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**Efficacy of peroral endoscopic myotomy compared with other invasive treatment options for the different esophageal motor disorders**

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**ABSTRACT**

**Introduction:** Peroral endoscopic myotomy (POEM) has been performed since 2008 on more than 5,000 patients. It has proven to be highly effective in the treatment of achalasia and has shown promising outcomes for other esophageal motility spastic disorders.

**Methods:** A literature review of the efficacy of POEM compared to the previous invasive treatments for different esophageal motility disorders was performed. The application in the pediatric and elderly populations and its role as a rescue therapy after other procedures are

also outlined.

**Results:** Short-term outcomes are similar to laparoscopic Heller myotomy (LHM) and pneumatic endoscopic dilation (PD) (clinical success > 90%) for achalasia subtypes I and II. Mid-term results are comparable to LHM and the outcome obtained after PD (> 90% vs ≈50%). With regard to type III achalasia, POEM efficacy is 98% compared to 80.8% for LHM and the PD success remains at 40%. With regard to spastic esophageal disorders (SED), POEM has an effectiveness of 88% and 70% for distal esophageal spasm (DES) and jackhammer esophagus (JE) respectively. A response of 95% in patients with sigmoid esophagus has been reported. POEM has been performed in pediatric and elderly populations and has obtained a higher efficacy than PD in pediatric series (100% vs 33%) without greater adverse events. Previous treatments do not seem to hinder POEM results with excellent response rates, including 97% in post LHM and 100% in a re-POEM series.

**Final considerations:** POEM has shown excellent short and mid-term results for all subtypes of achalasia but long-term results are not yet available. The promising results in SED may make POEM the first-line treatment for SED. A high-safety profile and efficacy have been shown in elderly and pediatric populations. Previous treatments do not seem to diminish the success rate of POEM.

**Core tip:** POEM has emerged as an efficient treatment option for all subtypes of achalasia and other scenarios (including previous treatments and elderly and pediatric populations). Short and mid-term results are comparable to LHM and are better than PD data. The clinical response rate of DES and JE may make POEM the first-line treatment for SED.

**Key words:** POEM. Esophageal motor disorders. Endoscopic treatment. Achalasia. Distal esophageal spasm. Jackhammer esophagus.

## INTRODUCTION

The Chicago classification (1) of esophageal motility disorders based on high resolution manometry (HRM) includes disorders associated with an impaired relaxation of esophagogastric junction (EGJ) such as achalasia type I, achalasia type II, achalasia type III

(spastic achalasia) and EGJ outflow obstruction (EGJOO). Abnormal behavior and discoordination between both muscle layers has recently been shown to be responsible for the different features of every subtype (2). There is no response to deglutition in both layers in type I achalasia. In type II, pressurization is mainly due to longitudinal muscle layer contraction and in type III, an uncoordinated activity of both layers has been assessed (3). EGJOO is a less well known condition based on an impaired relaxation of EGJ but with normal esophageal muscle function (4,5). These disorders have been traditionally treated by interventions aimed at decreasing lower esophageal sphincter (LES) relaxing pressure such as open or laparoscopic Heller myotomy (LHM), pneumatic endoscopic dilation (PD) and, most recently, with BoTox® injection.

Distal esophageal spasm (DES) and jackhammer esophagus (JE or hypercontractile esophagus) are defined in the current Chicago classification v3.0 as disorders not necessarily related to an impaired LES relaxation. DES is characterized by a normal mean integrated relaxation pressure (IRP) and  $\geq 20\%$  premature contractions. In DES, contraction of both layers can differ by more than eight seconds (6). Jackhammer esophagus is an extreme pattern of hypercontractility and is manometrically defined as at least two swallows with a distal contractile integral (DCI, the measure of contractile vigor)  $> 8,000$  mmHg/s/cm, and may be associated with esophagogastric junction outflow obstruction. Considering DES, jackhammer esophagus and type III achalasia as spastic esophageal disorders (SED), their combined prevalence is low (2% within the Chicago v.3 diagnostics) (7). Traditional treatments (LHM, PD) are not directed to the esophageal body muscle dysfunction but to lower LES relaxation pressure. This feature may explain the lower rates of symptom release in patients affected by spastic disorders.

