Outcome for Patients With Pathological Esophageal Acid Exposure After Laparoscopic Fundoplication

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Objective: The aim of the current study was to assess symptomatic outcome and need for surgical reintervention for patients identified with pathological esophageal acid exposure by routine postoperative 24-hour pH-monitoring.

Background: Although laparoscopic fundoplication is associated with excellent short- and midterm results, recurrent symptoms pose an important challenge. Postoperative pH-monitoring is considered the ''gold standard'' for diagnosing recurrent GERD and frequently used for routine postoperative follow up.

Methods: Analysis of prospectively collected data from patients who underwent laparoscopic fundoplication between April 1994 and June 2015 and underwent routine postoperative 24-hour pH-monitoring was performed. Symptomatic outcome and need for surgical reintervention up to 5 years was compared between patients with pathological and physiological postoperative esophageal acid exposure. Primary endpoints were heartburn score and need for surgical reintervention for recurrent reflux.

Results: A total of 309 patients in whom routine postoperative 24-hour pH-monitoring was performed were included. Pathological acid exposure was present in 33 patients (11%) compared with 276 patients (89%) with physiological acid exposure. During 5-year follow up, there were no differences in heartburn, dysphagia, or satisfaction scores. Eighteen percent of all patients with abnormal postoperative pH-studies underwent redo fundoplication during 5-year follow up.

Conclusions: Pathological acid exposure demonstrated by routine postoperative pH-monitoring was not associated with worse symptomatic outcome in terms of reflux control and satisfaction. A possible explanation for this finding is that laparoscopic fundoplication reduces the patients' ability to perceive reflux. This underlines the importance of assessing the association between symptomatic outcome and esophageal function tests in determining outcome of antireflux surgery.

Keywords: esophageal, gastroesophageal reflux, laparoscopy, pH monitoring, recurrence, treatment outcome

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Gastroesophageal reflux disease (GERD) is an important benign disorder of the gastrointestinal tract, affecting up to 20% of the Western population.[1] Laparoscopic fundoplication is considered the standard surgical procedure for patients diagnosed with objectified proton pump inhibitor (PPI)-refractory GERD. The 360° total (Nissen) fundoplication is the most frequently performed type of fundoplication worldwide, providing excellent long-term reflux control.[2–4] To reduce the incidence of side-effects associated with total fundoplication, including dysphagia and bloating, partial fundoplications have been developed. Depending on the type of partial fundoplication, the fundus is wrapped partially, either in an anterior or posterior fashion, around the distal esophagus. Recent meta-analyses have demonstrated a lower incidence of these side-effects after partial fundoplications.[5,6]

Recurrent reflux symptoms are an important problem with a significant impact on patient's quality of life and satisfaction with surgery.[7] Twenty-four-hour pH-monitoring is considered the ''gold standard'' for the diagnosis of recurrent GERD, by categorizing between pathological and physiological esophageal acid exposure. It is frequently used for routine postoperative follow up and determining outcome of fundoplication. The results of routine studies should be interpreted with caution however, since a pH-study demonstrating pathological esophageal acid exposure, does not have to be associated with symptoms. Furthermore, symptoms interpreted as recurrent reflux appear to demonstrate a weak correlation with esophageal acid exposure.[8]

So far, no data have been published regarding the outcome of patients identified with pathological esophageal acid exposure by routine postoperative pH-monitoring. In the current study, we compare 5-year symptomatic outcome and need for surgical reintervention between patients with pathological and physiological esophageal acid exposure.

METHODS

Study Designs and Participants

Prospectively collected data from patients who underwent primary laparoscopic total or partial fundoplication were analyzed. Patients had been included in 1 of 6 randomized clinical trials comparing laparoscopic Nissen fundoplication with versus without division of short gastric vessels,[9] Nissen versus 180° anterior partial fundoplication,[10] Nissen with anterior versus posterior hiatal repair,[11] Nissen versus 90° anterior partial fundoplication,[12] Nissen versus 270° posterior partial versus 180° anterior partial fundoplication,[13] and 270° posterior versus 180° anterior partial fundoplication,[14] of which the outcomes have been described. All patients gave written informed consent for inclusion in a prospective database. The diagnosis chronic PPI-refractory GERD was objectified through upper gastrointestinal endoscopy demonstrating unequivocal signs of GERD or 24-hour pH-monitoring demonstrating pathological esophageal acid exposure. Exclusion criteria included esophageal motility disorders, previous antireflux surgery, and the presence of a giant hiatal hernia (intrathoracic stomach > 50%).

