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Assessing esophageal function in achalasia: the old and the new

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Abstract

Achalasia is currently diagnosed according to the Chicago Classification v3.0 using high-resolution manometry and treatment focuses on disruption of the esophagogastric junction. A paper in this issue examines the utility of a timed barium esophagram with a 13 mm tablet challenge in differentiating achalasia from other diagnoses, finding 100% sensitivity. However, a large proportion of patients with non-achalasia dysphagia are also identified. Another paper in this issue proposes utilizing intra-procedure functional luminal imaging probe measurement during pneumatic dilation as a guide for upsizing dilations. This appears promising, but prospective validation is necessary before this becomes standard of care.

High-resolution manometry (HRM), along with the analysis algorithms initially put forth in the Chicago Classification (CC), and most recently updated in 2015 have led to a major reclassification of esophageal motility disorders[1]. Nowhere is this evolution more evident than in our concept of achalasia, now differentiated into three subtypes and proving to be substantially more prevalent than previously recognized[2, 3]. In fact, many disorders previously rendered to alternative diagnoses, or deemed to be "non-specific" are also now recognized to be either achalasia subtypes or cases of incompletely expressed achalasia[4]. In parallel with the global adoption of the CC, the functional luminal imaging probe (FLIP) has emerged as a novel technology capable of quantifying the distensibility of the esophagogastric junction (EGJ), and reduced EGJ distensibility has proven to be a key abnormality in achalasia. In fact, the detection of reduced EGJ distensibility can be complimentary to HRM in achalasia cases with equivocal, or even negative, HRM findings[5]. Furthermore, FLIP measurements can be made in real-time with sedated patients, thereby offering the potential to tailor treatment as the treatment is in progress. Together, these developments have reinvigorated our thinking about the management of esophageal motor disorders, in general and achalasia, in particular. Contained in this issue of the *Journal* are two papers pertinent to achalasia management: one exploring how an old methodology, the timed barium esophagram (TBE), fits into the new CC diagnostic paradigms, and the second on how FLIP might facilitate a more efficient protocol for pneumatic dilation (PD) in achalasia therapeutics.

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In the first paper, Blonski *et al.* report on a retrospective analysis of 309 patients comparing TBE (including a 13 mm barium tablet challenge) to HRM in the detection and differentiation of achalasia, EGJ outflow obstruction (EGJOO), and non-achalasia dysphagia as defined by CC v3.0[6]. Applying post-hoc determined cutoffs for barium retention height at 1 and 5 minutes, they report a sensitivity and specificity for TBE of 85% and 86%, respectively, for distinguishing achalasia from EGJOO and non-achalasia dysphagia using a retained barium height of 2 cm at the 5-minute time point. Adding barium tablet retention to the criteria for an abnormal TBE increased the sensitivity for detecting achalasia to 100% and for EGJOO to 60%. Test performance characteristics were substantially less robust for discriminating EGJOO from non-achalasia dysphagia. On the flip side (no pun intended) the specificity of an abnormal barium column height for achalasia vs non-achalasia was only 73% and for the combined criteria of barium column height or tablet retention, only 60%. So what does this mean in practice? The authors suggest that, “TBS can be used as a surrogate for esophageal manometry in untreated achalasia patients unable to tolerate this test or when the studies are poor quality or unclear.” However, using only the TBE result in deciding whether or not to render an achalasia therapy would then also apply that therapy to EGJOO and non-achalasia dysphagia patients 60% and 39.3% of the time, respectively, the proportions of those entities with a “positive” test. With the patient mix reported by Blonski et al, this would make the “number needed to harm” just 2.35. Put somewhat differently, 43% of the time you would be rendering an achalasia treatment for a patient with EGJOO or non-achalasia dysphagia. While rendering such therapy may prove appropriate in selected cases, few would advocate going that route without further confirmatory testing. Hence, we suggest further qualifying the statement made by the authors regarding the role of TBE in diagnostics. True, a completely negative TBE study makes an achalasia diagnosis very unlikely, but the converse of a positive study providing sufficient evidence to then pursue achalasia therapy is not supported by these data. Of course, there are situations, such as with profound esophageal retention or luminal dilatation that one would be comfortable going forward with just a TBE and endoscopy, but for equivocal cases, this does not suffice. Furthermore, a completely normal TBE may make achalasia extremely unlikely, but the patient may have EGJOO, which was not detected by the TBE in 40% of instances. Although admittedly a very heterogeneous group[7], about 20 to 30% of EGJOO cases end up being treated as achalasia[8–11].