Esophageal motility disorders have been defined differently during the evolution of the proposed classifications. The three current subtypes of achalasia were defined in the Chicago classification v.2 (8), with a different nomenclature in the Spechler and Castell (9) and the Chicago v.1 (10) classification. In addition, DES and jackhammer esophagus have been described based on different criteria, referring either to the velocity of the peristaltic wave propagation (10) or its distal latency (8). Hence, this may lead to bias when comparing the outcomes of the treatment with different techniques.

Peroral endoscopic myotomy (POEM) was first performed in 2008 by Inoue et al. (11). Since then, the technique has been adopted by several centers around the world with > 5,000 procedures performed (12). It has a proven short-term efficacy that is comparable to PD and LHM in patients diagnosed with any subtype of achalasia (13). Recent studies suggest that POEM can improve the symptom relief in SED via a longer myotomy. A long intrathoracic extension of the myotomy is challenging to achieve by LHM and not possible by a PD (14). The long-term efficacy results of POEM are promising, with similar outcomes to LHM and exceeding the long-term efficacy data after PD (15). POEM is a safe procedure with no deaths directly related with the procedure reported so far and with a similar complication rate to previous procedures (16-19).

### **POEM endoscopic technique**

Conventional POEM procedure includes four main steps (20):

1. Step 1. *Mucosal incision*. The point of entry can be the posterior or the anterior (21-23) wall of the esophagus. Following the injection of different solutions, a 1.5- to 2-cm longitudinal incision is performed either in the 5 to 6-o'clock position (posterior, guided by the spine print) or at the 1 to 2 o'clock position (anterior), approximately 10 cm above the EGJ. A cranial incision can be performed for a longer tunnel that is required for spastic disorders. Posterior incision may allow subsequent techniques, such as fundoplication, and aids to avoid fibrosis in the stitching areas.
2. Step 2. *Submucosal tunnel*. The tunnel is created distally by using a technique similar to endoscopic submucosal dissection. It is progressed over the muscle fibers of the EGJ until the first 2-4 cm of the gastric submucosal space.
3. Step 3. *Endoscopic myotomy*. Under direct endoscopic view 2 cm below the mucosal entry point, the circular muscular layer is selectively dissected until 2 to 3 cm below the EGJ. Muscle fibers are longitudinally dissected over a minimum length of 6 to 8 cm in the esophagus and at least 2 cm into the cardia according to the surgical standards of LHM. In the case of SED, such as JE or DES, myotomy should be guided via HRM findings. Most groups perform a partial myotomy, selectively dissecting the circular muscle layer (23). Full thickness myotomy reduces

the procedure duration, enhances the chances of recovery of esophageal contraction and the secondary adverse events are no more frequent than in partial myotomy. Nevertheless, one study that included 24 patients suggests that this procedure may enhance more reflux than a partial myotomy (24). A substantial reduction of lower esophageal sphincter (LES) tone is confirmed by opening the EGJ with gentle insufflation through the endoscope and easily passing an endoscope through the lumen of the esophagus.

4. Step 4. *Closure of mucosal entry.* After careful hemostasis, the mucosal incision site is closed with several hemostatic clips. Endoscopic suturing closure is a feasible option although, the procedure seems longer and more expensive than using hemostatic clips (25).

High definition endoscope and a carbon dioxide pump are employed during POEM. It must be performed under general anesthesia with endotracheal intubation with positive ventilation. A prior endoscopy with esophageal liquid/solid waste removal is recommended to prevent aspiration (26).

The number of procedures required to achieve expertise has not been standardized. In one series, POEM was slightly less effective in the first ten patients, although there were no differences in complication rates (15).

The duration is variable between reports from different groups. Ngamruengphong (27) et al. observed a medium lasting of 128 min in 100 consecutive patients. Fumagalli et al. (28) reported 118-139 min in redo myotomy and 62 minutes on naïve patients. Li CJ et al. completed the procedure in only 55 minutes in individuals older than 65 years old (29).

#### **GERD after POEM**

Gastroesophageal reflux disease (GERD) usually appears after POEM. Its prevalence is heterogeneous among series which employ different surveillance methods. GERD-related symptoms appear in a small number of patients (8.2 [15] to 16.8% [30]) and the GERD-Questionnaire score decreases globally in the quality of life (QoL) series (31). However, up to 60% of patients present some grade of esophagitis in the upper endoscopy six months after the POEM procedure (32). Abnormal pH testing is present in 16 to 68.4% in the different series (21). An adequate symptomatic and mucosal response to PPI has been globally described. One



retrospective meta-analysis found no significant differences in post procedure GERD between POEM and LHM (33).