Demographics included sex, age, body mass index (BMI), comorbidities categorized as diabetes and renal, pulmonary or cardiovascular disease, and a history of thoracic and/or abdominal surgery. Pre- and postoperative symptoms were assessed using structured questionnaires at different intervals. All patients were

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scheduled for preoperative upper gastrointestinal endoscopy and esophageal manometry. Preoperative 24-hour pH-monitoring was only performed on patients with no unequivocal reflux disease demonstrated by endoscopy and manometry. Because of trial-participation, routine 3 to 6 months postoperative upper gastrointestinal endoscopy, esophageal manometry, and 24-hour pH-monitoring was performed in all patients, independently of symptoms.

All patients who had undergone routine 24-hour pH-monitoring within 12 months after surgery were identified. Symptomatic outcome was assessed at 6 months, 1, 2, 3, and 5 years after surgery. Differences in symptomatic outcome and need for reoperation were analyzed for patients identified with pathological and physiological esophageal acid exposure. Patients in whom it was likely that abnormal esophageal acid exposure was caused by migration of the pH-probe were excluded.

Surgical Procedures

All primary fundoplications were performed between April 1994 and May 2015 in the participating tertiary centers in the Netherlands and Australia by experienced laparoscopic surgeons. Division of short gastric vessels was performed depending on the type of procedure and/or trial a patient was enrolled in.[9] After full esophageal mobilization, posterior and/or anterior crural repair using nonabsorbable sutures was performed, and a floppy 360° total, 270° posterior, or a 90° or 180° anterior partial fundoplication was constructed.[15,16]

Subjective Outcome

Subjective outcome was assessed using a structured questionnaire completed preoperatively, 6 months postoperatively, and on a yearly basis thereafter. For the current study, only changes in heartburn and dysphagia scores were compared between patients with pathological and physiological acid exposure up to five years after surgery. The presence and severity of heartburn was scored using a visual analog scale (0 = no heartburn; 10 = severe heartburn). The presence and severity of dysphagia was assessed for liquids and solids using a visual analog scale (0 = no dysphagia; 10 = severe dysphagia). In addition, a validated dysphagia score (Dakkak score 0 = no dysphagia; 45 = severe dysphagia) integrating dysphagia for various types of liquids and solids was applied.[17] The effect of surgery was ranked using the Visick grading system: complete resolution of symptoms (Visick I), mild symptoms easily controlled by simple care (grade II), moderate symptoms not interfering with social life/work (grade III), symptoms interfering with social life/work (grade IV), and symptoms worse than before surgery (grade V).[18] Overall satisfaction was scored by a visual analog scale (0 = dissatisfied; 10 = satisfied). The use of acid suppressing drugs was assessed, including PPIs, histamine H2-receptor antagonists (H2-blockers), antacids, and prokinetics, and patients were asked if they would opt for surgery again in retrospect. Symptomatic outcome for patients who had undergone surgical reintervention during 6-months to 5-year follow up was excluded beyond the date of reoperation.

Upper Gastrointestinal Endoscopy

Upper gastrointestinal endoscopy was performed preoperatively and 3 to 6 months postoperatively to assess postsurgical anatomy, healing of esophagitis, and the presence of any esophageal obstruction. The presence of reflux esophagitis was scored using the Savary-Miller classification.[19] Endoscopic findings were categorized as: no esophagitis, presence of esophagitis (grades 1–3), stricture (grade 4), or Barrett's esophagus (grade 5). A fundoplication was determined to be sufficient if the following criteria were met: (i) the fundoplication snuggly encircled the retroflexed endoscope at the gastroesophageal junction; (ii) when the stomach was insufflated with air, the fundoplication remained competent at endoscopy (no venting or belching of air); and (iii) the fundoplication was in an anatomically correct position and a hiatus hernia was not visualized.

Stationary Esophageal Manometry

Through transnasal introduction, a motility catheter was introduced into the esophagus and positioned with a sleeve sensor straddled across the lower esophageal sphincter (LES). After the proximal and distal border of the LES were determined using the pull-through technique, intraluminal esophageal pressures were recorded at 5, 10, and 15 cm above the proximal border. Mean resting pressure (mmHg), amplitude of contractions (mmHg), and the percentage of primary peristalsis of the distal esophagus were included, as well as the LES mean resting pressure (mmHg). A LES mean resting pressure $\geq$10 mmHg and propagation of at least 80% primary peristalsis during 10 swallows of 5-mL water boluses were defined as normal.

Ambulatory 24-hour pH-monitoring

Acid suppressing medication was ceased five days before the pH-study. A pH probe was introduced through the nose into the esophagus and positioned 5 cm proximal to the manometrically determined proximal border of the LES, after which it was connected to an ambulatory pH-recorder for 24 hours. Results of 24-hour monitoring were analyzed for the percentage of time during which the esophageal pH was less than 4 and the correlation between reported symptoms and recorded reflux episodes. A reflux episode was defined as pH $<$ 4 for at least 5 seconds. Categorization as pathological and physiological esophageal acid exposure was based on the percentage of time with pH$<$ 4, with pathological acid exposure defined as an acid exposure time of at least 4% of the total time.

