Editorial

Endoluminal *vs*. extraluminal cardiomyotomy for oesophageal achalasia

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Oesophageal achalasia is a relatively rare disorder characterized by the absence of peristalsis along the oesophageal body and failure of the lower oesophageal sphincter (LOS) to relax; as a consequence the food bolus often gets stuck in the distal oesophagus and the patient experiences dysphagia. Other related symptoms are regurgitation and chest pain. Although the exact causes of achalasia are still not known [there are some suggestions to a possible autoimmune pathogenesis activated by herpes simplex viruses (1)], the medical community has long been aware of how to alleviate the related dysphagia even before fully understanding the pathophysiology of the disease.

At the beginning of the past century in 1913, just at the verge of the first World War, Ernst Heller a German surgeon performed an "extramucosal myotomy" at the level of the gastric cardia, lowering the pressure maintained by the LOS and enabling food to naturally empty from the distal oesophagus reaching the stomach due to the effect of gravity (2). Seven years before, in 1906, Plummer had used a water-filled balloon to dilate the cardia and Stark designed an expanding metal dilator in the Twenties (3,4). Though cardia dilations were effective, they carried an excessive risk of oesophageal perforation so surgery was generally preferred. With the introduction of low-compliance, non-expandable balloons of increasing diameters (Rigiflex®, Boston Scientific, Ma, USA) the risk of perforation was substantially reduced, and endoscopic dilation became the treatment of choice for achalasia patients (5). At the end of the past century the introduction of minimally invasive surgery allowed performance of the so-called Heller myotomy with limited surgical morbidity and this procedure (with the addition of a partial fundoplication to prevent gastroesophageal reflux) became highly popularized (6).

The dawn of the new millennium has seen further, substantial improvements in the diagnosis and disease-tailored management of achalasia. First, the widespread dissemination in clinical practice of high resolution manometry (HRM). Differently from water-perfused manometry, HRM allows recording intraluminal pressures circumferentially at 1 cm intervals over the whole length of the oesophagus, the lower pharynx and the upper stomach and, by transforming these pressure data into a topographic color plot, this provides a continuous depiction of the pressure along the entire recorded segment throughout the time period (7). By using HRM a new classification of oesophageal motor disorders was formulated and oesophageal achalasia was categorized in three subtypes (I, II & III) with a prognostic relevance, the type three—characterized by the presence of spastic contraction in the distal oesophagus—being the most difficult to treat with conventional therapies (8). Secondly, the introduction and the rapid acceptance of peroral endoscopic myotomy (POEM). POEM is a new modality of performing endoluminal cardiomyotomy without visible external skin incisions using a flexible endoscope and creating a tunnel between the oesophageal mucosa and the muscular layer. At

the level of the GOJ the circular fibers are cut; the small hole in the esophageal mucosa is then sutured with clips. First described by Pasricha *et al.* (9) in an animal model, it was ushered in the clinical practice by Inoue *et al.* in 2008 (10). The new technique gained a wide popularity and has been enthusiastically embraced by the medical community (especially by interventional gastroenterologists with experience in operative oesophago-gastric endoscopy). As it is often seen when a new technique is introduced the potential for publication bias is at its greatest, and the early reports on POEM were extremely optimistic with almost no complications, rapid recovery and a good-result rate approaching 100% of treated patients (11-14).

The major advantages of POEM (beside being a scarless procedure), are the possibility of an easy extension of the myotomy upwards, obtaining a better treatment of the spastic forms of oesophageal motor disorders and of type III achalasia (where it is presumed that the disease involves the more proximal muscle layers) and an easier approach to re-interventions after failed LHM. The major drawback of POEM is a presumed high rate of post-treatment GERD, given the absence of any antireflux procedure after the LOS myotomy.

Most of the studies concerning POEM, however, are single arm cohort studies with retrospective design and few comparative studies with other techniques have been reported so far. One of these studies has been recently published on Diseases of the Esophagus by an Italian group (15). In this single center, retrospective study the Authors report on 74 myotomies for primary achalasia: 32 patients underwent POEM and 42 LHM. All patients were discussed in a multidisciplinary meeting with radiologist, surgeons and gastroenterologists. If both treatments were indicated, patients were selected for the technique for which they had been referred. The two groups had similar characteristics as regard age, symptom score and duration, and manometric characteristics, one patient in each group had type three achalasia. The duration of the procedure was significantly longer for LHM [LHM 76.5 (range, 54–152) *vs.* POEM 63.4 (range, 32–114); P=0.005]; the extent of myotomy was longer in POEM than in LHM: 12 (range, 10–15) *vs.* 9 (range, 7–10) cm; P=0.001, respectively. There were 3 severe (Clavien Dindo >3) adverse events: 1 after POEM (pneumothorax) and 2 after LHM (one bleeding from the trocar site and one acute respiratory distress syndrome). The length of hospital stay was in favor of LHM: 2 (range, 2–7) *vs.* 3 (range, 2–9) days after POEM. At a median follow up of 2 years, the symptomatic results were similar: in both group the median postoperative Eckardt score was 1. One patient had recurrent symptoms after POEM. Eighteen patients underwent physiology studies: the median post-treatment IRP was 9.7 (range, 5.7–60.5) mmHg for POEM and 8 (range, 3.5–14) mmHg in LHM. Four patients in both groups needed PPI for heartburn; 24-hour pH monitoring was positive in 28% of POEM patients and in 22% of LHM group (P=non significant). Endoscopy was performed in 20 patients and esophagitis was detected in 8 (4 grade A, 3 grade B and 1 grade C) after POEM (40%) and in one patient after LHM, grade A (5%) (P=0.04).