This is a comprehensive literature review of the efficacy of POEM, PD and LHM for the different esophageal motility disorders using a PubMed based search of ending on the 5<sup>th</sup> January 2017. Medical treatment is not included in this review due to its low efficacy and BoTox™ injection due to its reversible effects.

## **POEM VS OTHER TREATMENTS IN ESOPHAGEAL MOTILITY DISORDERS**

### **Achalasia**

#### ***Type I and type II achalasia***

##### **POEM**

POEM has proven to be an effective technique for symptom relief in achalasia. These are usually measured by the Eckardt Score. Short-term results (after three months) show a consistently significant improvement of the Eckardt score (> 3 points) in > 90% of patients (30,34-36) regardless of subtype (37). One study found a trend for a reduction of chest pain in ten patients with type I achalasia (37). A systematic review of 1,122 POEM from 22 studies demonstrated that the Eckardt score reduces from  $6.8 \pm 1.0$  to  $1.2 \pm 0.6$ , respectively (Eckardt score  $\pm$  standard deviation) (38). The benefits with regard to the quality of life have also been reported (31,39). Long-term studies monitoring weight have shown increases of around 4-4.5 kg 30 months after POEM (40). Curiously, a trend for a larger weight gain was observed in patients receiving full thickness myotomy vs circular myotomy (p 0.18) (21).

Long term results are also satisfactory and stable over time, with a > 90% response rate 36 months after treatment (15,24,41) and a very slight decrease to 88.5% in the third year with a median Eckardt score of 1 (30). One less optimistic study showed a decrease from 97% to 82.4% at 12 months after the POEM procedure (42).

In terms of objective measures, five minute timed barium swallow significantly decreases to 2.3 cm *versus* the initial 10.1 cm (34). Other studies consistently demonstrated this finding with esophageal emptying that improved from 40 to 90% in timed barium swallow and 93% of patients demonstrating > 90% emptying after one minute (43).

The HRM four seconds integrated relaxing pressure (4sIRP) parameter monitors the opening of LES. POEM improved relaxation of EGJ with a decrease in 4sIRP from  $30.78 \pm 2.9$  mmHg to  $13.46 \pm 1.4$  mmHg (27). As well as the 4sIRP improvement, other reports have demonstrated an improvement in LES basal pressure (40) which persists three years after POEM (30).

#### Pneumatic dilation

PD is an endoscopic technique focused on breaking LES muscular fibers with an inflatable balloon. The diameter of the balloon is not standardized and is calculated based on previous experiences from other studies, and thus cannot be adjusted on an individual basis. A 30 mm balloon is recommended initially (44). With regard to efficacy, 75-90% short term rates are reported (45), however, PD response falls significantly in long term studies. One-third of patients have a symptomatic relapse in the following 2-3 years and 70-80% may be rescued with a re-dilation (45). A meta-analysis showed a rate of 50% responders at five years and 25% at ten years (46). In addition, Eckardt et al. (47) registered a lower symptom free five-year survival (42-51%).

#### Laparoscopic Heller myotomy

LHM has been considered as the gold standard intervention for achalasia due to the adequate short and long-term results. Short-term efficacy of LHM is high, calculated at around 90% (44). It reaches 67-85% for type I and 95-100 for type II achalasia (48), and a post-hoc analysis demonstrated 81% in type I and 93% in type II (49). However, the results do not seem to be better than PD within the first two years (50,51). The effect of LHM is lower in sigmoid achalasia (13).

Two meta-analyses have studied LHM vs POEM. Marano et al. (33) concluded that there are no differences in the post-Eckardt score (< 1-year follow-up), operative time, post-operative pain score, analgesic requirements and complications, but the length of hospital stay was shorter in the POEM group. Zhang et al. (13) reported similar findings although a significant improvement in short-time post-Eckardt score was found.



A decrease in efficacy has been observed in LHM patients with only a 50-60% rate of “excellent controlled symptoms” over the long-term (five years) (51). Post-operative dysphagia in Dor fundoplication for GERD (in patients with a prior normal esophageal function) is around 3% (52). Thus, post-operative dysphagia may occur due to achalasia recurrence or fundoplication related dysfunction, thus identifying the cause is a challenge.

