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Is Toupet fundoplication the procedure of choice for treating gastroesophageal reflux disease? Results of a prospective randomized experimental trial comparing three major antireflux operations in a porcine model

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Abstract
Background Gastroesophageal reflux disease (GERD) is among the most common dysfunctions of the upper gastrointestinal tract. It interferes with quality of life and is a risk factor for the development of adenocarcinoma in the lower esophagus. Laparoscopic fundoplication is an effective treatment of GERD, but the physiologic mechanisms of the different available procedures had not been investigated to date.
Methods In this study, 28 German Landrace pigs underwent baseline manometry and 24-h pH monitoring followed by myotomy to induce reflux esophagitis. After new-onset reflux was proved, the pigs were randomized to groups based on four treatments: total fundoplication, anterior hemifundoplication, posterior hemifundoplication, and control. On days 10 and 60 after the intervention, the effectiveness of the different fundoplication modifications was compared with that of the control subjects by 24-h pH monitoring manometry. Finally, the pigs were killed, after which the minimum volume and pressure required to breach the gastroesophageal junction were recorded.
Results After myotomy, a significant increase in the reflux could be confirmed. The findings after fundoplication showed a significant decrease in the fraction of time that the pH fell below four and an increase in the vector volume compared with the measurement after myotomy. Total fundoplication and posterior hemifundoplication were highly effective, whereas measurements after anterior fundoplication still showed increased fraction times. Pharmacologic stimulation with pentagastrin showed an increase in the vector volume of the esophageal sphincter.
Conclusions Total fundoplication and posterior hemifundoplication are potent operations for the treatment of GERD. Anterior hemifundoplication reduces the reflux as well, but the effects are significantly less than with total and posterior fundoplication. Pharmacologic stimulation showed excellent results after posterior hemifundoplication, and a tendency to overcorrection was shown after total fundoplication.

Keywords Laparoscopic fundoplication · Gastroesophageal reflux · Nissen · Toupet · Experimental model

Gastroesophageal reflux disease (GERD) is one of the most common dysfunctions of the upper gastrointestinal (GI) tract. It is a serious health problem and a widespread disease, especially in Western developed countries, with 18% of the healthy population reporting reflux at least once a year and 1% of patients experiencing daily reflux [1]. In the United States, 6 billion US dollars are spent annually for H2 blockers and proton pump inhibitors (PPIs).

The reasons for GERD are discussed frequently. The high-pressure zone at the gastroesophageal junction has been identified as the determining factor in the prevention of reflux. Besides the inconveniences in daily life, continuous reflux of gastric and duodenal content has extensive effects. Findings show that 10% or more of the patients with reflux will experience esophagitis, 10% or more will

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experience a metaplasia of the epithelium (Barrett's esophagus) [2], and an additional 10% or more of these patients will experience an adenocarcinoma of the distal esophagus [3–5].

Medical therapies provide symptomatic relief for most patients, but the symptoms usually return after discontinuation of the medication. It must be considered that the pathoanatomic cause is not treated by these medications, so the causes for the reflux are unaffected. Proton pump inhibitors effectively suppress acid secretion, thus achieving effective symptomatic relief for most patients. Several studies have shown that the development of Barrett's esophagus and the carcinogenic effect are driven by bile reflux, so the development of lower esophageal cancer may be unaffected by current medical treatment methods [6].

Surgical interventions offer a GERD cure for most patients with a single intervention that can be performed by minimally invasive surgery, thus providing a maximum of patient comfort. This has led to the performance of an increasing number of antireflux surgeries during the past decade.

Different surgical procedures described in the 1950s have been being performed ever since. The common procedures applied today are plications of the gastric fundus, either total or partial. The mechanisms of action of these procedures and their effects on the physiologic mechanism of the esophageal sphincter have not been sufficiently investigated. Because Nissen fundoplication is the most commonly performed procedure, it is the only one that has been investigated experimentally in terms of its mechanisms of action, although this was about 30 years ago, when only open surgery was performed [2].

Alternatively, a number of surgeons prefer a partial fundoplication: the Toupet (270°) posterior hemifundoplication and the Dor (180°) anterior hemifundoplication [7, 8]. However, to date this approach is not supported by high-level evidence-based studies. The current study aimed to investigate and understand the mechanisms of action for the most commonly used surgical antireflux procedures in test subjects with proven reflux.

Materials and methods

Approval of the research protocol was obtained from the animal research committee of the Free and Hanseatic City of Hamburg. The study included 28 German Landrace pigs weighing 50 to 67 kg. Before surgery, all the animals were kept under comparable conditions at 18°C in isolated boxes for at least 72 h and underwent an examination by a veterinarian. The animals were starved for 24 h before the intervention with free access to water.

