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# The inability to belch syndrome: A study using concurrent high-resolution manometry and impedance monitoring

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## Abstract

**Introduction:** Although inability to belch has previously been linked to dysfunction of the upper esophageal sphincter (UES), its underlying pathogenesis remains unclear. Our aim was to study mechanisms underlying inability to belch and the effect of UES botulinum toxin (botox) injections in these patients.

**Methods:** We prospectively enrolled consecutive patients with symptoms of inability to belch. Patients underwent stationary high-resolution impedance manometry (HRIM) with belch provocation and ambulatory 24-h pH-impedance monitoring before and 3 months after UES botox injection.

**Results:** Eight patients (four males, age 18–37 years) were included. Complete and normal UES relaxation occurred in response to deglutition in all patients. A median number of 33(15–64) gastroesophageal gas reflux episodes were observed. Despite the subsequent increase in esophageal pressure (from −4.0 [−7.7–4.2] to 8 [3.3–16.1] mmHg; $p < 0.012$), none of the gastroesophageal gas reflux events resulted in UES relaxation. Periods of continuous high impedance levels, indicating air entrapment (median air presence time 10.5% [0–43]), were observed during 24-h impedance monitoring. UES botox reduced UES basal pressure (from 95.7[41.2–154.0] to 29.2 [16.7–45.6] mmHg; $p < 0.02$) and restored belching capacity in all patients. As a result, esophageal air presence time decreased from 10.5% (0–43.4) to 0.7% (0.1–18.6; $p < 0.02$) and esophageal symptoms improved in all patients (VAS 6.0 [1.0–7.9] to 1.0 [0.0–2.5]; $p < 0.012$).

**Conclusion:** The results of this study underpin the existence of a syndrome characterized by an inability to belch and support the hypothesis that ineffective UES relaxation, with subsequent esophageal air entrapment, may lead to esophageal symptoms.

KEYWORDS
belching disorder, high-resolution manometry, impedance, inability to belch, UES, upper esophageal sphincter

**Abbreviations:** DCI, distal contractile integral; DL, distal latency; HRIM, high-resolution impedance manometry; IRP, integrative relaxation pressure; LES, lower esophageal sphincter; TLESR, transient lower esophageal sphincter relaxation; UES, upper esophageal sphincter.

## 1 | INTRODUCTION

Belching or eructation is a physiological mechanism that enables venting of accumulated gaseous material from the stomach into the esophagus and pharynx. In healthy volunteers, intragastric air enters the esophagus via transient lower esophageal sphincter relaxations (TLESRs). The subsequent rapid increase in esophageal pressure to the level of the intragastric pressure, also known as common cavity phenomenon, causes distention of the esophageal body and stimulates stress receptors that will initiate upper esophageal sphincter (UES) relaxation and expulsion of air.[1,2]

In recent years, an increasing number of patients have been referred to our clinic because of an inability to belch, typically with symptoms of chest pain and audible gurgling noises from the chest. Although inability to belch as part of the gas-bloating syndrome occurs regularly post-fundoplication, an inability to belch from esophagus to oropharynx is rarely reported in medical literature, and its underlying etiology is virtually unknown. Three previous case reports described inability to belch and corresponding symptoms and attributed it to UES dysfunction.[3-5] A more recent study reported on 51 patients with inability to belch who were treated with injections of botulinum toxin (botox) into the cricopharyngeus muscle.[6] Interestingly, all patients reported ability to belch and relief of symptoms post-treatment, which may support the role of UES dysfunction in these patients.[6] Nonetheless, the question remains whether the symptoms are indeed the result of failure of the belch reflex pathway or are rather functional or behavioral in nature. Esophageal air transport patterns, UES physiology, and the effect of botox injections on UES function have never been objectively investigated in a series of consecutive patients.

Therefore, the aim of this study was to evaluate pathophysiological mechanisms underlying symptoms of inability to belch using concurrent high-resolution manometry and impedance monitoring with belch provocation and 24-h esophageal impedance monitoring. We aimed to assess the ability of the UES to relax in response to the influx of gas into the esophagus. Secondly, we aimed to study the effect of UES botox injections on pharyngoesophageal symptoms, UES pressure, and gas reflux patterns.

**Key Points**

- An increasing number of patients have been seeking medical attention because of a self-reported inability to belch associated with esophageal symptoms such as chest pain.
- Ineffective UES relaxation in response to gastroesophageal gas reflux was found to be the underlying cause of esophageal air entrapment, leading to esophageal symptoms in patients with inability to belch. Therapy with UES botox injections restored belching capacity in all patients.
- This study confirms the existence of a syndrome characterized by an inability to belch. Therapy with UES botox injections is a potential treatment for these patients.