#### Esophageal stenting

Esophageal stenting is still not currently widely used and recent evidence is lacking. There is no agreement with regard to the best diameter for stents (53). Studies achieving the best results employ a 30 mm partially covered SEMs for three to seven days with a 100% initial efficacy decreasing to 85% at ten years follow-up (54).

#### ***Type III achalasia***

Type III achalasia (spastic) is sometimes included in SED although its response to traditional treatments (such as PD or LHM) is better than DES or JE (49). In a specific analysis, 96.3% of type III achalasia patients responded well to POEM (12), and the only procedural difference in comparison with type I/II achalasia patients was the performance of a longer myotomy. A meta-analysis found a 92% efficacy (14).

LHM short-term for type III response is estimated at 86% (49), with some series showing a more limited effect (69.3%) at a median follow-up of 31 months (48). No long-term results were found specifically for type III achalasia. Forty-nine type III achalasia patients receiving POEM were compared to 26 receiving LHM with a significantly better clinical response (98% vs 80.8%), with a longer myotomy and less adverse events in the POEM group (55). In the review by Rohof et al. (49), a 40% success rate was observed after PD in ten patients with type III achalasia.

#### **Distal esophageal spasm**

The number of patients with DES treated with POEM is still low, although the results are promising. In a series of nine patients (20), a clinical response was found in 100%, including a significant relief of chest pain. Other short series have been published with complete symptom

relief and HRM guided spastic peristalsis cessation. These POEM procedures were no longer in duration (75-85 minutes) although myotomy length was more extended following HRM findings (56,57). The meta-analysis by Khan et al. identified four studies (a total of 18 patients) regarding POEM for DES with an 88% clinical response (14).

There are very few series regarding LHM for DES, one study reported 16/20 dysphagia and 100% chest pain relief (58). These results have not been reproduced by other groups, probably related to the difficulty of accessing the proximal esophagus, a factor that diminishes the efficacy of traditional LHM for SED (59).

### **Jackhammer (hypercontractile) esophagus**

In the series by Khashab et al. (12), ten patients with JE were included. The symptomatic response, although superior to medical treatment, is significantly inferior to other SED (type III achalasia and DES), reaching a 70% response with an Eckardt score after POEM of 2.6 compared to 0.86 for type III achalasia and one for DES.

Other studies (43) observed a 75% clinical response of chest pain and a case report revealed full symptomatic recovery after post POEM dilation of the spastic residual esophageal segment (60).

The review by Khan et al. including patients from the previously referred series estimates POEM efficacy at 72% (14).

The lower response of JE to POEM may not be related with procedure inefficacy but with a poor correlation of manometry findings with symptom development. JE patients may also present GERD and psychiatric comorbidity (61).

### **EGJ outflow obstruction**

POEM has not been widely applied for EGJOO. EGJOO in the absence of an underlying structural cause can potentially evolve to achalasia but it can also resolve spontaneously (62). However, an adequate response has been reported to acotiamide (4). Thus, long-lasting effect techniques such as POEM and LHM are suggested to be a second/third line treatment based on the response to botox, PD and LHM in short series, especially in cases with a long history of

dysphagia (63).

### **Special circumstances**

#### Sigmoid esophagus

Sigmoid esophagus is not a contraindication for a POEM approach. POEM is safe and effective under these circumstances (22,40) with series showing an overall treatment success of 95.6% and a morphological improvement in 95% of 23 patients. However, it is recommended that the procedure be performed by an expert since it is technically challenging and a trend to present more minor complications has been reported (64). Sigmoid esophageal shape has not been found as a predictor of a POEM treatment failure (65). Another study including individuals with > 30 mm dilation in the esophagram had an equal perforation and pneumothorax rate in comparison to those patients with a < 30 mm diameter (16). LHM effect is lower in sigmoid achalasia (13) but both approaches have not been compared in this condition.

#### Elderly patients

One study evaluated POEM in 15 patients over 65 year of age (29) and found a clinical response of 100% with an increase of quality of life. One third of the patients presented GERD but the symptoms were fully controlled with PPI. Another study (66) compared PD with POEM (21 vs 10) in > 65 patients without an increase of adverse events and no differences were found in short-term Eckardt decrease.