Study design

All the animals underwent baseline measurement at the beginning of the study. Upper GI endoscopy followed by manometry with and without pharmacologic stimulation was performed. A pH probe was placed, and 24-h pH monitoring was installed. After completion of these measurements, all the pigs underwent myotomy. The pigs underwent general anesthesia again 72 h later. Endoscopy, manometry, and pH-monitoring were performed again to measure and prove the effectiveness of the myotomy and to exclude complications such as perforation.

Only the animals with verified reflux at pH monitoring were included for further investigation. These animals then were randomly assigned either to therapeutic intervention or to the control group (7 per group). Gastroscopy and manometry were performed 10 days after the operative procedure with the animals under sedation again. Then, 60 days postinterventionally, the pigs underwent gastroscopy, manometry, and 24-h pH monitoring again. Finally, after completion of yield pressure and volume measurement, the pigs were killed (Fig. 1).

Anesthesia and analgesia

The animals were sedated with intramuscular ketamine (10 mg/kg body weight) after intubation anesthesia and analgesia were maintained by continuous intravenous infusion of ketamine 12.5 mg/kg/h and midazolame 0.5 mg/kg/h. The pigs were ventilated with a tidal volume of 10 to 15 ml/kg and a frequency of 10 to 18 per minute. Postoperative analgesia was achieved by administering 1 g of metamizole every 6 to 8 h. If necessary, piritramide was given additionally.

Gastroscopy and pH monitoring

Gastroscopy (Endoscope GIF Q 10 and GIF XQ 20; Olympus Optical Co GmbH, Hamburg, Germany) was performed with the animals under general anesthesia to exclude upper GI pathology and to place the pH-monitoring catheter under vision after the lower esophageal sphincter (LES) was located manometrically. Long-term pH monitoring (24 h) was performed using the technique established and described by our group [9].

Because no reference measurements and values were available, the results of the baseline measurement were set as normal. Pathologic reflux was defined as an increase in the fraction of time that a pH less than four was above the 90th percentile of the normal value.

Catheter placement was controlled by endoscopy. The probe was fixed by sutures and connected with a recorder

Fig. 1 Study design and timing

	Daily	Pre	Myotomy	3rd pod	Therapy	10th pod	60th pod	Section
Behavior of animals	X							
Upper GI Endoscopy		X		X		X	X	
Manometry		X		X		X	X	
Pharmacological Stimulation		X		X			X	
pH - Monitoring		X		X			X	
Yield Pressure/ Volume								X

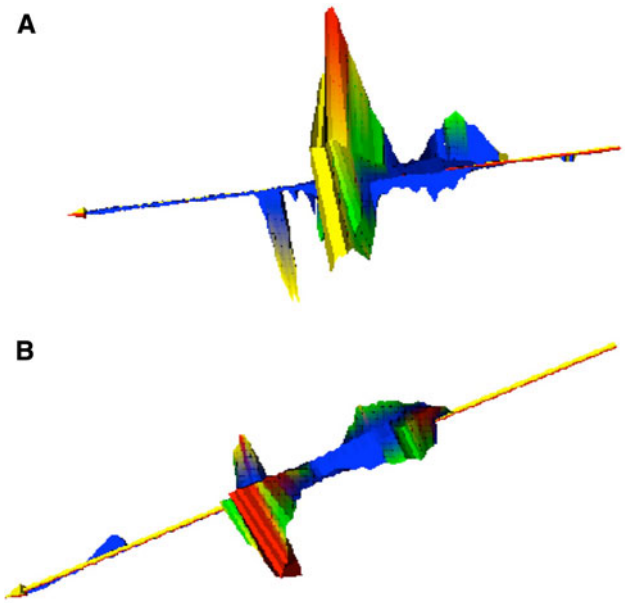


Fig. 2 Exemplary graph of a single lower esophageal sphincter (LES) before and after myotomy showing the loss of the high-pressure zone in rapid pull-through manometry

on the back of the pig in a modified elastic belly strap, as described previously [9].

The parameters of the pH monitoring were number of acid reflux episodes, number of long acid reflux episodes, duration of the longest acid reflux episode, time that pH fell below four, fraction of time pH fell below four, oscillatory index, reflux index, esophagus clearances, area of reflux, index of area of reflux, and Kaye value.

The DeMeester score could not be calculated as the ratio of the upright position to the supine position because it was not applicable in the pig model. Therefore, we used the fraction of time that that pH fell below four as the primary indicator of reflux because comparable sensitivity, specificity, and statistical accuracy has been described previously [9, 10].

