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Conflict of interest

The authors disclose the following: Prateek Sharma serves as a consultant for Takeda Pharmaceuticals. Philip Katz serves as a consultant for Torax.

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Esophageal Mucosal Impedance: Is It Time to Forgo Prolonged Gastroesophageal Reflux Recordings?



See “Mucosal impedance discriminates GERD from non-GERD conditions,” by Ates F, Yuksel ES, Higginbotham T, et al, on page 334.

For several decades, ambulatory 24-hour esophageal pH monitoring remained the sole tool for the assessment of gastroesophageal reflux. This tool, first introduced in 1969, is still being used to determine the

extent of esophageal acid exposure in patients with gastroesophageal reflux disease (GERD) with typical or atypical symptoms, patients who are candidates for surgical fundoplication and those who do respond to antireflux treatment.^{1,2} However, it has been repeatedly demonstrated that the catheter-based pH testing interferes with patients' reflux-provoking activities (food consumption, smoking, sleep, etc) primarily owing to a variety of side effects, including nose pain, runny nose, throat pain, throat discomfort, cough, chest discomfort, and headache.^{3,4} Consequently, not uncommonly GERD patients with significant esophageal mucosal involvement (erosive esophagitis, Barrett's esophagus, and others) or significant predisposing factors for gastroesophageal reflux demonstrated a normal pH test. Importantly, this was the main impetus for the development of the wireless pH capsule, which represented an attempt to improve patients' tolerability and thus the accuracy of the pH test both by reducing the impact of the test on patients' normal daily activities and by increasing its duration.^{5,6} In addition, the wireless pH capsule offered a new direction in technological development, which is miniaturization of esophageal function testing.⁷ However, the impedance + pH test, which was introduced in 1991 but approved by the Food and Drug Administration only in 2002, brought back the catheter-based assessment of gastroesophageal reflux.⁸ The main advantage of the impedance + pH test over the catheter-based pH test is the ability to determine the presence of gastroesophageal reflux through impedance rather than pH changes.⁹ Thus, impedance + pH can identify a reflux event through series of changes in esophageal impedance that occur sequentially from the distal to the proximal part of the esophagus. The pH sensor, which is embedded within 5 cm from the tip of the probe, determines if the reflux is acidic ($\text{pH} < 4$), weakly acidic ($4 \leq \text{pH} < 7$), neutral ($\text{pH} = 7$), or alkaline ($\text{pH} > 7$). Furthermore, the impedance changes can demonstrate if the reflux is liquid or mixed (gas + liquid), characteristics that seem to be important for esophageal sensation and thus symptom generation.¹⁰

In this issue of *Gastroenterology*, Ates et al¹¹ have reported on a novel technique, named mucosal impedance, that can discriminate between GERD and non-GERD conditions. The authors developed and validated a catheter that can traverse through the working channel of a regular endoscope and can measure the impedance of the esophageal mucosa through direct mucosal contact.¹² Two circumferential sensing rings, 3 mm in length and 2 mm apart, are mounted on a catheter with the distal ring 1 mm away from the tip. By applying a slight mucosal pressure, electrical conductivity between the 2 rings could be measured and, consequently, the impedance of the mucosa could be determined. Because there is an inverse relationship between electrical conductivity and impedance, an increase in electrical conductivity results in decrease in impedance and vice versa. In their study, the authors compared mucosal impedance values of 5 different groups of patients, erosive esophagitis, nonerosive reflux disease, functional heartburn, eosinophilic esophagitis, and achalasia. Mucosal impedance measurements were obtained at 2, 5, and 10 cm

above the gastroesophageal junction. The authors were able to demonstrate that patients with GERD had lower mucosal impedance values compared with non-GERD patients. In addition, patients with eosinophilic esophagitis had the lowest mucosal impedance values, which remain the same throughout the esophagus, unlike the others, which demonstrated an increase in mucosal impedance between distal and proximal esophageal measurements.