#### Pediatric patients

POEM can be performed with no technical modifications in children. It has been shown in several pediatric cohorts with patients > 2-years of age (67,21). The largest study included 27 individuals with success achieved in 26 during two years of follow-up. No complications or special technical difficulties were reported (68). The study by Nabi et al. (69) reported a 100% efficacy in 15 children during a one year follow-up, including radiological evidence.

In a comparative study of LHM and GERD, there were no differences with regard to mid-term efficacy or post GERD appearance (1/9) in nine patients treated with POEM or LHM. However,

one patient in the LHM group had an esophageal perforation. Operative time was shorter in the POEM group (70). Tan et al. (71) compared prospectively a cohort of patients with PD (9) and POEM (12) and found no complications and a clinical response of 33.3% vs 100% after 36 months of follow-up.

Rescue after other therapies

#### *Post-PD*

The largest study of post-PD POEM was performed by Ling et al. (72) with 21 consecutive patients achieving the same efficacy as naïve POEM. These authors and Teitelbaum et al. reported that previous PD was an independent factor for a longer POEM duration, while others studies reported no differences in duration or safety (74,75).

#### *Post LHM*

A series of 12, ten and five post LHM have been analyzed; no differences with regard to safety were found and the efficacy was 97-100% (76,77).

#### *Re-POEM*

One study that included four patients that received re-POEM due to symptom relapse reported three full responses at nine months of follow-up (15). Zhou et al. (78) performed re-POEM on 15 patients (post-Eckardt > 4) with a full symptomatic relief in 100% of cases and a decrease of 4sIRP from 25 to 9.5 mmHg. GERD was present in 33.3% of re-POEM. Other studies including 40% of patients with prior interventions (BoTox®, PD, BoTox® + PD, LHM) reported the same efficacy as naïve patients (93.2%) but no specific analysis was performed on pre-treated individuals (12).

### **FINAL CONSIDERATIONS**

POEM is a non-surgical “HRM guided” procedure that allows an extended myotomy of practically the full esophageal length. It has demonstrated excellent short and mid-term results for all achalasia subtypes with a similar safety profile as other techniques (PD and LHM). Long-

term efficacy data are promising but need to be assessed beyond the periods studied nowadays (three years).

Due to the extended elective myotomy, POEM is being used for the treatment of DES and JE with promising results that exceed the outcomes of other techniques. However, larger studies are still lacking.

Although POEM respects the anatomy of EGJ (His angle and phrenoesophageal ligament) and must not be followed by a fundoplication, post procedure GERD is one of the main concerns. Nevertheless, there is still no comparative evidence to suggest that the GERD rate is higher post-POEM than after surgical myotomy associated to partial fundoplication or after a PD procedure. Previous esophageal interventions do not seem to be a contraindication for POEM performed by experienced endoscopists, with successful series of post-LHM, post-PD, post-BoTox® and even post-POEM. It is not an issue for subsequent interventions such as PD or LHM. Randomized clinical trials comparing POEM with PD and LHM are needed, as well as longer term results. Briefly, POEM is a novel endoscopic treatment for achalasia with an efficacy similar to LHM. It is also a better approach for the treatment of SED such as DES and JE and allows the re-treatment of patients when any other technique fails.

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**Table 1. Studies comparing POEM vs other techniques**

<i>Comparison</i>	<i>Studies</i>	<i>Design</i>	<i>Main findings</i>
POEM vs LHM	Zhang et al. 2016 (10)	Retrospective meta-analysis	Lower short-term Eckardt in POEM group

	Marano et al. 2016 (30)	Retrospective meta-analysis	Shorter hospital stay in POEM
	Kumbhari et al. 2015 (52)	Retrospective regarding type III achalasia	Clinical success 98% POEM vs 80.8% LHM
	Caldaro et al. 2015 (66)	Prospective in a pediatric cohort	Shorter operation time and longer myotomy in POEM group
POEM vs PD	Wang et al. 2016 (63)	Retrospective in > 65-year cohort	36-months efficacy: no differences
	Tan et al. 2016 (67)	Retrospective in pediatric cohort	36-months efficacy: 100% POEM vs 33% PD