Several meta-analyses and systematic reviews have already demonstrated the feasibility of POEM as a technique (16) with a low morbidity similar to LHM (17). The clinical outcomes of POEM have been reported in a recent large multi-centre study: the initial 96% success rate at 6 months decreased to 91% at 2 years of follow-up, a similar success rate of the present study (18). Another large multicenter study from Europe reported an initial success rate of 97% at 3 months that decreased to 87% at 1-year follow-up (19). An even higher recurrence rate at mid-term follow-up (22% at 2 years) has been reported by Werner *et al.*, after an initial success rate at 3 months of 93.7% (20). These studies confirm that as expected and comparable to what is observed in LHM, there is a deterioration of the initial success rate of the myotomy along time. The medium term results of POEM mirror the results of LHM, as reported by the European Trial comparing LHM and pneumatic dilatation –90% success rate of LHM at 2 years (21) and by the Campos' meta-analysis with a success rate of 89.3% in 3,086 patients at a median follow-up of 35 months (22). It seems quite evident that, independently of the side from where the myotomy is performed—from inside or from outside—similar results are achieved.

The main problem of POEM—and the major reason of concern, is the suggested post-operative reflux. On this issue different and contrasting data exist, mostly depending on how the reflux is measured: subjective recording of symptoms, 24-hour pH monitoring or the damage caused on the oesophageal mucosa as visualized by endoscopy. The study by de Pascale *et al.* (15) reported a similar number of patients with symptoms and with positive pH monitoring in POEM and LHM patients, but a high number of patients with oesophagitis after POEM. Similar data have been observed by Werner *et al.* (20) with 36% of patients with oesophagitis grade A and B after POEM and by Teitelbaum *et al.* that reported 59.6% of patients

with oesophagitis, but only 15% with symptoms, whilst pH monitoring results were abnormal in 31% of patients (23). Familiari *et al.* reported the presence of GORD symptoms in 18% of the patients, oesophagitis at endoscopy in 20% and an abnormal acid exposure (>4.5% of the total time at a pH <4) in 50% of patients; a clinical relevant GORD was diagnosed in 30% of patients after POEM (24). The discrepancy between the number of symptomatic patients, of those with abnormal pH monitoring and of those with endoscopic oesophagitis may have several explanations: first, it is possible that symptoms of GORD are not reliable in achalasia patients, or in patients after POEM, because the achalasia itself or the long submucosal tunnel may hamper pain perception in the oesophagus (25); second, pH monitoring probably is not the optimal test for determining reflux in achalasia patients, since it does not discriminate true refluxes from the so called pseudo-refluxes due to the stasis of saliva, especially when the patient is in a supine position and the endo-oesophageal pH fluctuates around 4, if a manual analysis of the pH trace is not performed. Recently Salvador *et al.* (26) reported the outcome of pH monitoring after LHM on 423 patients: a positive pH study was found in 54 patients (12.8%), but 25% of those had pseudo-refluxes as described above. It is clear that if there is no agreement on the definition of reflux after cardiomyotomy for achalasia, also an apparently objective test such as pH monitoring may often be misleading. Thirdly, it is possible that not all the oesophageal inflammatory lesions are caused by gastric reflux. In any case, the observation of such a high incidence of postoperative oesophagitis in most of the studies based on western patients is a concerning finding. If the experience gained with LHM may help us in understanding this phenomenon, in the review by Campos *et al.* the reflux rate after LHM without antireflux procedure was 41.5% compared to 14.5% when an antireflux procedure was added (OR 4.2; 95% CI: 1.5–12.8; P=0.01), implying that when the main structure to prevent reflux is disrupted, it is most likely that reflux will occur.

Despite these concerns, POEM is a fascinating new method to perform cardiomyotomy and certainly has rightly entered in the armamentarium to treat achalasia. What the medical class needs to know now is how to tailor the treatments available for the need of each patient with achalasia and what should be the role of POEM in this treatment algorithm.

It has been suggested that a possible selective use of POEM is for treating Achalasia type III patients, where the spastic contractions extend along the esophageal body far proximally than the median extent of a cardiomyotomy as performed in LHM. It should be a taken in account, however, that LHM is effective in 85% of type III Achalasia patients (27) and given the low number of patients with these features, there are no reports to objectively support the statement that POEM is more effective than LHM. A second possible indication of POEM is for LHM recurrences: these may constitute an important use of the technique and there are already data indicating that POEM is an effective and relatively simple technique for managing recurrences or failure after LHM (28).

It is unlikely that an adequately sized randomized controlled trial comparing POEM and LHM will be performed in the next years, given the small differences, if any, between the two techniques; nevertheless large multicenter comparative studies with patients with similar characteristics adequately matched using a propensity score analysis are feasible and should be considered as the first priority. The second priority is to continuing the surveillance of the cohorts of patients enrolled in POEM studies to gather sound information on the long-term symptomatic outcome at 5 and 10 years. The third priority should be to find a consensus on the definition and on how to measure GORD in achalasia treated patients in order to understand and measure the real dimension of postoperative reflux, after POEM and the other available treatments.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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