Statistics

All data were transferred into a computerized database and analyzed using the statistical software package SPSS version 22.0 (SPSS, Inc., Chicago, IL). Data were expressed as mean (95% confidence interval) or number of patients (%). The χ^2test, or Fisher exact test where necessary, were used for comparing binary variables between groups, and the Mann-Whitney U test for continues variables. Statistical significance was defined as $P < 0.05$.

RESULTS

Available Symptomatic and Objective Outcome

Between April 1994 and May 2015, 309 patients underwent primary fundoplication and completed routine 24-hour pH-monitoring. Nissen fundoplication was performed in 153 patients (49%) and partial fundoplication in 156 patients (51%), including 270° posterior (n = 48, 16%), 180° anterior (n = 69, 22%), and 90° anterior partial fundoplication (n = 39, 13%). Preoperative symptomatic outcome was available for 284 (92%) patients and postoperative outcome for 270 patients (87%) at 6 months, 283 (92%) at 1 year, and 254 (82%) at 2 years. Seventy patients from the Dutch trial had not yet reached 3 and 5-year follow up, and were therefore excluded beyond 2 years.[14] Eight patients died during 3- to 5-year follow up because of causes unrelated to fundoplication. Of the remaining 234 patients, 184 (79%) and 195 patients (84%) completed 3- and 5-year follow up, respectively. This was after excluding patients who had undergone a reoperation during 5-year follow up.

Baseline Characteristics and Objective Outcome

Thirty-three patients (11%) were identified with pathological acid exposure and 276 (89%) with physiological acid exposure. There were no differences in age, BMI, presence of comorbidities,

TABLE 1. Baseline Characteristics of Patients with Available Routine Postoperative 24-Hour pH-Monitoring

	Pathological Acid Exposure n = 33	Physiological Acid Exposure n = 276
Sex (male)	17 (52%)	135 (49%)
Age, yrs	50.1 (46.0–54.1)	59.5 (47.2–71.8)
BMI (kg/m^2)	27.5 (24.5–30.5)	28.7 (28.1–29.4)
Presence of comorbidities		
Diabetes	0 (0%	6 (2.4%)
Pulmonary	8 (25%)	53 (22%)
Renal	0 (0%)	8 (3%)
Cardiovascular	7 (21%)	49 (18%)
ASA-classification		
I	9 (31%)	89 (40%)
II	15 (52%)	120 (54%)
III	4 (14%)*	11 (5%)
IV	1 (3%)	0 (0%)
Previous abdominal or thoracic surgery	16 (50%)	130 (50%)
Preoperative endoscopy		
Studied	31 (94%)	238 (86%)
Esophagitis	12 (40%)	109 (46%)
Stricture	2 (7%)	6 (3%)
Barrett's	10 (33%)†	37 (16%)
Hernia	18 (60%)	130 (58%)
Preoperative 24-hour pH-monitoring		
Studied, n (%)	26 (79%)	204 (74%)
Pathologic total acid exposure	22 (88%)	180 (88%)
Total percentage time pH<4	12.1 (9.1–15.1)	11.0 (9.8–12.3)
Preoperative esophageal manometry		
Studied, n (%	25 (76%)	240 (87%)
Resting pressure distal esophagus (mmHg)	0.1 (-1.6–1.7)	0.3 (-043–1.0)
Amplitude distal esophagus (mmHg)	60.9 (37.5–84.2)	63.9 (57.0–70.9)
Primary peristalsis distal esophagus (%)	81.4 (68.8–94.1)	88.2 (85.2–91.3)
LES resting pressure, mmHg	6.6 (2.2–10.9)	8.2 (7.2–9.2)
Type of fundoplication		
360° total	8 (24%)	145 (53%)
270° posterior partial	8 (24%)	40 (15%)
90° anterior partial	5 (15%)	34 (12%)
180° anterior partial	12 (36%)‡	57 (21%)

All data are expressed as n (%) or mean (95% confidence interval); BMI indicates body mass index; LES, lower esophageal sphincter.
*$P = 0.020$ pathological vs physiological acid exposure.
†P = 0.017 vs pathological acid exposure.
‡P = 0.047 vs physiological acid exposure.