## 2 | METHODS

### 2.1 | Study subjects

For this cohort study, we included patients that presented with symptoms of inability to belch who were referred for treatment with UES Botox injections to the clinic of a Dutch teaching hospital between October 2019 and March 2021. Symptoms were defined as chest pain, gurgling noises and/or bloating at least three times a week, in combination with a self-reported inability to belch. Patients with a history of preexisting pharyngoesophageal disorders or surgery, or the use of medication affecting esophageal motility were excluded. The study protocol was submitted to the local institutional review board. Formal evaluation was waived according to Dutch law (reference number W19_307#19.365). Written informed consent was obtained from all patients before study participation. The study was prospectively registered in the Dutch trial registry (NTR NL8494, trialregister.nl).

### 2.2 | Study protocol

All patients were studied before and 3 months after UES botox injections. Each study day consisted of two parts and started with a stationary part using esophageal high-resolution impedance manometry (HRIM) to evaluate esophageal motility and UES and LES pressures in the supine position (Figure S1). This was followed by a belch provocation test for which patients drank 500 ml of carbonated water (0 kcal, 7 g/L carbon dioxide gas). Using HRIM, gastroesophageal reflux of liquids and gas and UES function were recorded for the following 15 min in the upright position. Subsequently, patients went home with an ambulatory pH-impedance recording device. Gastroesophageal gas reflux patterns, air swallowing, and esophageal air presence time were monitored for 24 h. Gastric acid suppressants were discontinued 7 days before each study day. Pharyngoesophageal and abdominal symptoms and health-related quality of life were evaluated before and after treatment. A detailed description of the HRIM and ambulatory pH-impedance study protocol can be found in Appendix A in supplemental material

### 2.3 | Botulinum toxin injection in the upper esophageal sphincter

The botox injection procedures were carried out at the outpatient clinic during brief general anesthesia. The procedure was performed as described by Bastian et al[6] In short, a laryngoscope

was introduced to visualize the cricopharyngeus muscle. A 25-gauge butterfly needle was used with a laryngoscopy forceps. A total dose of 180 U of Dysport (equivalent to 50 U of Botox) in 1 ml was divided and injected over several locations of the sphincter. All procedures were performed by one and the same otorhinolaryngologist.

### 2.4 | Data analysis

Key esophageal pressure topography metrics were calculated according to the Chicago classification V4.[7] For each gastroesophageal gas reflux event recorded during the 15-min recording HRIM period, intraluminal pressures immediately before and during the gas reflux event at the level of the UES and in the esophageal body were measured. Esophageal air presence time was defined as the percentage of time with continuous high impedance values ≥3000 Ω. A detailed description on data analysis methods and the used definitions can be found in Appendix B in supplemental material

### 2.5 | Statistical analysis

Throughout the manuscript, data are presented as median with range. Statistical analysis was performed using SPSS statistics (version 24; SPSS). Comparisons were analyzed using the Wilcoxon signed rank test. Differences were considered statistically significant, when $p < 0.05$.

## 3 | RESULTS

### 3.1 | Patient characteristics and initial presentation

In total eight patients (four males, age 18–37 years) were included (Table 1). All patients described a long history of episodic gastroesophageal symptoms associated with gurgling noises in the chest and a self-reported inability to belch despite feeling the urge to do so during symptom episodes. Gurgling noises from the chest (100%), chest pain (75%), and bloating 100%) were the most commonly reported symptoms. Other symptoms included epigastric pain (53.5%), hiccups (37.5%), flatulence (37.5%), and nausea (37.5%). None of the patients reported symptoms of dysphagia or odynophagia. All patients described the inability to belch for as long as they could remember and reported avoidance of carbonated drinks and certain foods that would increase abdominal gas. Symptoms reportedly could be relieved by lying in the supine position. Occasionally, patients induced vomiting to vent air. Upper endoscopy and video laryngoscopy were performed in all patients. Besides incomplete glottal closure ($n = 1$) and a vocal cord polyp ($n = 1$), no major laryngopharyngeal abnormalities were found. A small endoscopic hiatal hernia was observed in three patients.

