POEM: Concept to Research Laboratory

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Introduction

Given that the first experiments involving submucosal endoscopic esophageal myotomy in a porcine model were published in 2007, the interval uptake of peroral endoscopic myotomy (POEM) into clinical practice has been impressively swift. While the procedure remains limited to specialized practitioners and centers, it has become a valuable therapeutic option for the management of achalasia with outcomes that rival benchmarks established by more conventional surgical alternatives. Historical perspective helps to contextualize POEM as the conceptual outgrowth of a much longer therapeutic lineage rather than a de novo innovation to be added to the proceduralist's armamentarium. Reflecting on the specific differences between submucosal endoscopic myotomy and the interventions (both experimental and established) that preceded it allows for a clearer understanding of the ways in which POEM represents a novel therapeutic paradigm, for spastic esophageal disorders in particular and for endoscopy in general. Looking ahead, distant milestones in this conceptual evolution might include technical elaboration made possible by novel endoscopic devices or, intriguingly, molecular therapies that might render endoscopic therapy for achalasia obsolete.

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History of Achalasia Therapy

Discussing the conceptual origins of POEM merits a brief historical review of achalasia therapy in general. This chronology begins in the late seventeenth century, when English physician Thomas Willis (1621–1675) described the successful use of whalebone dilatation in a case of dysphagia. In his treatise on the subject, Willis speculated that the patient's symptoms were due to an obstruction at the level of the proximal stomach. "Cardiospasm" was formalized as a clinical entity in 1821, corresponding with classically reported symptoms of dysphagia and regurgitation and anatomical findings of a diffusely dilated esophagus in the absence of any discernible structural blockage [1].

Etiological hypotheses regarding this process were wide-ranging through the nineteenth century, including congenital muscular hyperactivity, extrinsic compression from nearby viscera, and nervous degeneration [1]. The term "achalasia" was coined at the turn of the twentieth century, favored by certain practitioners over "cardiospasm" on a mechanistic basis. The newer word was derived from Greek and suggested more explicitly a presumed failure of the lower esophageal sphincter (LES) to relax [2]. A semantic debate between these two disease models continued over the next few decades, though both attended to the LES as the primary site of pathology [3, 4]. Mechanical dilatation remained a frequently employed therapy, with pneumatic dilators by and large supplanting their hydrostatic predecessors in the latter part of the twentieth century [5, 6].

The advent of surgical therapy for achalasia also occurred in the early 1900s. The first such procedure was described in 1910 and involved a small vertical incision over the cardia that was then closed with transverse sutures. The German surgeon Ernest Heller (1877–1964) revised the cardioplasty 4 years later, using a transabdominal approach, to perform longer, extramucosal incisions on both the anterior and posterior aspects of the cardia [7]. Other surgical procedures were devised for achalasia therapy that did not address the lower esophageal sphincter directly (e.g. megaesophageal plication or side-to-side esophagogastrostomy) but abandoned relatively quickly in the face of poor outcomes [8].

Pathophysiology

Research from bench to bedside has continued to reinforce attention to the lower esophageal sphincter as the essential site of physiological dysfunction in achalasia. Early manometric analyses clarified abnormal LES relaxation as a hallmark feature of this clinical entity, and esophageal outflow obstruction remains a necessary but not sufficient criterion for making the diagnosis [9]. Clinical achalasia subtypes have since been further defined by variable manometric abnormalities of the esophageal body, ranging from absent contractility to panesophageal pressurization to premature contractile sequences consistent with spasm [10].

Muscular dysfunction was in turn tied to aberrancies in neural control, as inhibitory signaling by nitric oxide was recognized as the primary mediator of appropriate LES relaxation. Histopathological evaluation of resected

specimens from patients with both early-stage and late-stage achalasia has demonstrated chronic inflammation leading to progressive injury of nervous tissue with eventual depletion of myenteric ganglion cells [11, 12]. Several investigators have conjectured that this process represents an autoimmune phenomenon, possibly tied to an infectious trigger [13]. Significant variations within this histological pattern by clinical achalasia subtype, however, suggest that achalasia pathogenesis may be marked by significant heterogeneity that is not yet fully appreciated [14].

Directed attention toward lowering LES resting pressure has led to other interventions that are not exclusively mechanical in approach. Intrasphincteric injection of botulinum toxin in patients with achalasia, for example, has been shown to result in symptomatic, manometric, and radiological improvement, albeit on a temporary timescale [15]. This intervention remains clinically relevant for its limited harm profile, well suited to individuals concerned about long-term postoperative side effects or in whom more aggressive surgical intervention is deemed prohibitively high-risk. Therapeutic inquiry has continued to explore novel means of intervening on the LES that might optimize the balance among convenience, safety, and permanence.