TABLE 2. Objective Outcome of Patients With Postoperative Pathological and Physiological Esophageal Acid Exposure

	Pathological acid exposure n = 33	Physiological acid exposure n = 276
Postoperative endoscopy		
Studied	22 (67%)	188 (68%)
Interval, months	3.7 (2.8–4.6)	3.8 (3.5–4.2)
No esophagitis	10 (48%)	149 (81%)
Esophagitis	4 (19%)*	11 (6%)
Stricture	0 (0%)	1 (1%)
Barrett's	7 (33%)	23 (13%)
Hernia	0 (0%)	7 (4%)
Insufficient fundoplication	1 (7%)	0 (0%)
Postoperative 24-hour pH-monitoring		
Interval, months	4.4 (3.8–5.1)	3.8 (3.7–4.0)
Total percentage time pH<4	10.3 (8.0–12.5)†	0.6 (0.5–0.7)
pH<4 between 4 to 7%	13 (19%)	–
pH<4 more than 7%	20 (61%)	–
SI≥50%, no (%)	3 (13%)	11 (4%)
Postoperative esophageal manometry		
Studied	21 (64%)	236 (86%)
Interval, months	3.9 (2.9–4.9)	3.7 (3.4.–3.9)
Resting pressure distal esophagus mmHg	0.3 (-2.2–2.8)	−1.0 (−1.6–0.4)
Amplitude distal esophagus, mmHg	60.3 (29.1–91.5)‡	77.6 (71.0–84.3)
Primary peristalsis distal esophagus	74.7 (43.5–106.0)	86.4 (82.6–90.2)
LES resting pressure, mmHg	16.4 (7.8–25.1)§	22.6 (20.5–24.8)

All data are expressed as n (%) or mean (SD) or n (%); SI, % of reflux associated symptom episodes.
LES indicates lower esophageal sphincter.
*$P = 0.029$ vs Physiological acid exposure.
†$P < 0.001$ vs Physiological acid exposure.
‡$P = 0.024$ vs Physiological acid exposure.
§$P < 0.001$ vs Physiological acid exposure; Sufficient fundoplication: n = 57 data missing.

or previous abdominal or thoracic surgery between the 2 groups (Tables 1 and 2). There were more patients with ASA score 3 in the group of patients with pathological acid exposure ($P = 0.033$). Preoperative heartburn scores [4.2 (3.1–5.3) vs 4.9 (4.5–5.3), $P = 0.31$], dysphagia scores for liquids [1.3 (0.4–2.2) vs 0.8 (0.6–1.1), $P = 0.33$] or solids [2.1 (1.1–3.1) vs 2.0 (1.6–2.3), $P = 0.86$], and Visick scores (Visick score 3–5: 100% vs 95%, $P = 0.32$) were similar. A total of 253 patients (92%) were dependent on daily acid suppressing medication preoperatively, with no differences between the 2 groups.

Preoperative upper gastrointestinal endoscopy demonstrated more patients with Barrett's esophagus in the group with pathological acid exposure [10 (33%) vs 37 (16%), $P = 0.0177$. Preoperative manometry demonstrated similar esophageal peristalsis and LES resting pressures. Twenty-four-hour pH-monitoring revealed a similar preoperative total percentage of time pH < 4 ($P = 0.16$). Pathological postoperative acid exposure was more frequent after partial compared with Nissen fundoplication [25/156 (16%) vs 8/153 (5%), $P = 0.002$).

Routine postoperative upper gastrointestinal endoscopy demonstrated a higher prevalence of esophagitis among patients with pathological acid exposure (19% vs 6%, $P = 0.029$). Patients with pathological acid exposure demonstrated a lower mean contraction amplitude of the distal esophagus (60.3 vs 77.6, $P = 0.024$), and a lower mean LES pressure (16.4 mmHg vs 22.6 mmHg, $P < 0.001$). Within the group of patients with pathological postoperative acid exposure, there was no significant decrease in esophageal acid exposure compared with the preoperative state (mean percentage of time pH < 4 12.1% preoperative to 10.3% postoperative, $P = 0.38$). In 14 of these patients there was an increase in total acid exposure compared with the preoperative state. Symptom analysis did not demonstrate differences in correlation between symptoms and reflux events identified at pH-monitoring between the two groups ($P = 0.07$; Table 2).

Symptomatic Outcome

Postoperative symptomatic outcome is summarized in Tables 3 and 4. Because of surgical reintervention during follow up, 11 and 6 patients with pathological and physiological acid exposure respectively were excluded from further follow up. Six months after surgery, there was a significant decrease in heartburn score among patients with pathological acid exposure (4.4 preoperative to 1.1

TABLE 3. Postoperative Control of Heartburn and Presence of Dysphagia During 5-Year Follow Up

