal acid reflux persists and causes symptoms	Esophageal pH monitoring on PPI
“Normal” levels of acid reflux cause symptoms	Esophageal pH monitoring on PPI
Non-acidic reflux causes symptoms	Esophageal impedance monitoring on PPI
Non-GERD esophageal disorder causes symptoms	Esophageal biopsy, manometry
Extra-esophageal disorder causes symptoms	Tests for heart disease, gastroparesis, etc.
Symptoms are functional	No specific test available