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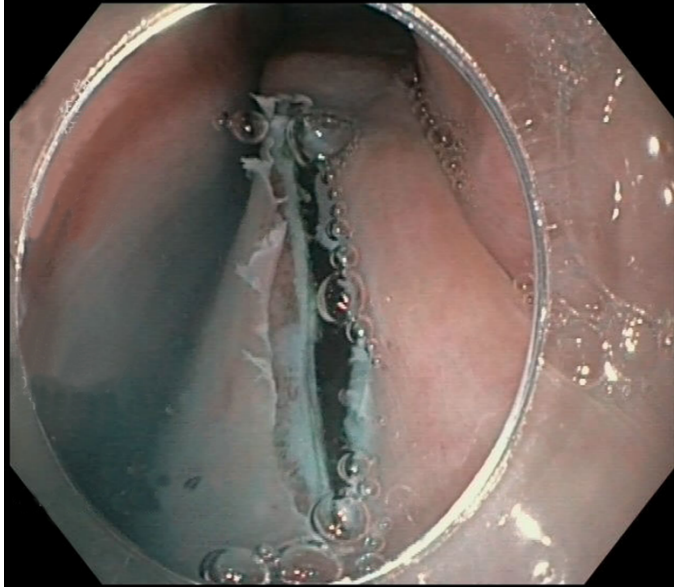


Fig. 1. Step 1. A 1.5 cm longitudinal incision is performed in the posterior position after injection of indigo carmine and colloid solution.

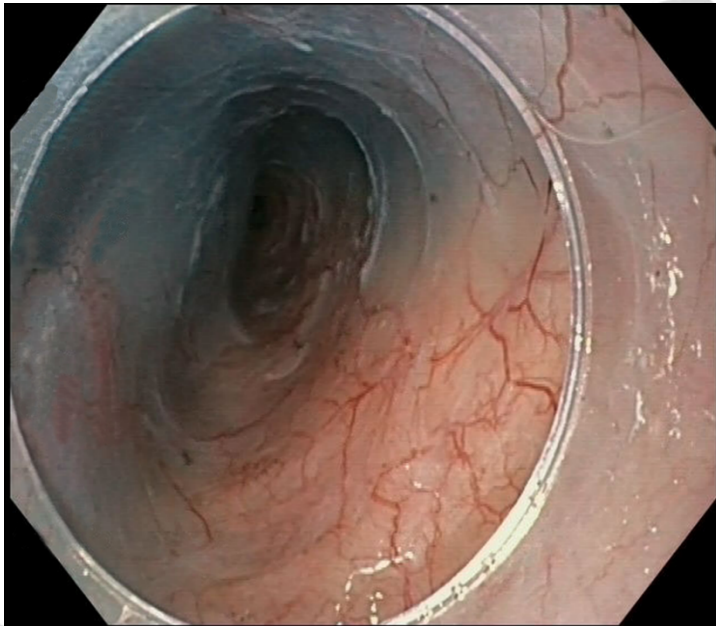


Fig. 2. Submucosal tunnel global view. The mucosal side is at the top of the image and the muscular side at the bottom.

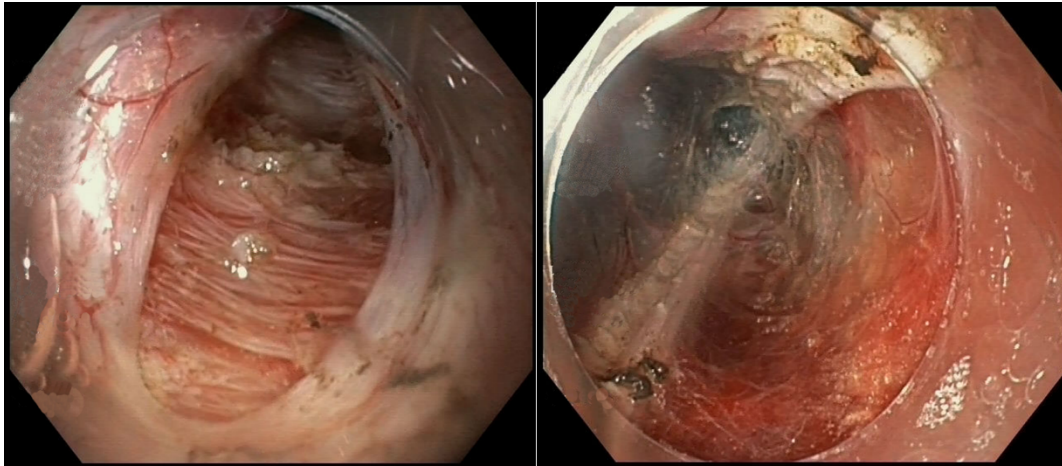


Fig. 3. Left: dissection of the circular muscle bundle. Right: full thickness myotomy at the distal part of the tunnel.