	6-month Postoperative		1-year Postoperative		2-year Postoperative		3-year Postoperative		5-year Postoperative	
	Path.	Phys.	Path.	Phys.	Path.	Phys.	Path.	Phys.	Path.	Phys.
Visual analog scale heartburn										
Mean score	1.1	0.5	1.4	0.8	1.7	1.5	1.7	1.4	0.9	1.5
95% confidence interval	(0.2–2.0)	(0.4–0.7)	(0.4–2.4)	(0.6–1.0)	(0.7–2.6)	(1.2–1.8)	(-0.1–3.5)	(1.1–1.8)	(0.2–1.6)	(1.2–1.9)
Heartburn, categorical										
None or mild heartburn (0–3)	89.7%	94.1%	81.5%	94.1%*	77.3%	82.6%	91.7%	83.8%	100.0%	82.8%
Moderate (4–6)	3.4%	5.0%	11.1%	3.5%	18.2%	11.7%	0.0%	10.8%	0.0%	13.3%
Severe (7–10)	6.9%	0.8%	7.4%	2.4%	4.5%	5.7%	8.3%	5.4%	0.0%	3.9%
Visual analog scale dysphagia										
Liquids										
Mean score	0.7	0.7	0.5	0.9	0.6	1.1	0.7	1.0	1.2	1.2
95% confidence interval	(0.2–1.2)	(0.5–0.9)	(0.1–0.9)	(0.6–1.1)	(-0.5–1.1)	(0.8–1.4)	(-0.3–1.6)	(0.7–1.3)	(-0.3–2.6)	(0.8–1.5)
Solids										
Mean score	1.9	1.6	1.1	1.8	1.6	2.1	1.0	2.2	1.4	2.3
95% confidence interval	(0.9–2.9)	(1.3–1.9)	(0.3–2.0)	(1.5–2.0)	(0.6–2.5)	(1.8–2.4)	(-0.5–2.5)	(1.8–2.6)	(0.0–2.8)	(1.9–2.7)
Dakkak dysphagia score (0–45)										
Mean	8.1	6.1	5.8	8.0	6.3	9.2	5.0	8.5	7.6	8.9
95% confidence interval	(4.1–12.0)	(5.0–7.1)	(2.3–9.2)	(6.8–9.2)	(2.7–9.8)	(7.9–10.5)	(1.3–8.7)	(7.1–10.0)	(2.7–12.4)	(7.5–10.2)
Use of acid suppressing drugs	25.9%	13.4%	19.2%	16.0%	30.0%	18.6%	25.0%	15.7%	16.7%	19.0%

All data are expressed as mean (95% confidence interval) or n (% of patients who responded to questionnaire).
Path. indicates pathological esophageal acid exposure; Phys., physiological esophageal acid exposure.
*$P = 0.03$ vs pathological acid exposure.

postoperative, $P < 0.001$), with 21 patients (67%) reporting complete absence of heartburn. Of the 14 patients demonstrating an increase in total acid exposure, only 1 (7%) reported an increase in heartburn score at 6 months compared with the preoperative state, with 9 patients (65%) reporting a decrease in heartburn score. At all postoperative intervals, there were no differences in heartburn scores between the 2 groups (Fig. 1). At 1 year, more patients with physiological acid exposure were categorized with none or mild heartburn (VAS 0–3) compared with those with pathological acid exposure ($P = 0.03$). This difference was not sustained at 2, 3, and 5 years. There were no differences in dysphagia at all postoperative intervals. Although significantly more patients with Barrett's esophagus were diagnosed with pathological esophageal acid exposure, there were no differences in pre- or postoperative heartburn scores between patients with vs. without Barrett's esophagus.

Satisfaction scores were similar for both groups. Only at 1 year, more patients with pathological acid exposure were categorized as having a 'fair and poor' outcome (25.9% vs 13.5%, $P = 0.04$). Visick scores were similar and there was no difference in the number of patients indicating that they considered their original decision to have surgery to be correct, with approximately 91% of the patients reporting they would again opt for surgery.

Recategorizing pathological and physiological acid exposure based on pH <4 for $\geq$ 7% (n = 20) and less than 7% (n = 289) of the total time respectively, did not significantly alter the previously described results, with no differences in heartburn and dysphagia scores between the 2 groups, apart from a significantly higher dysphagia (0–45) score for physiological acid exposure at 3 years (mean score 1.3 vs 8.5, $P = 0.029$). Furthermore, satisfaction scores, Visick scores or the number of

TABLE 4. Satisfaction Score, Visick Score and Overall Outcome During 5-Year Follow-Up