Manometry

Esophageal "stationary" and "rapid pull-through" manometry was applied to retrieve manometric characteristics of the LES and vector volume (VV), respectively. It was performed using a water-perfused manometry system including a hydraulic capillary infusion pump with a constant pressure of 110 kPA and a flow rate of 0.7 ml/min/capillary (electrical infusion pump type PIP-4-8; MUI Scientific, Mississauga, Canada), external transducers (pvb Medizintechnik GmbH, Kirchseeon, Germany), and an amplification system (PC Polygraf HR up to 8ch S/N 71-3214; Medtronic Synectics, Stockholm, Sweden). The data were recorded on a commercial PC with special analyzing software (version 2.04 Oesophageal Manometry Analysis Module 2.03; Medtronic, Duesseldorf, Germany). The catheters used had six capillaries (internal diameter, 0.8 mm) around a central tube (Zinetics Medical, Salt Lake City, UT, USA) with openings either spirally or radially arranged.

For the subsequently performed motorized rapid pull-through, the catheter was reintroduced into the stomach, and the proximal end was connected to a catheter-puller (1723 Catheter-Puller; Medtronic), which pulled the catheter through the LES at a speed of 10 mm/s. These measurements were repeated three times and averaged Fig. 2.

Pharmacologic stimulation

To test physiologic response to stimuli, a pharmacologic stimulation of the smooth muscles was induced, and rapid pull-through manometry was performed three times: at

baseline with intact sphincter, after myotomy with proven reflux, and 60 days after fundoplication. Contraction of the LES was achieved by injecting pentagastrin 3 μg/kg (half-life, 10 min). Glucagon 100 μg/kg was used for relaxation of the sphincter (half-life, 5 min). Then, 45 s after injection of pentagastrin, five measurements were performed within a 10 min interval of each other. The results of the last measurement were equal to the baseline, so evaluation of glucagon could start. After the injection of glucagon, four additional measurements in intervals of 2 min were performed. The last measurement showed normal values again.

Yield pressure and volume

Yield pressure and volume are defined as the pressure and volume necessary to burst the high-pressure zone permanently at the gastroesophageal junction. This is a rather unphysiologic examination, but the results represent the maximum capacity of the respective antireflux procedure. The stomach is filled through a small catheter inserted transpylorically, and the postpyloric duodenum is tied.

In this study, the pressure in the stomach was measured with an electronic pressure transducer probe (Standard Instruments GmbH, Karlsruhe, Germany). The instillation of blue-colored water in 50 ml increments in the stomach was monitored by gastroscopy to detect the opening point of the esophageal sphincter. Afterward, the pigs were killed.

Myotomy

With the animals under general anaesthesia as described earlier, left subcostal laparotomy and preparation of the gastroesophageal junction were performed, followed by complete extramucosal cadiomyotomy, including the distal esophagus and the gastroesopahgeal junction. Intraoperative endoscopy ensured a macroscopically sufficient result and excluded perforation.

Antireflux procedures

All the animals underwent laparoscopy. After mobilization of the left liver lobe, the lesser curvature was dissected to identify the gastroesophageal junction. Both diaphragmatic crura were dissected. No dissection of the greater curvature was necessary in this model.

The randomization of the laparoscopic intervention was now completed. In the control group (group 4), no further treatment was administered. All fundoplications were performed with the endoscope placed in the esophagus to ensure that the fundoplication was not too tight.

Total 360° fundoplication (Nissen-Rosetti) (group 1). A posterior hiatoplasty was performed with two stitches and a short floppy circumferential fundoplication pulling the fundus around the distal esophagus. The plication was sutured with three stitches placed 1 cm apart, with the second stitch including the anterior wall of the esophagus to prevent the telescope phenomenon.

Posterior 270° hemifundoplication (Toupet) (group 2). The fundus was fixed to the esophagus with three stitches to each side, thus leaving approximately 90° of the circumference. No hiatoplasty was performed, but the fundus back wall was fixed to the left and right crura respectively with two stitches each.

Anterior hemifundoplication (Dor) (group 3). After posterior hiatoplasty with two stitches, Dor fundoplication was performed by folding the anterior wall of the fundus over the gastric cardia and suturing it to the edge of the esophagus and to the right crus of the diaphragm. The loose part of the fundus then was pulled to the right across the ventral aspect and fixed to the right side of the esophagus with another three stitches. Additionally, sutures joined the anterior gastric wall and the anterior rim of the esophageal hiatus.

Statistical analysis

We used StatView (version 4.5; SAS Software, Cray, NC, USA) for statistical analysis. Parametric data are presented as mean and standard error of the mean (SEM). Nonparametric data are presented as median and range. The impact of the treatment within the groups was analysed using Student's *t*-test. For intergroup comparison, analysis of variance (ANOVA) or repeated-measure ANOVA was applied where indicated. If significance was detected in intergroup comparison, a post hoc analysis was added using the Bonferrni/Dunn test. Significance levels were set at a P value less than 0.05.