### 3.2 | High-resolution impedance manometry

Esophageal motility was classified as ineffective ($n = 5$) or absent ($n = 2$) in the majority of patients with a median DCI of 237 (17–754) mmHg·cm·s and a distal latency of 7.1 s (5.0–10.0). Complete

**TABLE 1** Baseline characteristics of included patients ($n = 8$)

| | *n* | % | Median (range) |
|---|---|---|---|
| Demographics | | | |
| Male sex | 4 | 50.0 | |
| Age at inclusion (years) | | | 27 (18–37) |
| BMI | | | 26.0 (18.3–24.9) |
| Symptoms at presentation | | | |
| Gurgling noises from the chest | 8 | 100.0 | |
| Bloating | 8 | 100.0 | |
| Chest pain | 6 | 75.0 | |
| Epigastric pain | 5 | 52.5 | |
| Hiccups | 3 | 37.5 | |
| Flatulence | 3 | 37.5 | |
| Nausea | 3 | 37.5 | |
| Laryngoscopic findings | | | |
| Vocal cord polyp | 1 | 12.5 | |
| Incomplete glottal closure | 1 | 12.5 | |
| Endoscopic findings | | | |
| Sliding hiatal hernia | 3 | 37.5 | |

Abbreviations: BMI, body mass index; *n*, number of patients.

and normal UES relaxation occurred in response to deglutition in all patients, with UES resting and residual relaxation pressures that fell within the normative range (95.7 (41.2–154.0) mmHg and −0.8 (−6.2–2.7) mmHg, respectively). Likewise, LES relaxation and resting pressures were normal (median IRP 7.2 (3.8–16.2) mmHg and basal LES pressure 20 (10.9–33.7) mmHg, respectively; Table 2).

### 3.3 | Provocation (carbonated water drink) test

The basal UES pressure averaged 67.3 (53.5–101.5) mmHg during the 15-min recording period. After ingestion of the carbonated water, all patients began have spontaneous gastroesophageal gas reflux events and experienced typical gastroesophageal symptoms. A median number of 33 (15–64) gas reflux episodes up to the level of the lower border of the UES were observed. Despite the increase in esophageal pressure during these episodes, from −4.0 (−7.7–4.2) to 8 (3.3–16.1) mmHg ($p < 0.012$), none resulted in UES relaxation in any of these patients. The average UES pressure in response to arrival of the gas reflux event (115.2 [80.8–161.3] mmHg) was significantly higher than average basal UES pressure prior to the gas reflux event (67.3 [53.5–101.5] mmHg, $p < 0.012$); in other words; there was an increase in UES pressure instead of the expected UES relaxation. The gastroesophageal gas reflux episodes did elicit secondary peristalsis in 6 (75%) patients, with a median of 92.7% (78.3–100) of the gas reflux episodes being followed by secondary contractions. These contractions transported the esophageal air back to the stomach, which was observed as a return to baseline impedance level in antegrade direction. The typical sequence of events during a gastroesophageal gas reflux episode is presented in Figure 1. Striking were the periods of repetitive gas reflux where air seemed to oscillate up and down in the esophagus (Figure 2). In the two patients with a manometric diagnosis of absent contractility, there was also absence of secondary peristalsis in reaction to gastroesophageal gas reflux. These patients had longer periods of continually high impedance values during the 15-min recording period, complicating the recognition of the separate gas reflux episodes.

### 3.4 | Ambulatory 24-h pH-impedance monitoring

During 24-h pH-impedance monitoring, patients reported a median of 9 (6–126) symptom episodes of inability to belch. The majority of these episodes (89.2% [66.7–100.0]) were associated with gastroesophageal gas reflux impedance patterns. During the ambulatory recording period, a median of 81 (7–185) gas reflux events occurred, but few air swallows (median 12 [4–41]) and supragastric belches (median 0 [0–1]) were observed (Table 3). In line with the repetitive gas reflux pattern observed on HRIM, similar periods of continuous high impedance levels, indicating air entrapment, were observed in 7 (87.5%) patients (Figure 3). The median 24-h esophageal air presence time was 10.5% (0.0–43.4). In one patient with normal esophageal peristalsis, no esophageal air entrapment was observed. Both occurrences of gastroesophageal gas reflux episodes and air entrapment were rare in the supine position (1 [0–9] and 0 [0.0–1.3], respectively). The median acid exposure time was 2.2% (0.0–20.2) and the number of mixed and pure liquid reflux episodes fell within normal ranges 6 (1–17) and 6 (1–46), respectively. Two patients with severe ineffective or absent esophageal motility had a pathological acid exposure, primarily as a result of long periods of stasis in the night.

### 3.5 | Effect of treatment

#### 3.5.1 | Symptom appraisal

All procedures were performed without complications. The majority of patients ($n = 6$) experienced swallowing difficulties the first 2 weeks post-treatment, which resolved spontaneously in all cases. Five patients reported to be able to belch spontaneously after treatment with UES botox injections. Three patients still needed an extra maneuver to vent air, for example, contraction of the abdominal muscles to increase abdominal pressure or tilting of the head to the side. Seven patients (87.5%) were satisfied with the effect of botox therapy and described a complete or almost complete relieve of symptoms. One patient had persistent symptoms of bloating and continued to experience mild symptoms of chest pain, while the sensation of gurgling noises had disappeared. Post-treatment VAS symptom scores for gurgling noises, bloating, retrosternal pain, epigastric pain, hiccups, and flatulence all improved significantly (all $p < 0.03$; Figure S2). QoL scores significantly improved post-treatment from 81% (69–85) to 91% (71–96; $p < 0.03$).