	6-Month Postoperation		1-Year Postoperation		2 -Year Postoperation		3-Year Postoperation		5-Year Postoperation	
	Path.	Phys.	Path.	Phys.	Path.	Phys.	Path.	Phys.	Path.	Phys.
Satisfaction score (0–10)										
Mean score	8.2	8.5	8.2	8.6	8.6	8.3	8.9	8.5	8.6	8.4
95% confidence interval	(7.1–9.3)	(8.2–8.8)	(7.2–9.2)	(8.3–8.8)	(7.6–9.6)	(8.0–8.6)	(7.6–10.3)	(8.2–8.9)	(7.3–9.8)	(8.1–8.8)
Patient satisfaction, categorical										
Excellent and good (7–10)	84.0%	88.2%	74.1%	86.5%	86.4%	86.1%	91.7%	86.4%	81.8%	87.6%
Fair and poor (0–6)	16.0%	11.8%	25.9%*	13.5%	13.6%	13.9%	8.3%	13.6%	18.2%	12.4%
Visick score										
Visick 1 and 2	78.6%	78.2%	62.5%	80.2%	84.6%	66.3%	66.7%	76.8%	72.7%	81.1%
Visick 3, 4, and 5	21.4%	21.8%	37.5%	19.8%	15.4%	33.7%	33.3%	23.2%	27.3%	18.9%
Opt for surgery again										
Yes	89.7%	94.9%	88.5%	90.0%	100%	91%	91.7%	89.3%	91.7%	91.2%
No	10.3%	5.1%	11.5%	7.6%	0.0%	6.1%	8.3%	7.1%	8.3%	7.2%
Unsure	0.0%	0.0%	0.0%	2.4%	0.0%	3.0%	0.0%	3.6%	0.0%	1.7%

All data are expressed as mean (SD) or n (% of patients who responded to questionnaire).
Path. indicates pathological esophageal acid exposure; Phys., physiological esophageal acid exposure.
*$P = 0.04$ vs physiological acid exposure.

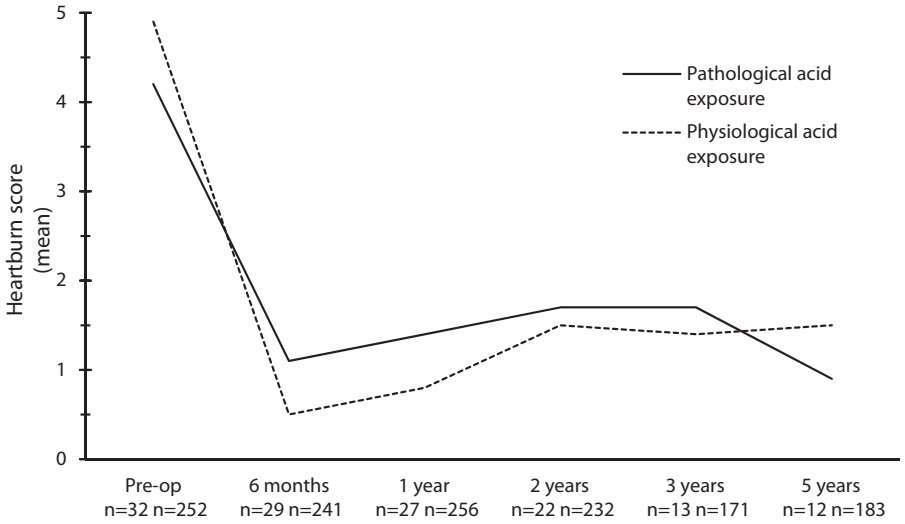

FIGURE 1. Changes in mean heartburn score during 5-year follow up for patients with pathological (pH <4 equal to or more than 4% of the time) and physiological (pH<4 less than 4% of the time) postoperative acid exposure.

patients indicating they who would still opt for surgery in retrospect as well were similar.

There were no differences in use of acid suppressing drugs. At 5 years, 17% and 19% of the patients reported to use acid suppressing medication on a daily basis, which was a significant reduction compared with the preoperative state for both groups ($P = 0.013$ and $P < 0.001$ respectively, Fig. 2).

Surgical Reintervention

Seventeen patients (6%) underwent surgical reintervention for recurrent reflux, persistent dysphagia or hiatal hernia, with a mean interval between primary fundoplication and reoperation of 25 months (Table 4). There were more reoperations in the group of patients with pathological acid exposure (n = 6 [18%] vs n = 11 [4%], $P = 0.001$) based on a higher number of reoperations for recurrent GERD (n = 6 [100%] vs n = 3 [27%], $P = 0.009$). Patients who underwent reoperation for recurrent GERD reported higher heartburn scores at all postoperative intervals, compared with those who did not undergo surgical reintervention ($P = 0.002$, $P = 0.013$, $P = 0.016$, $P = 0.005$, $P = 0.024$). Within the group of patients with pathological acid exposure, reoperation was performed at 4, 7, 17, 31, 33, and 53 months after primary fundoplication. Of the 14 patients who demonstrated an increase in postoperative esophageal acid exposure, 5 underwent redo fundoplication for recurrent GERD.

