

*Reflux symptoms in treated achalasia*

*Ponds et al*

### **Supplement 1**

This appendix has been provided by the authors to give readers additional information about the study.

### **Reflux symptoms and oesophageal acidification in treated achalasia patients are often not reflux related**

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## 1. Study subject and inclusion criteria

## 1.1 Eligibility criteria

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## 1. Study subject and inclusion criteria

### 1.1 Eligibility criteria

#### Inclusion criteria

Treated achalasia patients with gastro-oesophageal reflux symptoms

- Diagnosis of idiopathic achalasia confirmed by oesophageal manometry that shows the following criteria:
  - Aperistalsis or simultaneous contractions in the oesophageal body.
  - LOS dysrelaxation.
- Treatment of achalasia with one of the following procedures:
  - Endoscopic balloon dilatation
  - Surgical Heller myotomy
  - Per-oral endoscopic myotomy (POEM)
- Minimum total score on the Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) of  $\geq 8$ .
- Gastro-oesophageal symptoms after treatment lasting more than 3 months.
- Age 18-80 years.
- Written informed consent.

Treated achalasia patients without gastro-oesophageal reflux symptoms

- Diagnosis of idiopathic achalasia confirmed by oesophageal manometry that shows the following criteria:
  - Aperistalsis or simultaneous contractions in the oesophageal body.
  - LOS dysrelaxation.
- Treatment of achalasia with one of the following procedures:
  - Endoscopic balloon dilatation
  - Surgical Heller myotomy
  - Per-oral endoscopic myotomy (POEM)
- Maximum total score on the Gastro-Oesophageal Reflux Disease Questionnaire (GORDQ) of  $< 8$ .
- No gastro-oesophageal symptoms after treatment.
- Age 18-80 years.

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- Written informed consent.

**Exclusion criteria**Treated achalasia patients with gastro-oesophageal reflux symptoms

- Pseudoachalasia.
- Upper gastrointestinal malignancy.
- Chagas disease.
- Peptic ulcer disease.
- Inability to stop PPI, H2-receptor antagonist or prokinetic drug for two weeks
- Presence of an extremely dilated oesophagus body >5 cm

Treated achalasia patients without gastro-oesophageal reflux symptoms

- Pseudoachalasia.
- Upper gastrointestinal malignancy.
- Chagas disease.
- Peptic ulcer disease.
- Inability to stop PPI, H2-receptor antagonist or prokinetic drug for two weeks
- Presence of an extremely dilated oesophagus body >5 cm

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## Tables

	Patients with acid hypersensitivity (n=25)	Patients without acid hypersensitivity (n=13)	<i>P</i>
<b>Achalasia subtype at diagnosis</b> (n (%))			0.64
Type I	9 (36)	4 (31)	
Type II	15 (60)	8 (62)	
Type III	1 (4)	1 (8)	
<b>Achalasia treatment</b> (n (%))			0.90
Pneumodilation <sup>#</sup>	1 (4)	1 (8)	
Laparoscopic Heller's myotomy	7 (28)	2 (15)	
Peroral endoscopic myotomy	7 (28)	4 (31)	
Pneumodilation* and laparoscopic Heller's myotomy	7 (28)	4 (31)	
Pneumodilation* and peroral endoscopic myotomy	3 (12)	2 (15)	
<b>Disease duration</b> (years (mean (SD)))	8.2 (7.0)	7.8 (5.7)	0.85
<b>24-hour pH-impedance monitoring</b>			
<b>Acid exposure time</b> (AET: % of time pH <4; mean (95% CI))			
Total	13.9 (7.3 to 20.5)	9.2 (3.4 to 14.9)	0.33
Upright	10.8 (5.3 to 16.2)	4.8 (2.2 to 7.4)	0.05
Supine	18.0 (7.7 to 28.4)	15.2 (4.1 to 26.3)	0.73
<b>Pathological acid exposure</b> (AET pH<4 in >6%; n (%))	17 (68)	7 (54)	0.39
<b>Baseline impedance</b> (Ω; median (IQR))			
Proximal	2411 (1649-3150)	2220 (1780-2773)	0.55
Distal	487 (368-660)	476 (339-750)	1.00
<b>Endoscopy</b>			
Reflux oesophagitis (n (%))	11 (44)	3 (23)	0.29
<b>High resolution manometry</b>			
Basal LOS pressure (mmHg, median (IQR))	3 (2-6)	3 (3-7)	0.70
Integrated relaxation pressure (mmHg, median (IQR))	6.6 (3.3-8.6)	5.9 (3.7-9.3)	0.87
<b>OGJ distensibility</b> (at 50 mL, mmHg/m <sup>2</sup> , median (IQR))	5.2 (4.5-7.0)	4.8 (2.7-5.8)	0.11

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<b>Timed barium oesophagogram</b>			
Barium column at 5 min (cm, median (IQR))	1.4 (0-2.5)	1.7 (0-2.6)	0.81
Oesophageal diameter (cm, median (IQR))	2.5 (2-3.1)	2.3 (2-2.8)	0.93
<b>Perception oesophageal mechanical distension</b>			
Volume first perception (mL, median (IQR))	50 (40-70)	70 (65-70)	0.01
Symptom intensity (VAS, median (IQR))	2.9 (0.3-5.9)	0 (0-1.9)	0.05
Distension sensitivity score (median (IQR))	47 (0-160)	0 (0-7)	0.02

**Table 1.** Factors related to acid hypersensitivity.

Abbreviations: AET, acid exposure time; CI, confidence interval; LOS, lower oesophageal sphincter; OGJ, oesophagogastric junction; IQR, interquartile range; VAS, visual analogue score.