#### 3.5.2 | High-resolution impedance manometry and provocation test

High-resolution impedance manometry studies were repeated at 3-months follow-up. The calculated UES basal pressure during 10 wet swallows, and the averaged UES nadir pressure in response to gastroesophageal as reflux during the 15-min recording, showed a significant decrease compared to the baseline values (Figure 4A,B). Distal latency reduced from 7.1 (5–10) to 6.7 (5.0–9.0) $p < 0.03$. Treatment did not change LES resting and relaxation pressures (both $p > 0.05$), nor did it change DCI ($p = 0.05$) Before treatment, none of the gastroesophageal gas reflux events resulted in UES opening. At follow-up, 30 (5–100)% of the gas reflux episodes were followed by UES opening with a median duration of 400 ms (100–700). The number of gastroesophageal gas reflux episodes reduced from 33 (15–64) to 12 (3–36) $p<0.02$; Figure 4C. In three patients, there was a large reduction in gastroesophageal gas reflux events; after a couple of initial belches in the beginning of the 15-min recording period, the gas was already expelled. In the remaining patients, there was reduction in gas reflux as well;

**TABLE 2** High-resolution impedance manometry parameters before and after UES botox treatment

| | Baseline | | After treatment | | |
|---|---|---|---|---|---|
| | Median | range | Median | range | *p*-value |
| 10 wet swallows (5 ml) | | | | | |
| Upper esophageal sphincter (UES) pressures | | | | | |
| Basal pressure (mmHg) | 95.7 | 41.2–154.0 | 29.2 | 16.7–45.6 | **0.017** |
| IRP (mmHg) | −0.8 | −6.2–2.7 | −5.9 | −7.8–2.0 | 0.263 |
| Lower esophageal sphincter (LES) pressures | | | | | |
| Basal pressure (mmHg) | 20.0 | 10.9–33.7 | 20.5 | 11.2–41.9 | 0.866 |
| IRP (mmHg) | 7.6 | 3.8–16.2 | 9.5 | 3.2–12.3 | 0.575 |
| Esophageal motility parameters | | | | | |
| DCI (mmHg·s·cm) | 237 | 17–754 | 390.5 | 22.0–948 | 0.050 |
| DL (s) | 7.1 | 5.0–10.0 | 6.7 | 5.0–9.0 | **0.027** |
| Diagnosis according to Chicago classification | | | | | |
| Normal motility | 1 | | 1 | | |
| Ineffective esophageal motility | 5 | | 6 | | |
| Absent contractility | 2 | | 1 | | |
| 15-min recording after provocation test | | | | | |
| Liquid reflux episodes | 4 | 0–11 | 4 | 0–11 | 0.916 |
| Gastroesophageal gas reflux episodes | 33 | 15–64 | 12 | 3–36 | **0.017** |
| % followed by secondary peristalsis | 85.3 | 0–100 | 42.5 | 0–100.0 | 0.249 |
| % followed by UES opening | 0 | 0–0 | 30.0 | 5.0–100.0 | **0.012** |
| Duration UES opening | NA | – | 400 | 100–700 | – |
| Averaged intraluminal pressures* | | | | | |
| UES basal pressure preceding gas reflux event | 67.3 | 53.5–101.5 | 35.6 | 12.3–45.1 | **0.012** |
| UES pressure upon arrival of gas reflux event | 115.2 | 80.8–161.3 | 38.3 | 18.3–108.5 | **0.012** |
| UES nadir pressure during gas reflux event | 63.4 | 51.0–89.2 | 13.5 | 9.2–38.2 | **0.012** |
| Intra-esophageal pressure preceding gas reflux event | −4.0 | −7.7 – 4.2 | −3.8 | −8.8 – −0.9 | 0.310 |
| Intra-esophageal pressure during gas reflux event | 8.0 | 3.3–16.1 | 10.9 | 3.0–20.8 | 0.310 |

Abbreviations: DCI, distal contractile integral; DL, distal latency; IRP, integrative relaxation pressure; LES, lower esophageal pressure; UES, upper esophageal sphincter.

*For each gastroesophageal gas reflux episode, intraluminal pressures immediately before and during the gas reflux event at the level of the UES and in the esophageal body were recorded and averaged per patient.