Although the study demonstrated that mucosal impedance assessment can differentiate GERD patients from those who do not have GERD, the main question is what factors determine mucosal impedance? This is a pivotal question, because these factors will drive the results of the test. The impedance + pH test measures the impedance of esophageal content that passes between 2 sensing rings and thus determines the characteristics of the content (gas, liquid, or both) and if the content moves orad or caudad. The surrounding esophageal tissue provides the baseline impedance measurements, ranging from 1500 to 4000 Ohm, when the impedance + pH catheter is placed in the esophageal lumen. Erosive esophagitis and Barrett's esophagus have been shown to reduce baseline impedance levels.¹³ However, the mucosal impedance catheter measures transepithelial resistance and permeability, which are driven by mucosal structural changes.¹⁴ Consequently, any injurious agent that compromises epithelial integrity may lead to mucosal structural changes that can result in alteration of mucosal impedance recordings. Although injurious agents related to gastroesophageal reflux are very common, other, non-reflux-related injurious agents (eg, medications, fungal and viral infections) can also result in structural abnormalities that are likely to be associated with impedance changes. The non-reflux-related esophageal mucosal structure abnormalities may not be differentiated from reflux-related esophageal mucosal changes by the mucosal impedance catheter. Interestingly, in this study patients with achalasia demonstrated a higher mucosal impedance values even when compared with functional heartburn patients. Patients with long-standing achalasia tend to develop friability of the esophageal lining owing to luminal stasis which denotes chronic mucosal inflammation.^{15,16}

A more important question is whether mucosal impedance testing will replace gastroesophageal reflux testing (impedance + pH, catheter-based pH testing, and the wireless pH capsule). Although mucosal impedance testing is simple and easy to perform, it provides no information on the degree, type, and patterns of a patient's gastroesophageal reflux. Mucosal impedance testing is unable to differentiate between acidic and nonacidic mucosal structural changes, which require different therapeutic approaches.^{17,18} In addition, it does not have the capability of determining whether a patient's reflux is primarily during nighttime or daytime. Again, each reflux pattern may require a different therapeutic strategy.^{19,20} Mucosal impedance is also unable to determine the height of reflux episodes and the association between reflux events and symptoms. The technique also has limited value in assessing improvement, although not necessarily normalization, of gastroesophageal reflux after medical, endoscopic, or

surgical intervention. Presently, the main role of impedance + pH is to stratify patients with heartburn who failed twice daily proton pump inhibitor therapy into 3 groups—those who have nonacidic reflux as the underlying cause of their symptoms, those with residual acidic reflux as the underlying cause of their symptoms, and those with functional heartburn.²¹ This type of stratification may not be achieved with mucosal impedance.

Although it is unlikely that mucosal impedance will replace current tests that evaluate the extent of gastroesophageal reflux, its simplicity and the availability of immediate results make it a highly attractive diagnostic tool for a busy practicing gastroenterologist. Currently, mucosal impedance can be done only through the endoscope. Thus, an indication for both tests is required before consideration of mucosal impedance testing in patients.

Mucosal impedance may be an important tool in evaluating patients who cannot tolerate transnasal probes, such as impedance + pH or the catheter-based pH test that are placed for a period of 24 hours. More important, the technique is very well equipped to differentiate between GERD and functional heartburn patients, a common dilemma in clinical practice. It is also possible that mucosal impedance will complement the other esophageal function tests and will provide an additional information regarding integrity of the esophageal mucosal structure.

More research is needed to further determine the exact role of mucosal impedance in clinical practice and specifically in evaluating patients with GERD-related symptoms. Future development of probes that are not dependent on upper endoscopy will make it a versatile technique. Better definitions of mucosal impedance thresholds for different GERD-related disorders are needed. Assessment of the role of mucosal impedance in other esophageal disorders that lead to structural changes (such as eosinophilic esophagitis) of the esophageal mucosa is also necessary. Regardless, this unique and novel technique provides an important breakthrough in the development of diagnostic tools for GERD. It is an exciting tool that is simple to use and likely to improve the current management of patients with GERD, especially those who are not responsive to antireflux treatment.

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Augmenter of Liver Regeneration Links Mitochondrial Function to Steatohepatitis and Hepatocellular Carcinoma



See “Liver-specific deletion of augmenter of liver regeneration accelerates development of steatohepatitis and hepatocellular carcinoma in mice,” by Gandhi CR, Cahillet JR, Nalesnick MA, et al, on page 379.