Vector volume was defined as the primary end point. Based on an educated guess, a difference of 100% for the VV at the LES (sufficient fundoplication vs control condition) was assumed. The calculated number needed to treat with a 5% alpha mistake for 80% power was six per group.

Results

Baseline values

Myotomy was performed in 28 German Landrace pigs. Five animals had to be excluded from the study (two for insufficient myotomy, one for perforation after myotomy, two for postoperative ileus). Baseline results were defined

to be the normal values because no reference values were available.

The mean operation time for myotomy was 120 min (range, 95–255 min). A significant reduction in the pressure and resistance parameters could be detected by manometry 72 h after myotomy. Vector volume was reduced from 1,960.51 ± 151.4 to 890.89 ± 61.39 cm^3 ($P < 0.0001$). Mean and median sphincter pressures also were significantly reduced. Monitoring of pH showed an increase in acid reflux. The fraction of time that pH fell below four increased significantly, from 3.5 ± 0.68% to 14.5 ± 2.4% ($P = 0.0006$).

Stimulation of the native esophageal sphincter with pentagastrin led to a significant increase in the mean and maximum pressure and VV (10,980.47 ± 2,588.7 cm^3; $P = 0.0042$). After injection of glucagon, a significant reduction (compared with baseline) of the mean and maximum pressure and VV (960.67 ± 136.4 cm^3; $P = 0.0126$) was seen due to relaxation of the high-pressure zone.

Reaction to pharmacologic stimuli after myotomy was reduced. After injection of pentagastrin, VV was significantly increased to 6,057.5 ± 1,667.0 cm^3 ($P = 0.04$), whereas a significant reduction in the mean and maximum pressure was found after injection of glucagon. However, the reduction of VV was not significant (642.43 ± 83.74 cm^3).

Post-therapeutic values

Manometry

Because the VV represents the most sophisticated value in manometric assessment, the presented results focus on this value. Corresponding results were seen for mean and median sphincter pressure.

Total fundoplication On day 10 after Nissen fundoplication, we found a massive, significant increase (vs. postmyotomy values) of the VV to 4,699.67 ± 1,093.9 cm^3 ($P = 0.001$). The increase missed statistical significance just marginally compared with normal value ($P = 0.06$). On day 60, a slight decrease in the pressure parameters was observed, but VV still was significantly increased compared with postmyotomy values (3,056.33 ± 819.9 cm^3; $P = 0.0023$).

Posterior hemifundoplication After Toupet fundoplication, VV was 2,873.42 ± 351.9 cm^3 on day 10. This represented a significant increase compared with postmyotomy value ($P < 0.0001$). No significant differences compared with the normal values were found. In this group, on day 60, a slight decrease compared with day 10 was observed as well. The VV of 2,636.94 ± 347.1 cm^3 still was increased significantly compared with the values after myotomy ($P = 0.0004$).

Anterior hemifundoplication A VV of 2,114.37 ± 234.1 cm^3 was measured on day 10, and a VV of 1,198.55 ± 250.9 cm^3 was measured on day 60, thus showing a significant increase compared with postmyotomy values ($P < 0.0001$) but a decrease in the parameter compared with day 10. On day 60, the VV lost statistical significance compared with the postmyotomy values.

Control group A significant decrease in the pressure parameters on day 10 compared with postmyotomy values (890.89 ± 61.39; $P = 0.004$)) was found. The VV decreased significantly compared with the normal value of 320 ± 70.1 cm^3 ($P = 0.003$). The manometry on day 60 showed a slight increase in the parameters. The VV of 562.92 ± 49.4 cm^3 still was decreased significantly compared with the postmyotomy values ($P = 0.03$) and the normal value ($P = 0.008$).

Intergroup comparison All the fundoplication groups showed a significant increase in VV compared with the status after myotomy. This increase was most distinct in the Nissen group, with a VV significantly higher than in all the other groups. Toupet fundoplication showed a less distinct but still obvious increase, with VV significantly higher than in the control group or the anterior hemifundoplication group. Until the end of the trial (day 60), VV in the Nissen and Toupet fundoplication groups remained significantly higher than in the other groups (Fig. 3). No significant difference was detected between Nissen and Toupet fundoplication.