Bold values denote statistical significance at the $p < 0.05$ level.

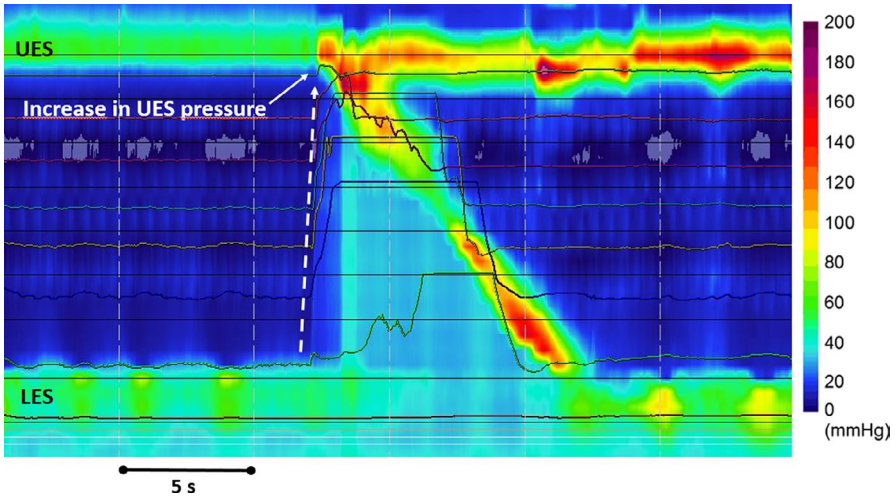


**FIGURE 1** Gastroesophageal gas reflux event recorded with high-resolution impedance manometry in a patient with inability to belch. The sequence of events during a gas reflux event was characterized by: (1) retrograde flow of air from the stomach up to the level of the UES; (2) an increase in esophageal pressure to the level of the gastric pressure (common cavity phenomenon) (3) an increased or unchanged UES pressure; (4) failure of UES relaxation with consequently no venting of air across the UES (5) secondary peristalsis transporting the air from the esophagus back to the stomach

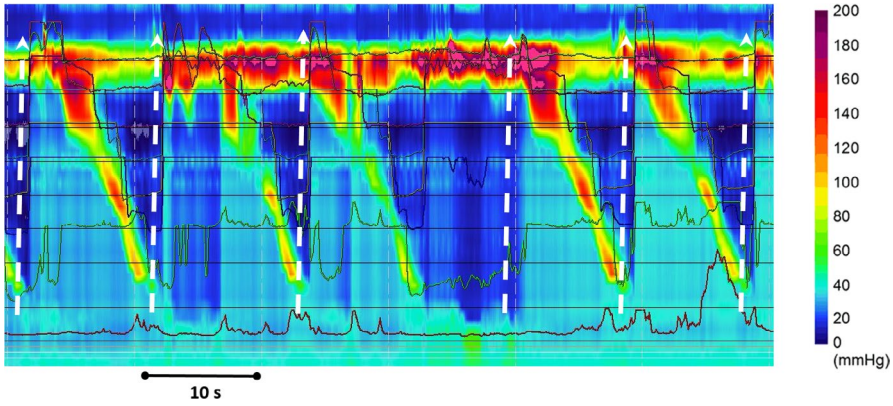


**FIGURE 2** Repetitive gas reflux pattern recorded with high-resolution impedance manometry in a patient with inability to belch. Retrograde flow of gastric air (white arrows), in absence of subsequent UES relaxation, cleared from the esophageal body by secondary peristalsis and then immediately refluxed back into the esophageal body

however, the effect was less pronounced and UES opening occurred later. No difference was found between the proportion of the gastroesophageal gas reflux episodes that were followed by secondary peristalsis ($p = 0.249$).

### 3.5.3 | pH-impedance monitoring

Post-therapy, esophageal air presence time had decreased significantly from 10.5% (0–43.4) to 0.7% (0.1–18.6; $p < 0.02$; Figure 4D). Likewise, the number of reported symptoms had significantly decreased after treatment (9 [6–126] vs 0 [0–15]; $p < 0.02$). Treatment did not reduce the number of gastroesophageal gas reflux episodes (81 [7–185] vs. 57 [13–130]; $p = 0.624$), nor did it change esophageal acid exposure times, the number of liquid and mixed reflux episodes, supragastric belches, and air swallows (all $p > 0.05$).