Steatohepatitis, an advanced stage of fatty liver disease that encompasses alcoholic and nonalcoholic steatohepatitis (NASH), can progress to liver cirrhosis and hepatocellular carcinoma (HCC). NASH is associated with obesity and type II diabetes, and the prevalence of NASH-induced HCC is a health concern worldwide. Therefore, a better understanding of the molecular players involved in NASH-HCC is of clinical relevance. Augmenter of liver regeneration (ALR encoded by *GFER*) is a hepatocyte growth factor originally identified in the regenerating liver of rats and dogs after partial hepatectomy.¹ ALR is mainly produced and secreted by hepatocytes and is the mammalian homolog of Erv, a sulfhydryl oxidase of the mitochondrial intermembrane space, first described in yeasts. Along with Mia40, ALR functions in the import of nuclei-encoded Fe/S cluster proteins to the mitochondrial intermembrane space by an oxidation-dependent mechanism; consequently, ALR enhances oxidative phosphorylation capacity of liver mitochondria (Figure 1).^{2–5} In this issue of *Gastroenterology*, Gandhi et al⁶ provide a novel scenario in which ALR links mitochondrial function to steatohepatitis and HCC development, which illuminates our understanding for the role of ALR in liver pathophysiology.

To unravel the hepatic physiological function of ALR, Gandhi et al generated hepatocyte-specific, ALR-deleted mice (ALR-L-KO) by the albumin-Cre/LoxP system. Two-week-old ALR-L-KO mice exhibited low levels of adenosine triphosphate (ATP), reduced mitochondrial respiratory function, increased oxidative stress, reduced glutathione (GSH) levels, and increased Bax expression and caspase 3 activation, contributing to extensive hepatocyte apoptosis. Hepatic levels of carbamyl-palmitoyl-transferase 1a (CTP1a), ATP synthase subunit ATP5G1 and TFAM, a key activator of mitochondrial transcription, were reduced in ALR-L-KO mice, whereas electron microscopy showed mitochondrial

swelling and abnormalities in the number and shape of cristae. Moreover, 2-week-old ALR-L-KO mice exhibited steatosis, increased liver triglycerides and cholesterol content and decreased expression of acetyl-coenzyme A carboxylase, sterol regulatory element-binding protein 1c, and peroxisome proliferator-activated receptor- α , a regulator of mitochondrial fatty acid β -oxidation. These findings indicate that increased lipid accumulation was not owing to increased lipogenesis, but rather a consequence of impaired mitochondrial fatty acid β -oxidation, consistent with the reduced levels of CTP1a in ALR-L-KO mice. Thus, these data indicate a critical role for ALR in mitochondrial function, ATP synthesis, and fatty acid transport, which impacts on hepatocellular apoptosis and steatosis. The onset of liver injury and steatosis was not accompanied by inflammation at this early age as demonstrated by unchanged levels of inflammatory cytokines and minimal CD45 staining, although there was mild pericellular fibrosis and hepatic stellate cell activation (α -smooth muscle actin [SMA] staining). These data indicate that, at 2 weeks after birth, the lack of ALR induces early stage steatohepatitis.

In general, deletion of target gene expression by the albumin-Cre-LoxP technology occurs progressively from 1 week after birth and takes several months to complete. The expression of ALR in the ALR-L-KO mice is minimal at 2 weeks of age. Quite intriguingly, liver ALR expression gradually increases in 4- and 8-week-old ALR-L-KO mice, although levels did not reach those found in wild-type mice, reflecting the re-expression of ALR in hepatocytes, the major cell source of ALR production and secretion. Native ALR is modified posttranscriptionally from a 22-kDa protein to 3 forms of 36-, 38-, and 40-kDa molecular weight.⁷ The predominant form re-expressed in the ALR-L-KO mice was the 40-kDa isoform. The rebound in the 40-kDa form was sufficient to rescue mitochondrial impairments, and to normalize mitochondrial respiration, ATP levels, expression of TFAM and ATP5G1, and mitochondrial GSH depletion, which controls hepatocellular survival and sensitization to oxidative stress.^{8,9} The improvement in mitochondrial function translated in reduced hepatic steatosis and normalization of triglycerides and cholesterol levels. Interestingly, TUNEL staining, caspase-3 activation, and hepatocyte apoptosis decreased again in 4- and 8-week-old ALR-L-KO mice, an