Early Endoscopic Myotomy

Efforts to mitigate the invasiveness of transabdominal Heller myotomy corresponded with a more general rise of interest in minimally invasive surgical techniques. The first laparoscopic and thoracoscopic cardiomyotomy procedures were successfully performed in the early 1990s [16, 17]. A logical extension of these developments was to consider endoscopic rather than surgical approaches to myotomy. Earlier, more straightforward attempts at treating achalasia with flexible endoscopy had been made but were met with limitations. The first example of endoscopic myotomy for achalasia was described by Ortega et al. in 1980, well before the first reports of laparoscopic surgical myotomy were published. Using an independently designed electrosurgical knife introduced through the biopsy channel of the endoscope, Ortega et al. performed an intraluminal myotomy procedure on six dogs, optimizing their technique through the course of these animal experiments. The authors then performed the procedure on a series of 17 patients with achalasia. Improvement was reported along all relevant dimensions, including subjective symptomatic reports as well as posttreatment radiographic and manometric evaluation [18].

This technique received little published attention in the intervening years, however, and its uptake was likely limited by concerns surrounding both efficacy and safety. Myotomy length, for instance, was limited to 1 cm through this prototypical endoscopic approach, as compared with the long or extended myotomy allowed by a conventional surgical approach with correspondingly better symptomatic outcomes [19]. Additionally, myotomy depth as reported by Ortega et al. was limited to 3 mm, with more aggressive incisions presumably increasing the risk of bleeding

and perforation. Finally, this remained a blind procedure, and so clearly not for the faint-hearted.

Third Space Endoscopy

With percutaneous and intraluminal access perceived as the only two available modes for performing therapeutic incision of the LES, surgery remained the definitive option for achalasia therapy, with endoscopic dilatation maintaining relevance as an intermediate approach, a compromise between invasiveness and efficacy [20]. However, in parallel with the experiments performed under the Natural Orifice Tranluminal Endoscopic Surgery (NOTES) paradigm, which was at the forefront of attention within the therapeutic endoscopy community at the time, another novel initiative, led by Christopher J. Gostout at the Mayo Clinic, was gathering steam. A desire to perform en bloc resection of larger lesions drove interest in the development of submucosal fluid cushions that could be used to delaminate the mucosa from the submucosa [21]. The creation of a submucosal tunnel, establishing distance between points of entry and exit into the working space, constituted a novel innovation with the added benefit of protecting against leaking intraluminal contents in the event of perforation [22].

In 2007, the first practical therapeutic exploitation of this space was made using a novel experimental approach to myotomy described in a porcine model. In the experiments performed by Pasricha et al., the circular muscle of the LES could be incised under direct visualization through an endoscopic approach without disruption of the esophageal adventitia in a procedure called "submucosal endoscopic esophageal myotomy" [23]. Specifically, a dilating balloon was used to separate the mucosa from the muscularis propria in order to create a novel working space for endoscopic therapy at the esophagogastric junction. Technical success was achieved in each of four animal experiments, with significant reductions in LES pressure reliably observed after the procedure.

As with many notable events in medicine, the clinical translation of this technique might have languished were it not for serendipity. During a visit to Australia, Dr. Pasricha was giving a lecture on endoscopic myotomy attended by, among others, Haru Inoue. As a master surgeon and endoscopist, Inoue expressed his interest to Pasricha and advised that he would attempt the technique in patients over the next several months. In 2010, the first clinical report by Inoue et al. appeared, in which the procedure was renamed "POEM." The technique was modified for therapeutic use in humans, replacing balloon-mediated separation of submucosal tissue planes with an endoscopic submucosal dissection (ESD) technique and, using a triangle-tip knife, extension of the incision at least 2 cm below the esophagogastric junction. In their series of 17 consecutive patients, the authors reported complete technical success and no serious short-term complications. Significant post-treatment reductions in both LES pressure and clinical dysphagia scores were observed [24].

Technical Maturation

Several critical questions remained unanswered in the early days of endoscopic myotomy via submucosal approach. In contrast to the conventional surgical approach, for example, the boundaries of incised muscle were not kept physically separated after submucosal myotomy, raising theoretical concern for tissue healing leading to recurrent elevations in LES tone over time. The risk of gastroesophageal reflux as a function of LES disruption (particularly in the absence of partial fundoplication, which had become a standard prophylactic adjunct to surgical myotomy) was also uncertain. More generally, the extent to which the apparent success of POEM in experimental contexts could be recapitulated in clinical settings and preserved over long-term follow-up intervals would necessarily take time to understand.