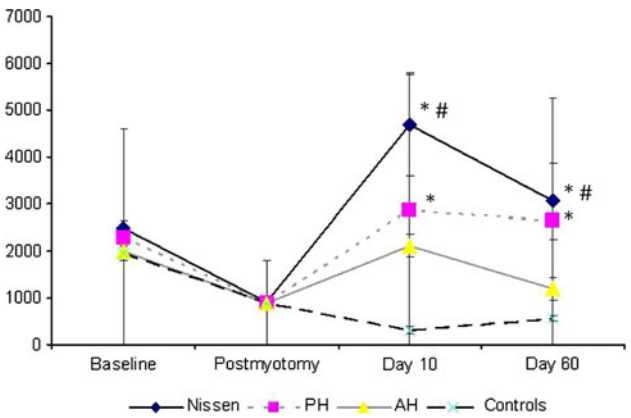


Fig. 3 Values of vector volume at baseline, after myotomy, and on days 10 and 60 after different antireflux procedures (data are presented as mean ± SEM) day 10/day 60: 10th/60th pod post fundoplication; PH: posterior hemifundoplication = Toupet, AH: anterior hemifundoplication = Dor; * $p<0.05$ vs. controls, # $p<0.05$ vs. AH

pH monitoring

Every procedure showed a more or less distinct effect on pH recordings. Almost no acid reflux was identifiable in the total fundoplication group. The fraction of time that pH fell below four was reduced to 0.075 ± 0.075%. Compared with the postmyotomy value, this was a highly significant reduction ($P < 0.0001$). Compared with the normal value, this was not significant but below the 10th percentile of the normal value.

In the posterior hemifundoplication group, reflux also was greatly reduced. Compared with postmyotomy value, the fraction time the pH fell below four was significantly decreased to 2.22 ± 1.8% ($P < 0.0001$) and to approximately the 50th percentile of normal values. Reflux was significantly reduced in the anterior hemifundoplication group compared with the postmyotomy value ($P = 0.0014$; fraction of time pH < 4, 10.03 ± 1.3%). In the control group, significant reflux was detected after myotomy (fraction time pH < 4, 18 ± 5.1%; $P = 0.0007$) and remained at the same high level until the end of the trial.

Intergroup comparison showed significant differences between the control group and the Nissen ($P < 0.0001$) and Toupet ($P < 0.0001$) fundoplication groups, whereas the anterior hemifundoplication group did not differ significantly from the control group (Fig. 4). No significant differences were found between posterior hemifundoplication and total fundoplication.

Pharmacologic stimulation

After fundoplication pentagastrin induced a strong contraction of the LES after both total and partial posterior fundoplication, causing VV to reach values above those of the native sphincter, with the highest value for the Nissen fundoplication. When after glucagon injection the rates of decrease were analyzed, the total fundoplication group was found to relax up to 70% and the posterior hemifundoplication group up to 32% compared with 51% in the native sphincter. In contrast, the anterior hemifundoplication group and the control group showed no relevant relaxation.

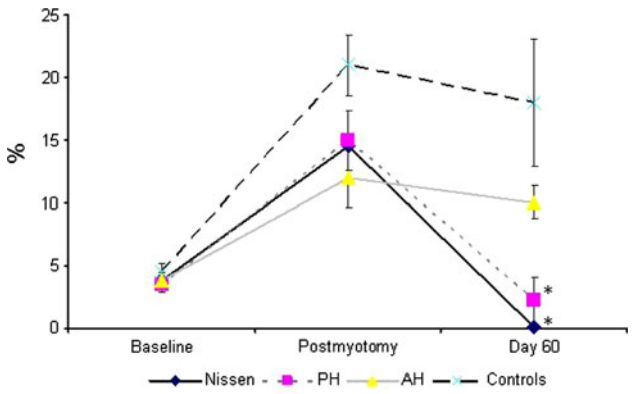


Fig. 4 Values for fraction of time that pH fell below four at baseline, after myotomy, and on day 60 after different antireflux procedures (data are presented as mean ± SEM) day 60: 60th pod post fundoplication; PH: posterior hemifundoplication = Toupet, AH: anterior hemifundoplication = Dor; * p<0.05 vs. controls

Yield volume and yield pressure

After completion of the measurements on day 60, the yield pressure and yield volume were measured. In a previous study of three pigs without prior surgery, the volume necessary to overcome the esophageal sphincter was found to be 4,383.3 ± 1,281 ml. The corresponding pressure was 18.0 ± 8.0 mmHg. The results of this measurement are shown in Fig. 5.

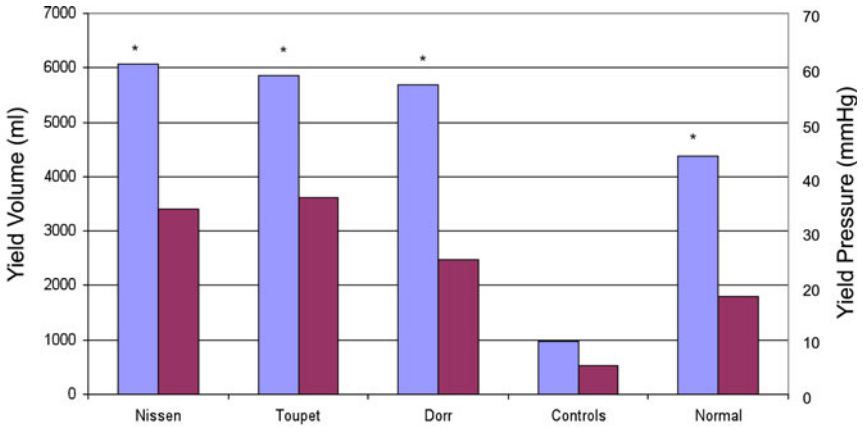
Statistical analysis showed a significantly lower yield volume in the control group compared with all the other groups ($P < 0.0001$) and with normal value ($P = 0.0032$). No significant differences were found between the different fundoplications.