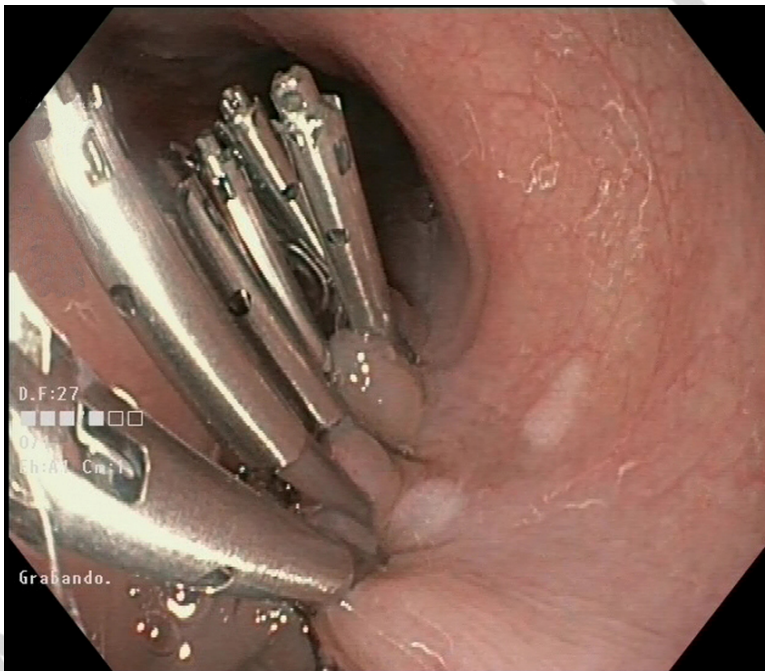


Fig. 4. Longitudinal incision closure by hemoclips.