The strength of early reports, however, allowed for long-term data to accrue. The first author of the first clinical application of POEM, Dr. Inoue, has recently noted the completion of the thousandth such procedure at his center, marking this milestone as senior author of a manuscript, detailing technical insights gained as function of this experience [25]. Elsewhere as well, retrospective data sets of increasing size have suggested that the procedure's technical and clinical efficacy remain robust, that severe complications are rare, and that side effects such as reflux can be well managed medically [26]. Attention is now oriented toward particular clinical scenarios in which POEM may offer an advantage over laparoscopic surgery, such as the spastic achalasia subtype, in which a relatively long myotomy may be endoscopically performed, extending as needed to the proximal boundary of contractile dysfunction [27].

It is interesting to reflect upon the fact that POEM seems to have changed the dialog surrounding the currently moribund NOTES paradigm by virtue of its successful example. A clear distinction should be made, however, between traditional NOTES, involving largely hypothetical transvisceral approaches to organs extrinsic to the gastrointestinal lumen, and third space endoscopy, referring to procedures that use submucosal tunneling along with the skills required for endoscopic mucosal resection and, in certain cases, endoscopic ultrasound [28]. Aside from POEM, procedures falling under the rubric of third space endoscopy include, for example, peroral pyloromyotomy and submucosal tunneling with endoscopic tumor resection [29, 30]. In addition to therapeutic intervention, potential applications of these techniques include specialized drug or device delivery and deep tissue sampling for various other neurogastroenterological diagnoses that are as yet poorly characterized [31].

Future Trends

As POEM becomes steadily more entrenched within the suite of available treatments for patients with achalasia and other esophageal motor disorders, new challenges and opportunities will arise to help determine its ultimate position within the

therapeutic landscape. Most basically, definitive evidence at the level of randomized controlled trials comparing outcomes of endoscopic versus surgical myotomy is still forthcoming and will clarify the logic of the procedure's wider dissemination. Accumulating data on postprocedural outcomes may also eventually facilitate building predictive models identifying which patient populations are best positioned to undergo one particular therapeutic intervention over another.

Existing as it does at the crossroads of surgery and endoscopy, POEM also poses challenging questions regarding which subset of clinicians should be performing the procedure in the future. As with other endoscopic skills that are shared between gastroenterologists and surgeons, POEM might remain a shared territory for practitioners from diverse training backgrounds, particularly as its technical description becomes more streamlined and widespread. Incentives built into the contemporary healthcare environment tend to favor low-cost alternatives, in which case, all else being equal, endoscopy suites may hold the advantage over operating rooms in the long run. Regardless, professional societies with vested interest in the procedure will likely soon be gathering to formalize credentialing guidelines.

Disagreement among specialty groups has been implicated in the reduction of interest over time in the traditional NOTES concept, in light of which active collaboration between interest groups seems vital to the practical advancement of third space endoscopy moving forward [32]. As opposed to NOTES, however, the sustainability of third space endoscopy is bolstered by its offer of a viable and robust solution to an unmet need (over and above an incremental improvement in cosmesis). In general, techniques requiring an increase in overall complexity and required skill sets to a degree that is out of proportion with the need they purport to meet will stand as poor examples of disruptive technology over time.

Given the significant amount of time and energy that has been devoted to POEM's technical refinement, it is somewhat surprising to consider that the endoscopic tools with which the procedure is performed have not yet been customized to the task. While commentators have discussed the strengths and weaknesses of various existing accessories, the endoscopic design area has not yet manufactured instruments specifically tailored to the purpose of POEM. As subtle and effortless as the procedure might become in progressively experienced hands, it retains an improvisatory, ad hoc quality in light of this hardware legacy. Engineering investments in new devices for third space endoscopy could help to flatten the procedural learning curve and perhaps even facilitate further technical innovation within the submucosal tunneling paradigm.

Finally, it is worth considering the hypothetical impact of novel approaches to achalasia and related processes that might, in the far future, subvert the relevance of even minimally invasive procedures such as POEM. Relatively recent population-level analyses have identified potential loci of genetic susceptibility to the development of idiopathic achalasia as well as a relative frequency of comorbid allergic and autoimmune disorders within this population [33, 34]. Ongoing investigation into the pathogenesis of these disorders might one day yield molecular insights into restoring lost neurons at the lower esophageal sphincter, or perhaps preventing their deterioration in the first place [35]. Understanding endoscopic myotomy as a

fundamentally palliative procedure places added emphasis on pathophysiological investigation as the primary point of departure for new conceptual models in managing gastrointestinal dysmotility.

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