Discussion

Gastroesophageal reflux disease (GERD) is a widespread disorder that not only deteriorates the quality of life but also causes serious and potentially life-threatening complications. There is a known context of chronic gastroesophageal or duodenogastroesophageal reflux, reflux esophagitis, epithelial metaplasia (Barrett's esophagus), dysplasia, and adenocarcinoma of the distal esophagus [5, 11]. Furthermore, we have found an increase in the incidence of both reflux disease and adenocarcinoma [12], making the disease and its treatment even more relevant.

Primary treatment of GERD is conservative. Although medical treatment has shown very good effects [13], it is symptomatic rather than curative for most patients. Surgery offers a cure by physically preventing reflux into the esophagus.

Parallel to the increase in GERD incidence, the operative management has not been completely changed but still has taken a turn by the establishment of minimal access surgery in that field. During recent decades, large patient cohorts have undergone laparoscopic fundoplication using all sorts of different techniques. The most common procedures are Nissen fundoplication, Toupet fundoplication, and Dor fundoplication [14–17]. Nissen fundoplication, the well-investigated and understood technique during this time, also was the preferred operation. In several clinical trials, other known but not frequently performed techniques were used [14–17]. Clinical results still are variable, and it still is debated whether total fundoplication is mandatory



		Nissen	Toupet	Dorr	Controls	Normal
Yield volume (ml)	Mean	6078	5850	5680	983	4383
	SEM	371	694	584,9	334	1281
Yield pressure(mmHg)	Mean	34	36,25	24,8	5,33	18
	SEM	6,6	4,7	6,25	1,45	8

Fig. 5 Yield volume and yield pressure on day 60 after different antireflux procedures

[18, 19] or whether partial fundoplication achieves similar results [15, 16]. Although a recent metaanalysis supports the latter [20], comparable long-term clinical results and basic insight into the function of partial fundoplications have been lacking.

Only two experimental studies comparing different antireflux procedures were available [21, 22]. The first trial had one major drawback: the antireflux procedure was performed on an intact sphincter, thus not representing the clinical situation of GERD [21] and making postoperative measurements difficult to interpret. In the second trial, no pH monitoring was performed [22]. Additionally, the results are questionable because a pressure of 0 mmHg after myotomy was measured in all the pigs [22]. These data contradict our findings and are in contrast to the clinical situation of patients with reflux.

Therefore, we established a model of gastroesophageal reflux in pigs with proven reflux by measurements that were standard in human diagnostics. In this context, long-term pH monitoring was established in a pig model for the first time [9].

Despite its potential limitations, an animal model was necessary because data on the basic function of fundoplications were available only for the Nissen technique to date [23]. Although several clinical observational studies were available, basic and advanced functional assessment, neither feasible nor ethical in humans, was necessary for a full understanding of the efficacy and physiologic reaction of different antireflux procedures.

Although medical treatment is the primary treatment of choice, antireflux surgery has gained widespread acceptance because it is performed by minimal access surgery. Currently, it is the "gold standard" [24, 25] for this type of surgery. Different techniques to prevent reflux described over several years currently can be performed easily by minimal access surgery.

Pharmacotherapy (PPIs, H2 receptor-blockers, antacids, and supportive medication) provides good reduction of symptoms for most patients, but symptoms usually recur after discontinuation of the medication because the pathoanatomic problem is not influenced or solved [6]. For most patients, surgical interventions offer a cure for GERD with a single intervention. Different surgical procedures have been described since 1967.

Recently, a randomized controlled trial comparing open and laparoscopic total fundoplication with an 11 year follow-up period showed a long-term success rate of 85% for both open and laparoscopic surgery [26]. The number of disrupted plications was significantly greater in the open group [14]. In a meta-analysis [27], a significantly shorter hospital stay and a lower rate of complications were detected in the minimal access group.

The most commonly performed procedure, Nissen fundoplication [28], shows good results (75–85%) in long-term follow-up studies. Even for elderly patients, it can be performed with good results and low morbidity. Rosenthal et al. [29] found that 94% of the patients were satisfied with the result after Nissen fundoplication. In a prospective randomized trial, the Nissen procedure was superior to conservative treatment with PPIs in terms of symptom control [30]. Balci and Turkcapar [31] found a significant increase in the quality of life and the control of symptoms for more than 90% of their patients. Overall, 90% of the patients were satisfied with the result of the fundoplication.