## 4 | DISCUSSION

In the past few years, an increasing number of patients have been seeking medical attention because of a self-reported inability to belch in combination with esophageal or abdominal symptoms. This phenomenon, however, is barely described in literature, and underlying pathophysiological mechanisms are largely unknown. This is the first study that objectively assessed a group of these patients using combined HRM and impedance monitoring. Our findings provide evidence of the existence of a syndrome characterized by an inability to belch and support the hypothesis that ineffective UES relaxation in reaction to gastroesophageal gas reflux leads to esophageal air entrapment, which in turn causes esophageal symptoms. Patients were treated with UES botox injections, which reduced UES basal pressures and restored belching capacity in all patients. As a result, esophageal air presence time and esophageal symptoms improved in all patients at 3-month follow-up.

**TABLE 3** pH- parameters before and after UES botox treatment

| | Baseline | | After treatment | | |
|---|---|---|---|---|---|
| | Median | Range | Median | Range | *p*-value |
| Symptom episodes of inability to belch* | 9 | 6–126 | 0 | 0–15 | **0.018** |
| Symptoms associated with gastroesophageal gas reflux (SI, %) | 89.2 | 66.7–100.0 | 86.7 | 66.7–100.0 | 0.655 |
| Acid exposure time (%) | | | | | |
| Total | 2.2 | 0–20.2 | 3.4 | 0.4–15.0 | 0.779 |
| Upright | 1.6 | 0.1–9.0 | 4.7 | 0.4–10.9 | 0.161 |
| Supine | 1.9 | 0.0–48.4 | 0.5 | 0.0–25.6 | 0.327 |
| Reflux episodes, n | 17 | 2–48 | 40 | 3–128 | 0.092 |
| Liquid | 6 | 1–46 | 16 | 1–61 | 0.128 |
| Mixed | 6 | 1–17 | 14 | 2–67 | 0.068 |
| Gas reflux episodes, n | 81 | 7–185 | 57 | 13–130 | 0.624 |
| Upright | 81 | 6–185 | 50 | 13–129 | 0.674 |
| Supine | 1 | 0–9 | 1 | 0–13 | 0.917 |
| Supragastric belches, *n* | 0 | 0–1 | 0 | 0–24 | 0.109 |
| Air swallows, *n* | 12 | 4–41 | 21 | 13–42 | 0.161 |
| Esophageal air presence time, % | 10.5 | 0–43.4 | 0.7 | 0.1–18.6 | **0.017** |
| Upright | 17.3 | 0.0–54.0 | 1.2 | 0.1–27.8 | **0.017** |
| Supine | 0.0 | 0.0–1.3 | 0.0 | 0.0–0.0 | 0.180 |

Abbreviations: *N*, number of patients; SI, symptom index.

*Esophageal symptoms specific for inability to belch (eg, gurgling noises from the chest or retrosternal pain) were taken into account.

Bold values denote statistical significance at the $p < 0.05$ level.