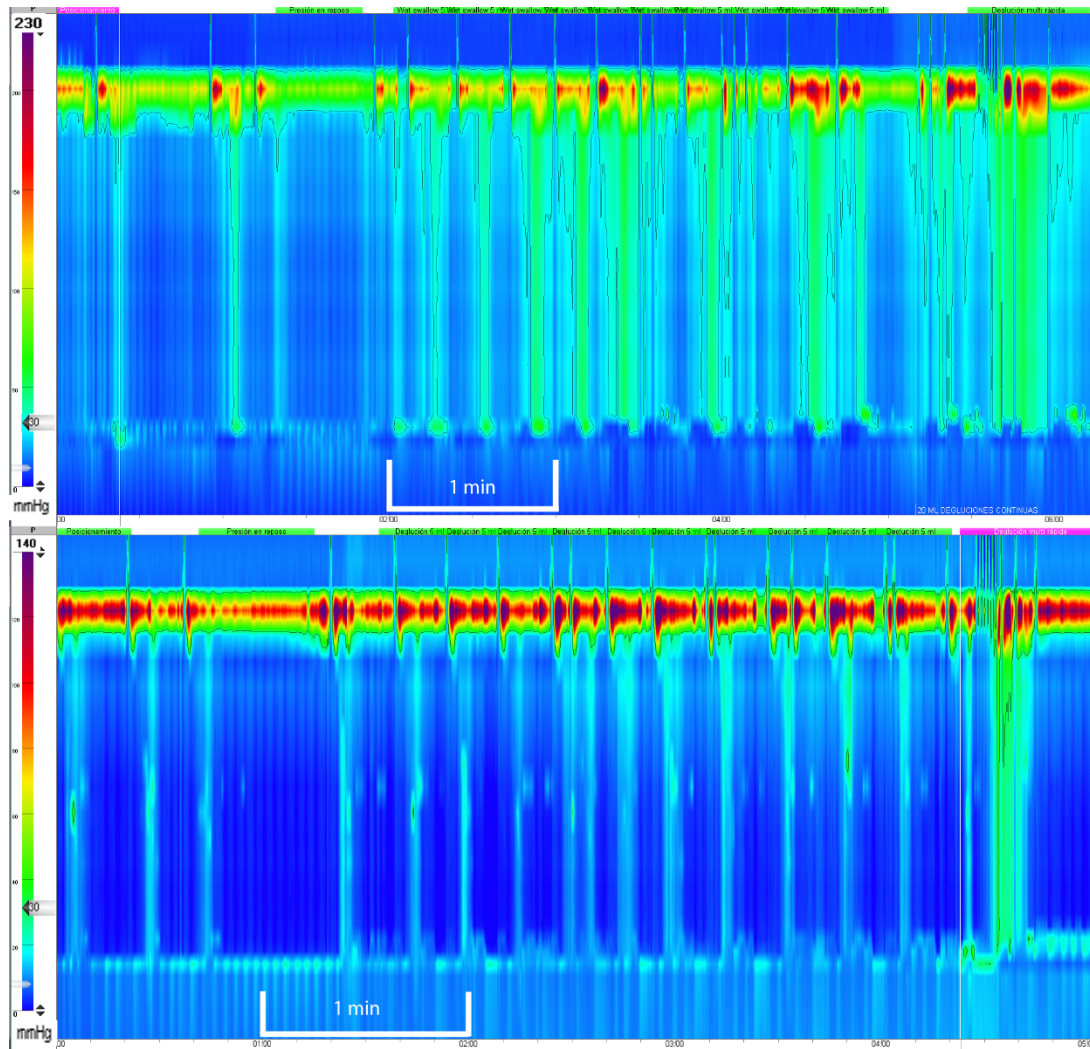


Fig. 5. HRM (water perfused, 22 channels, MMS™, Enschede, The Netherlands). Full-length study of a patient with type II achalasia pre (up) and post (down) POEM procedure including baseline pressure recording, ten swallows with 5 ml and a drink challenge with 200 ml of water. Referred to atmospheric pressure. Isobaric contour line at 30 mmHg.

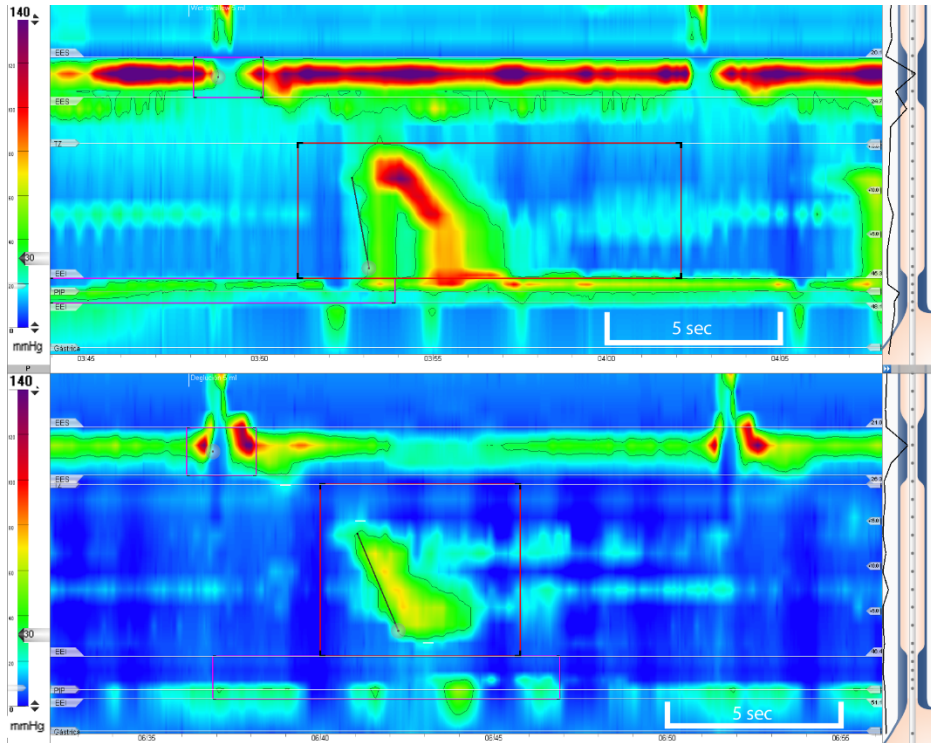


Fig. 6. HRM (water perfused, 22 channels, MMS™, Enschede, The Netherlands). A single 5 ml water swallow from a patient diagnosed with type III achalasia pre (up) and post (down) POEM procedure. Referred to atmospheric pressure. Isobaric contour line at 30 mmHg. There is no pressure ramp and the myotomized area is shown at the distal esophagus.