The second achalasia management paper by Wu *et al.* in this issue of the *Journal* addressed the role of FLIP in guiding PD therapy[12]. Current evidence suggests little difference in efficacy between PD, laparoscopic Heller myotomy or per-oral endoscopic myotomy (POEM) for managing achalasia as measured by patient reported outcomes[13, 14], but PD often requires sequential treatments with progressively larger dilators (30 mm, 35 mm, 40 mm) to achieve that equivalent efficacy. Current practice is to begin conservatively with a 30 mm dilation and to determine the need for subsequent dilations based on clinical response as assessed after a relatively brief follow-up interval. FLIP may offer an interesting alternative here. FLIP uses impedance planimetry to determine the distensibility of the EGJ, reported as the distensibility index (DI) in $mm^2/mmHg$[15]. The DI has been reported to be low in untreated achalasia patients and in patients with poor symptomatic outcomes following achalasia treatment using a cutoff value of 2.8 $mm^2/mmHg$[5, 16, 17]. Studies have also

successfully utilized intra-operative FLIP to assess the adequacy of myotomy during laparoscopic Heller myotomy or POEM[17–21]. Wu *et al.* propose extending that paradigm to PD based on a series of 54 achalasia patients with FLIP studies done before and immediately after PD. They report that an incremental increase of 1.8 mm^2/mmHg or more in the DI was a good predictor of clinical response with positive and negative predictive values of 89% and 81%, respectively. Furthermore, subgroup analysis showed poor response in those with normal pre-PD DI (averaging 4.8 mm^2/mmHg). This may suggest that FLIP has utility in selecting patients likely to benefit from PD. The authors acknowledge that although using an incremental improvement in DI rather than achievement of a predetermined target value may make intuitive sense, it is a departure from what has been done in prior analyses and will need to be prospectively tested. If validated, it may well be suitable to use as an intra-procedural guide for upsizing dilators during PD. However, it is important to note that implementing that practice true to the investigator's protocol would require a FLIP software upgrade (or some fast work in the procedure suite), as their DI determinations were not done from the visual display on the FLIP device, but with a MatLab program that manipulated the pressure/cross sectional area data points into pressure vs *mean* cross sectional area plots

In summary, both the studies by Blonski *et al.* and Wu *et al.* are valuable additions to our knowledgebase on using functional testing to guide the informed management of achalasia, a disease that has certainly experienced a resurgence of interest with the adoption of HRM and the CC as diagnostic methods. Adding to that excitement is the addition of FLIP technology as a real-time functional assessment of the EGJ and POEM as a minimally invasive therapeutic technique. However, not all that is new is necessarily better and not all that is old is necessarily obsolete. The TBE (with a tablet challenge) has enduring value not only as a means of detecting subtle anatomical constrictions at the EGJ, but also as a means of corroborating the functional significance of esophageal motility disorders. On the other hand, FLIP technology is very promising, but is still in its infancy. Much work remains with respect to standardizing the metrics of measurement and establishing its niche in disease management. Most importantly, recognize that there is no single silver bullet to managing esophageal motor disorders. Circumstances exist in which the merit of any one test modality prevails over all others. The easy cases are easy. However, complex cases often require the use of complimentary tests (EGD, TBE, HRM, FLIP), integrating and prioritizing the findings among tests in order to achieve optimized clinical management.

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