DISCUSSION

The definition of ''surgical failure'' plays an important role in the discrepancy in reported failure rates after laparoscopic fundoplication.[20,21] Using symptoms suggestive of recurrent reflux as a marker of surgical outcome causes a potential overestimation of the

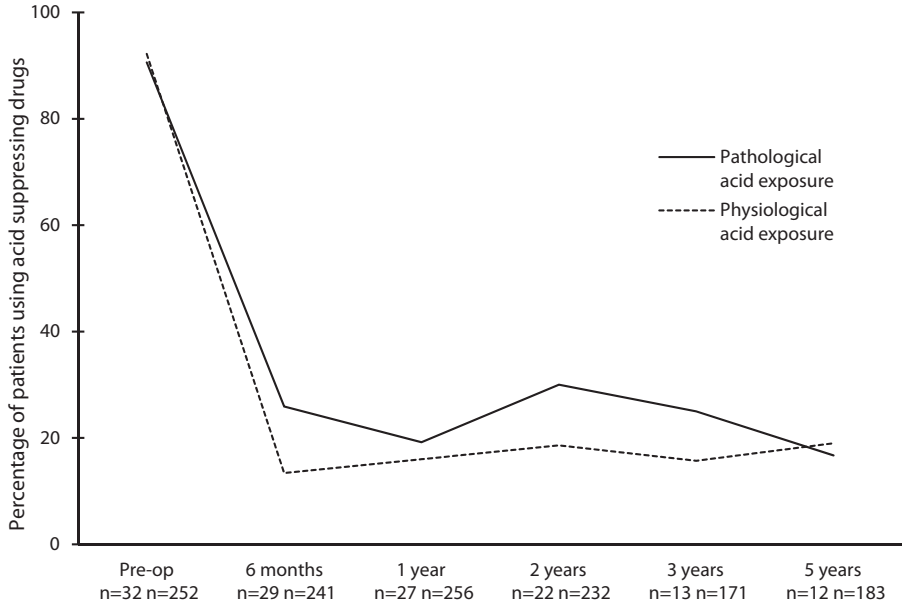

FIGURE 2. Changes in the use of acid-suppressing drugs for patients with pathological (pH<4 equal to or more than 4% of the time) and physiological (pH<4 less than 4% of the time) postoperative esophageal acid exposure during 5-year follow-up.

TABLE 5. Surgical Reinterventions Performed During 5-Year Follow-Up

	Pathological Esophageal Acid Exposure n = 33	Physiological Esophageal Acid Exposure n = 276
Surgical reintervention, n (%)	6 (18%)*	11 (4%)
Mean time to reintervention (months)	24.2 (4.8–43.6)	25.1 (13.3–36.9)
Indication for reintervention (n)		
Recurrent GERD	5 (83%)†	3 (27%)
Dysphagia	0 (0%)	6 (55%)‡
Recurrent GERD and persistent dysphagia	1 (17%)	0 (0%)
Hiatal hernia	0 (0%)	2 (18%)
Type of reoperation (n)		
Redo fundoplication	4 (67%)§	1 (9%)
Redo fundoplication with HH repair	2 (33%)	4 (40%)
HH repair with redo fundoplication	0 (0%)	3 (30%)
Release hiatus / widening hiatus	0 (0%)	2 (20%)
Adhesiolysis	0 (0%)	1 (9%)

All data are expressed as mean (95% confidence interval) or n (%).
GERD indicates gastroesophageal reflux disease.
*$P = 0.001$ vs physiological acid exposure.
†$P = 0.009$ vs physiological reflux.
‡$P = 0.043$ vs pathological reflux.
§$P = 0.028$ vs physiological reflux.

true ''failure rate'', since it has been demonstrated that abnormal pH-studies are found in only 23–39% of these patients.[8,22–24] Therefore, postoperative 24-hour pH-monitoring is considered to be the ''gold standard'' for objectifying recurrent symptoms.

We identified 33 patients (11%) with pathological acid exposure through routine postoperative 24-hr pH-monitoring because of participation in a randomized trial, and who could therefore be considered to be objectified ''failures.'' Compared with patients with physiological acid exposure, there was no difference in symptomatic outcome or satisfaction during 5-year follow-up, indicating that routine postoperative pH-monitoring should not be used as a sole marker for outcome of fundoplication.

In 2000, Eubanks et al[21] published the results of routine postoperative pH-monitoring performed in 228 patients 12 weeks after laparoscopic fundoplication. Forty-seven patients (21%) were identified with pathological acid exposure, of whom 38 (17% of total) had symptoms less than once a week, and were regarded as having false negative pH-studies. Mid- to long-term follow-up of these patients was not provided. Our findings are in line with these results. As addressed by Eubanks et al[21] a possible explanation for these apparently ''false positive'' pH-studies is that the postoperative reduction in esophageal acid exposure has been enough to stop, or at least significantly reduce the patients' perception of reflux.[21] Esophageal acid exposure is still present, as demonstrated by pH-monitoring, but the patient is not perceiving it as such. If this is the case, our study indicates that this positive effect of fundoplication could be maintained for up to 5 years, with only 18% requiring surgical reintervention for recurrent GERD.