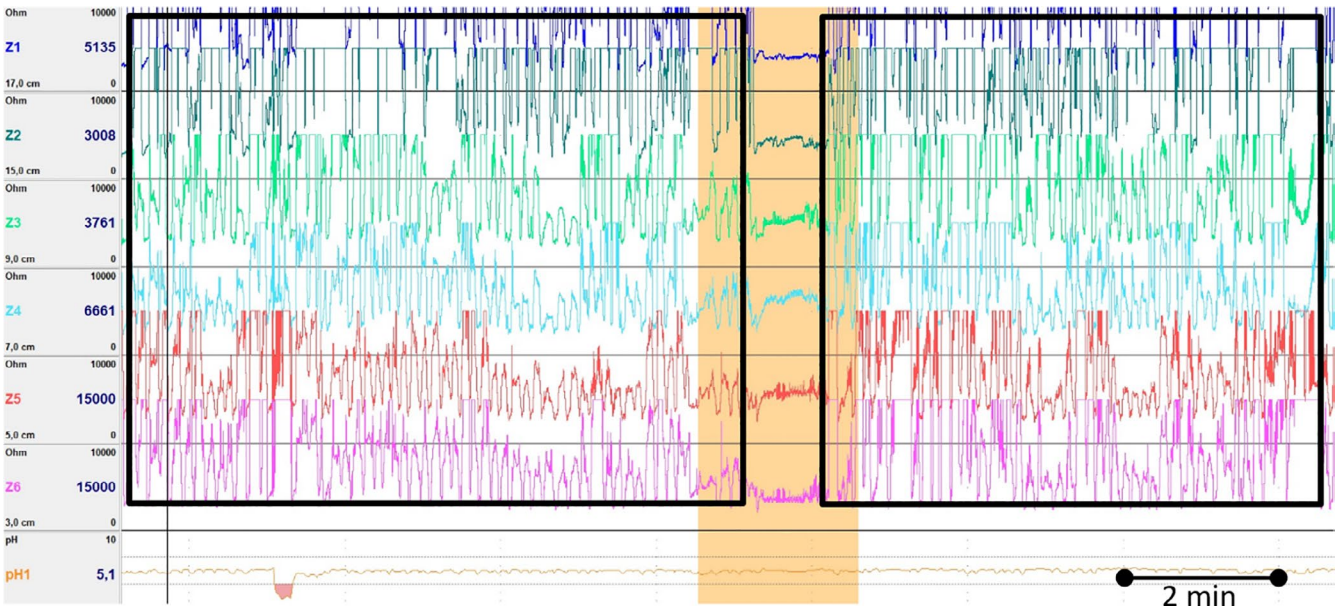


**FIGURE 3** Esophageal air entrapment observed as periods (black rectangles) of continuous high impedance levels recorded with ambulatory pH-impedance monitoring in a patient with symptoms of inability to belch. The orange rectangular area represents the 2 min window the subject experienced a symptom

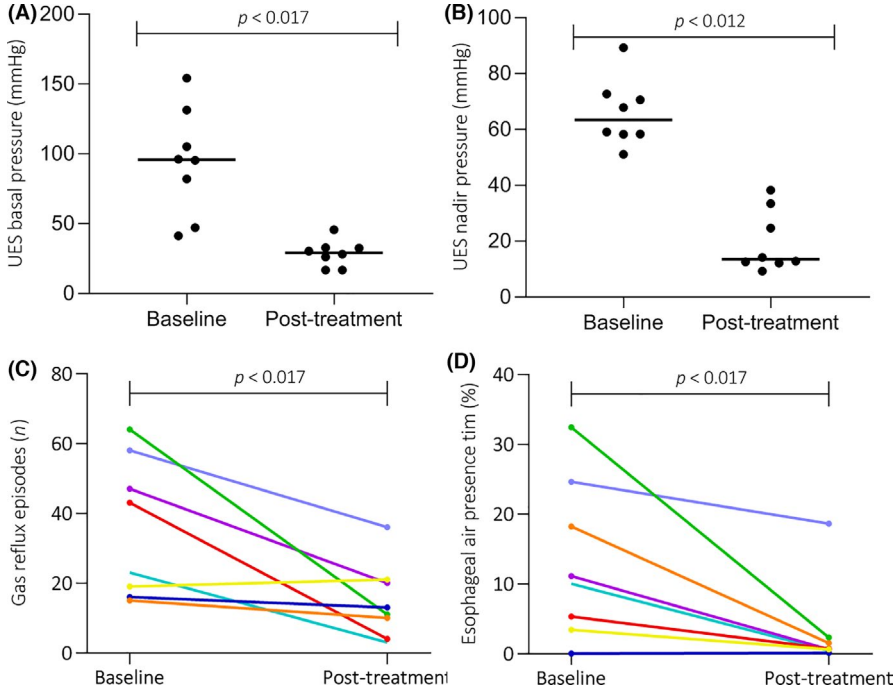


**FIGURE 4** Upper esophageal sphincter basal pressure (A), average UES nadir pressure in reaction to gastroesophageal gas reflux (B), the total number of gastroesophageal gas reflux episodes observed during 15-min HRIM recording (C) and air presence time calculated during 24-h ambulatory pH-impedance monitoring (D) at baseline and post-treatment. After treatment, the UES basal and nadir pressure decreased significantly, facilitating UES opening and venting of air ($p < 0.02$). As a result, the number of gastroesophageal gas reflux episodes and air presence time reduced significantly ($p < 0.02$)

The typical clinical and manometric presentation of an inability to belch was previously described in case reports by Kahrilas et al. and by Waterman et al[4,5] The patients described presented with similar repetitive gas reflux patterns and absence of UES relaxation, despite complete UES relaxation in response to deglutition, as was observed in our study subjects. In line with the previously reported findings, we found that the reflexogenic UES relaxation in response to an increase in esophageal pressure fails. It is noteworthy that the altered UES belch reflex in our patients was not simply an absent response but a paradoxical UES contraction. Contraction of the UES in combination with secondary peristalsis has been described as part of another UES reflex, usually activated by slow distention of the esophagus and thought to be important to prevent reflux of fluid boluses.[8] Surprisingly, seven out of eight patients in our cohort were diagnosed with ineffective or absent esophageal motility. Although this could be a coincidental finding, it is plausible that (severely) ineffective motility contributes to esophageal air entrapment, which more readily will lead to bothersome symptoms that will urge the patient to seek medical consultation.