One major concern was the rate of early postoperative dysphagia, which ranged from 2.4 to 27%, although only 2.7% of the patients needed reoperation [32].

Other authors have presented large series of posterior hemifundoplications, with up to 97% of the patients satisfied with the result of the operation. A temporary postoperative dysphagia rate was found for 2 to 23% of the patients [17, 32, 33]. A recently published prospective randomized trial comparing the Nissen and Toupet operations found equal results concerning restoration of LES function and control of symptoms [17].

Anterior hemifundoplication is less common [34]. In a randomized trial comparing total and anterior fundoplication, Watson et al. [35] found similar clinical outcomes. However, Nissen fundoplication achieved superior control of reflux symptoms.

The long-term follow-up results in a randomized controlled trial comparing anterior and posterior fundoplication showed a significant disadvantage of the Dor fundoplication in terms of symptom (heartburn and acid regurgitation) control [15].

In recent years, endoscopic treatment of GERD has been published. In a recently published systematic review, Fry et al. [36] concluded that endoluminal therapy for patients with GERD can reduce the PPI dosage and provide a solution to reflux-associated symptoms, but the scientific and clinical data on safety and efficiency currently are insufficient. After initial encouraging results with endoscopic gastroplication, no clinical improvement of symptoms and no corresponding reduction in PPI intake were found after 18 months [37].

An alternative intervention is the use of radiofrequency energy (Stretta procedure), in which thermal energy is applied in the submucosa. Overall, the data of the Stretta procedure show an improvement in the quality of life and in the reduction of PPI intake, but no long-time results are available. Therefore, this technique cannot be advocated as standard procedure [38].

Several experimental studies have examined the effects of different fundoplication techniques. But because some of these studies used sufficient esophageal sphincters, they are not comparable with the pathologic situation of reflux [21, 39, 40]. Other examinations have used an ex vivo model without the influence of innervations. Watson et al. [22] assessed only two pigs after a follow-up period of 6 weeks. No pH monitoring was recorded in this trial. Yau et al. [41] found a lower esophageal sphincter pressure after anterior hemifundoplication than after total fundoplication. All these trials lacked both a sufficient model and a complete workup.

The current trial was designed to investigate the reaction of different fundoplications in an experimental setting after proven insufficiency of the LES and to examine the impact on their physiologic contraction induced by injection of pentagastrin in our setting. The pig is a well-established model for studying reflux with various questions. We established 24-h pH monitoring in the model [9] to prove reflux with the same means as in humans.

After insufficiency of the LES and reflux had been confirmed, the different laparoscopic fundoplications were performed. Postoperative assessment was based on manometry and pH monitoring. Manometry has a sensitivity of 84% and a specificity of 89% for detecting insufficiency of the LES. When manometry is used in combination with pH monitoring, 91% of the patients with reflux caused by sphincter insufficiency can be detected. The most important and subtle parameters for distinguishing reflux are sphincter VV and the fraction of time that esophageal pH is reduced.

Physiologic values for the fraction of time that pH fell below four in the pigs were not available for comparison and thus were retrieved from baseline measurements as described previously [9]. This parameter has sensitivity and specificity comparable with the De-Meester score [10] routinely applied in humans but not applicable in this model. After myotomy, an increase in the fraction of time that pH fell below four was found as expected. This was reduced to physiologic values after all the different fundoplications and showed no significant differences between the three therapy groups. As expected, the VV was significantly reduced after myotomy and increased again after all three modifications of fundoplication [22, 41]. However, 60 days after the procedure, only total fundoplication and posterior hemifundoplication demonstrated a significant difference compared with control subjects. Anterior hemifundoplication failed to be significant, so it seems to be insufficient for clinical use to treat reflux disease as described previously [21].

Total fundoplication demonstrated an excessive increase in VV 10 days after the operation, then, slightly diminished over time. Posterior hemifundoplication showed a significant but moderate increase that remained more or less at the same level over time. This accords with clinical findings of early dysphagia after total fundoplication [32].

Additional "purely experimental" parameters also were measured for further understanding. Previous studies found a comparable reduced yield pressure and yield volume in an insufficient esophageal sphincter [22]. In our trial, no significant differences between the three therapy groups were found, whereas all the groups differed significantly from the control group.