#Pneumodilation up till 35-mm balloon. \*Pneumodilation up till 40-mm balloon.

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	Patients with pathological acid exposure (n=24)	Patients without pathological acid exposure (n=14)	<i>P</i>
<b>BMI</b> (kg/m <sup>2</sup> ; mean (SD))	26.2 (4.3)	24.8 (2.7)	0.27
<b>High resolution manometry</b>			
Basal LOS pressure (mmHg, median (IQR))	3 (2-4.8)	4.6 (3-9.3)	0.034
Integrated relaxation pressure (mmHg, median (IQR))	6.2 (3.1-8.7)	6.4 (4-10.5)	0.56
<b>OGJ distensibility</b> (at 50 mL, mmHg/m <sup>2</sup> , median (IQR))	5.5 (4.6-7.0)	4.6 (3.4-5.5)	0.032
<b>Timed barium oesophagogram</b>			
Barium column at 5 min (cm, median (IQR))	0 (0-1.8)	2.5 (1.2-3.1)	0.002
Oesophageal diameter (cm, median (IQR))	2.2 (2-3)	2.7 (2-3.4)	0.18
<b>24-hour pH-impedance monitoring</b>			
<b>Baseline impedance</b> ( $\Omega$ , median (IQR))			
Proximal	2163 (1865-2739)	2763 (1585-3260)	0.23
Distal	487 (347-730)	493 (348-702)	0.88
<b>Acid perfusion test</b>			
Time to perception (min, median (IQR))	8 (4-27.5)	9 (5.5-30)	0.46
Symptom intensity (VAS, median (IQR))	5.5 (0.6-8)	4.1 (0-7)	0.48
Perfusion hypersensitivity score (median (IQR))	82 (1-135)	64 (0-170)	0.82
<b>Perception oesophageal mechanical distension</b>			
Volume first perception (mL, median (IQR))	70 (50-70)	60 (40-70)	0.60
Symptom intensity (VAS, median (IQR))	1.5 (0-4.3)	1 (0-5.2)	0.82
Oesophageal distension sensitivity score (median (IQR))	0 (0-84)	9 (0-174)	0.61

**Table 2.** Factors related to pathological acid exposure.

Abbreviations: BMI, body mass index; CI, confidence interval; LOS, lower oesophageal sphincter; IQR, interquartile range; OGJ, Oesophagogastric junction; VAS, visual analogue score.

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	Laparoscopic Heller's myotomy (n=20)	Peroral endoscopic myotomy (n=16)	<i>P</i>
<b>24-hour pH-impedance monitoring</b>			
<b>Acid exposure time</b> (AET: % of time pH <4; mean (95% CI))			
Total	8.1 (3.6 to 12.5)	19.1 (10.2 to 28.1)	0.02
Upright	6.5 (2.3 to 10.7)	12.5 (5.4 to 19.6)	0.12
Supine	9.6 (3.4 to 15.9)	28.5 (13.3 to 43.7)	0.02
<b>Pathological acid exposure</b> (AET pH<4 in >6%; n (%))	11 (55)	13 (81)	0.16
<b>Acidification patterns</b> (% of time; mean (95% CI))			
Acid reflux with normal clearance	0.08 (0.01 to 0.14)	0.2 (0.06 to 0.33)	0.10
Acid reflux with delayed clearance	2.8 (0.07 to 5.57)	7.6 (1.1 to 14.1)	0.16
Acid fermentation	3.5 (0.8 to 6.12)	5.6 (1.4 to 9.8)	0.34
Stasis of ingested acidic food	3.8 (-1.04 to 8.58)	6.7 (-0.9 to 14.6)	0.46
Unclassified	0.3 (-0.1 to 0.73)	1.8 (-0.98 to 4.6)	0.28
<b>Number of acidification events</b> (median (IQR))			
Acid reflux with normal clearance	0 (0-1)	0.5 (0-2.8)	0.15
Acid reflux with delayed clearance	0 (0-1)	1.5 (0-3)	0.07
Acid fermentation	0 (0-1.8)	0.5 (0-2.5)	0.57
Stasis of ingested acidic food	0 (0-1)	0 (0-2)	0.23
Unclassified	0 (0-1)	0 (0-0.8)	0.79
<b>Number of patients per acidification pattern</b> (n (%))			
Acid reflux with normal clearance	6 (30)	8 (50)	0.22
Acid reflux with delayed clearance	8 (40)	10 (63)	0.18
Acid fermentation	8 (40)	9 (56)	0.33
Stasis of ingested acidic food	6 (30)	7 (44)	0.39
Unclassified	6 (30)	4 (25)	0.74
<b>Endoscopy</b>			
Reflux oesophagitis (n (%))	7 (35)	7 (44)	0.59
<b>Acid perfusion test</b>			
Time to perception (min, median (IQR))	6 (4-20)	14 (4-30)	0.26
Symptom intensity (VAS, median (IQR))	5.4 (1.1-7.8)	3.8 (0-7.9)	0.65
Perfusion sensitivity score (median (IQR))	112 (8-172)	35 (0-110)	0.12



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<b>Perception oesophageal mechanical distension</b>			
Volume first percepton (mL, median (IQR))	60 (40-70)	70 (50-70)	0.36
Symptom intensity (VAS, median (IQR))	3 (0-5.2)	1.2 (0-2.6)	0.26
Distension sensitivity score (median (IQR))	13 (0-170)	0 (0-71)	0.26

Table 3. Outcome 24-hour pH-impedance, oesophagogastroduodenoscopy and provocation tests per treatment group.

Abbreviations: AET, acid exposure time, CI, confidence interval; IQR, interquartile range; VAS, visual analogue score.