In line with the high success rates for UES botox treatment reported by Bastian et al, we observed a similar high efficacy in our subjects. As expected, botox therapy reduced the resting tone of the UES. Although three patients still needed additional maneuvers to force out air, all patients eventually showed manometrically UES relaxation in response to esophageal distention and were able to belch audibly. Several etiologies might underlie the UES dysrelaxation observed in these patients, including structural abnormalities, failure of neurophysiological mechanisms, or subconsciously learned behavior. Absence of any abnormalities found during upper endoscopy and video laryngoscopy rules out structural pathologies as an underlying cause. We found normal reflux of gas across the LES with rapid pressure increases in the proximal esophagus, suggesting that an effective stimulus was present. The observed normal UES resting and relaxation pressures in response to deglutition point toward failure of the belch reflex pathway on a neurophysiological level, rather than to a problem of the UES opening muscles. During swallowing, the cricopharyngeal muscle relaxes and remains inactive while the UES lumen opens under the influence of distracting muscles, pharyngeal propulsion, and distention forces generated by bolus passage.[9,10] This suggests that pharyngeal contraction and bolus flow during deglutition could hypothetically compensate for an ineffective UES opening as a result of an impaired neuro-motor function. A previous physiological study confirmed that opening muscles are not active during belching.[11] Absence of these driving forces can mask UES dysrelaxation during swallowing. The observation that a muscle relaxant such as botulinum toxin enabled belching in all study patients supports the hypothesis that an alteration in neurophysiological function, either motor or sensory, underlies UES dysrelaxation, rather than an ineffective stimulus. Another important possibility for UES dysrelaxation in response to gastroesophageal gas reflux is a subconsciously learned behavioral response to avoid aspiration. This might explain why we see a paradoxical increase in UES pressure followed by secondary peristalsis in our subjects. The finding by Bastian et al., that the therapeutic benefit of botox appears to last longer than its pharmacological effect, further supports this theory. Bastian et al. suggest that the temporally reduction in UES tone somehow retrains the patient to use the sphincter permanently in retrograde function. However, it must be stressed that further research is warranted before more definitive conclusions can be drawn regarding the pathogenesis of inability to belch. Moreover, the follow-up duration of our study was only 3 months, so the long-term efficacy of botox was not evaluated.

Inability to belch as underlying cause of gas-related symptoms is an unknown phenomenon and the vast majority of physicians is unaware of its existence. Currently, there are no guidelines or standardized diagnostic or therapeutic protocols for these patients. Although Bastian et al. suggest that the clinical syndrome can be diagnosed based upon symptoms alone, the list of potential causes that can give similar gastroesophageal complaints is long. Therefore, we recommend to first exclude important alternative diagnoses, before continuing with botox therapy. A diagnostic upper endoscopy and video laryngoscopy are helpful to rule out structural pathologies. Standard HRM is advised to assess esophageal motility. Impedance monitoring has a high sensitivity and reproducibility for the detection of air swallows and all types of reflux events, including gas reflux, and it is recommended to exclude alternative diagnoses such as aerophagia.[12,13] Additionally, we emphasize the importance of stimulating awareness among physicians to encourage better disease recognition, especially since there seems to be an effective therapy available that resolves symptoms in most patients.

Some limitations must be acknowledged. First, in absence of a control group, this study was not equipped to produce normative data on esophageal air presence time and UES pressures in response to gastroesophageal gas reflux, which would have been helpful to define normal values for diagnostic purposes. Second, it is important to realize that this study was conducted in a small cohort. Although the number of subjects was adequate to generate convincing data on pathophysiological mechanisms associated with the inability to belch syndrome, further research is necessary to elucidate the exact cause of the defective belch reflex and to determine the true effect of botox therapy in these patients, preferably in a sham-controlled setting.

In conclusion, the findings of this study underpin the existence of a syndrome characterized by an inability to belch and suggest that a defective belch reflex underlies impaired UES relaxation. UES Botox therapy enabled belching in all patients and reduced esophageal air entrapment and esophageal symptoms.

## CONFLICT OF INTEREST

RON, JAS, BK, JO, DH, LC, JMS, and AS have no financial or personal competing interests. AB received research funding from Nutricia, Norgine, SST, Thelial and Bayer and received speaker and/or consulting fees from Laborie, EsoCap, Medtronic, Dr. Falk Pharma, Calypso Biotech, Robarts, Reckett Benkiser, Regeneron, AstraZeneca.

## AUTHOR CONTRIBUTIONS

RON, BK, JAS, LC, AB, and AS played a role in planning of the study. RON, JAS, JO, and AB had a role in conducting the study. RON and JO were involved in the acquisition of data. RON, BK, JMS, and AB had a role in collecting and/or interpreting data. RON played a role in drafting the manuscript. JAS, BK, DH, LC, JMS, AS, and AB played a role in reviewing and revising the manuscript for important intellectual content. All authors approved the final draft submitted.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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