Another explanation for the lack of symptoms in patients with pathological acid exposure could be a ''placebo-effect'' of antireflux surgery. This is supported by the results of a randomized trial comparing an injectable esophageal prosthesis with a sham procedure for the endoscopic treatment of GERD.[25] The trial was prematurely terminated because of lack of efficacy and the occurrence of complications after prosthesis placement. Interestingly, patients who received the sham procedure demonstrated significant improvement in regurgitation symptoms and quality-of-life at 6-months, indicating a significant ''placebo effect.'. However, one would expect this effect to resolve over time, which is not the case in our cohort of patients.

Routine postoperative upper gastrointestinal endoscopy demonstrated esophagitis to be more prevalent among patients with pathological acid exposure, indicating ongoing esophageal acid exposure. This is further supported by the lower mean contraction amplitude and LES resting pressure in patients with pathological acid exposure. These findings indicate that despite the lack of accompanying reflux symptoms, there is ongoing abnormal esophageal acid exposure. Only two of the patients who had not previously been diagnosed with Barrett's esophagus and who demonstrated pathological postoperative esophageal acid exposure had undergone additional postoperative upper gastrointestinal endoscopy (2.5 and 3 years, respectively), and this failed to demonstrate Barrett's esophagus on both occasions. The majority of patients did not undergo additional endoscopic follow-up beyond the routine 3 to 6 months follow up as it was not clinically indicated.

Patients with pathological acid exposure underwent more redo fundoplications for recurrent GERD compared with patients with physiological acid exposure. However, only six of the 33 patients (18%) with an abnormal pH-study underwent redo surgery, indicating that one in every five patients identified with abnormal postoperative acid exposure indeed has an indication for redo surgery and/or is willing to undergo reoperation because of the severity of recurrent symptoms. This is supported by the fact that postoperative endoscopy did not reveal a higher rate of insufficient wraps compared with patients with physiological acid exposure. Hunter et al. reported outcome of routine postoperative pH-monitoring performed six to 12 weeks after laparoscopic fundoplication.[26] Seven of the 55 patients (13%) were found to have an abnormal pH-study, of whom nil reported symptoms and only one required reoperation (not specified).

Our findings indicate that merely the presence of an abnormal routine postoperative pH-study should not be considered to be an independent marker for ''wrap failure,'' and these results should not be used in isolation as an indication for surgical revision. We have only performed routine postoperative pH-monitoring when patients participated in a randomized clinical trial. When patients present with recurrent symptoms in clinical practice, however, full workup should include pH monitoring and a careful history taking, with assessment of typical reflux symptoms, including heartburn and regurgitation. Analysis of the association between symptoms and reflux episodes at pH-monitoring, as well as barium swallow radiology to determine the position of the wrap, upper-gastrointestinal endoscopy to assess the presence of esophagitis and wrap insufficiency, and esophageal manometry to exclude possible esophageal motility disorders should all be undertaken, and the results considered carefully and in context before deciding to revise the fundoplication.

Pathological acid exposure was more frequent after partial compared with total fundoplication. Two previous randomized trials have demonstrated 90° anterior partial fundoplication to be associated with less adverse side effects, like bloating and inability to belch, but also less effective long-term reflux control compared with total fundoplication. Indeed, in the current study more patients who had undergone laparoscopic 90° anterior partial fundoplication underwent recurrent surgery compared with patients who underwent Nissen fundoplication, 270° posterior or 180° anterior partial fundoplication [5/39 (13%) vs 12/270 (4%), $P = 0.032$].

For the current analysis, pathological acid exposure was defined as pH<4 for ≥4% of the total time. One could argue that a cut-off value of ≥7% would be more appropriate, as pH<4 between 4% and 7% of the time are sometimes considered to be equivocal

reflux. Hence, we performed a further analysis after recategorization based on pH<4 for ≥7% (n = 20) versus less than 7% (n = 289). However, this did not significantly alter the previously described results or conclusions, with no differences in mean heartburn and dysphagia score, or in satisfaction with surgery.

A possible limitation of this study is the fact that symptomatic follow up was not available in all patients. However, we included 309 patients with available routine postoperative 24-hour pH-monitoring and report up to 5-year follow up using structured questionnaires for 83% of the patients, which compares favorably to what is to be expected with these type of surveys.[27] Since symptomatic outcome was available preoperatively and at all postoperative intervals, detailed insight in outcome of patients identified with abnormal acid exposure is provided. Another limitation is the fact that data regarding symptom association probability (SAP) of routine pH-studies was not available and could not be included.

In conclusion, postoperative pathological acid exposure demonstrated by routine pH-monitoring is not necessarily associated with worse symptomatic outcome in terms of reflux control, dysphagia or satisfaction with surgery. A possible explanation for this finding includes the effect of fundoplication on reducing the patients' ability to perceive reflux. This underlines the importance of assessing the association between symptomatic outcome and results of objective esophageal function tests in determining the outcome of antireflux surgery.

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