The results of pharmacologic stimulation were measured by pull-through manometry, with VV as the determining parameter. Examination of the pharmacologic stimulation of the esophageal sphincter was introduced by Siewert et al. [23]. The action of pentagastrin and glucagon on the esophageal sphincter was confirmed in other trails. The

necessary dose was found to be 3 μg/kg for pentagastrin and 20–100 μg/kg for glucagon. Therefore, these doses were used to prove effects of the different wraps on the lower esophagus in our study.

Siewert et al. [23] examined the results after complete myomectomy of the gastroesophageal junction and total fundoplication to evaluate the reaction to contraction or relaxation stimuli of the wrap itself. Our study is the first to pick up this idea and test the reaction to respective stimuli in posterior and anterior hemifundoplication and in total fundoplication using a reflux model. Our study confirmed the finding that the gastric or fundic muscles of the wrap react to stimulation independently. This was demonstrated by a very strong reaction after total and posterior fundoplication but not after anterior fundoplication compared with the reaction of the normal (nonmyotomized) sphincter. This again demonstrates that total fundoplication leads to an excessive correction far beyond normal and beyond that of posterior hemifundoplication, which still remains slightly above normal. This once more shows overcorrection of total fundoplication, with clinical relevance corresponding to possible reduced quality of life due to possible side effects such as dysphagia and bloating. In anterior hemifundoplication and control subjects, the pharmacologic stimulation exhibited minimal effects, again showing that this procedure is not sufficient for the treatment of reflux disease.

In summary, our study demonstrated that both total and partial fundoplication, if performed as posterior hemifundoplication, effectively suppresses reflux. This is achieved by an effective augmentation of the insufficient LES. In addition, both techniques demonstrate reactions especially to contraction stimuli. Similar results could not be demonstrated with anterior partial fundoplication.

In attempts to distinguish between total and posterior partial fundoplication, our results show that total fundoplication constantly results in a higher unphysiologic correction that may account for the postoperative problems often observed in the clinical setting. In contrast, posterior hemifundoplication shows results closer to normal in all the different specimens examined.

Conclusions

Clinical evidence shows that fundoplication is an effective technique for the treatment of reflux, delivering good and long-term symptom relief and reducing the risk of esophageal cancer in certain patient groups. Our results add the necessary experimental and basic evidence that the mechanisms of action are sufficient pressure augmentation and reaction to physiologic stimuli, resulting in effective reflux prevention with the use of both total and partial posterior fundoplication.

Toupet fundoplication tends toward a more physiologic correction, thus in our judgment making it the preferable technique. In contrast, anterior fundoplication is found to be less effective, thus strongly suggesting that this is not an ideal technique for the treatment of patients with GERD.

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References

1. Eisen G (2001) The epidemiology of gastroesophageal reflux disease: what we know and what we need to know. Am J Gastroenterol 96:S16–S18
2. Conio M, Filiberti R, Blanchi S, Ferraris R, Marchi S, Ravelli P, Lapertosa G, Iaquinto G, Sablich R, Gusmaroli R, Aste H, Giacosa A (2002) Risk factors for Barrett's esophagus: a case-control study. Int J Cancer 97:225–229
3. Corley DA, Buffler PA (2001) Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the cancer incidence in five continents database. Int J Epidemiol 30: 1415–1425
4. Chen X, Yang CS (2001) Esophageal adenocarcinoma: a review and perspectives on the mechanism of carcinogenesis and chemoprevention. Carcinogenesis 22:1119–1129
5. Lagergren J, Bergstrom R, Lindgren A, Nyren O (1999) Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 340:825–831
6. Vigneri S, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di MF, Battaglia G, Mela GS, Pilotto A (1995) A comparison of five maintenance therapies for reflux esophagitis. N Engl J Med 333:1106–1110
7. Swanstrom LL (1999) Partial fundoplications for gastroesophageal reflux disease: indications and current status. J Clin Gastroenterol 29:127–132
8. Watson DI, Jamieson GG (1998) Antireflux surgery in the laparoscopic era. Br J Surg 85:173–1184
9. Gawad KA, Wachowiak R, Rempf C, Tiefenbacher WJ, Strate T, Achilles EG, Blochle C, Izbicki JR (2003) Ambulatory long-term pH monitoring in pigs. Surg Endosc 17:1556–1560
10. DeMeester TR, Wang CI, Wernly JA, Pellegrini CA, Little AG, Klementschitsch P, Bermudez G, Johnson LF, Skinner DB (1980) Technique, indications, and clinical use of 24-hour esophageal pH monitoring. J Thorac Cardiovasc Surg 79:656–670
11. Dulai GS, Guha S, Kahn KL, Gornbein J, Weinstein WM (2002) Preoperative prevalence of Barrett's esophagus in esophageal adenocarcinoma: a systematic review. Gastroenterology 122: 26–33
12. Fouad YM, Makhlouf MM, Tawfik HM, el-Amin H, Ghany WA, el-Khayat HR (2009) Barrett's esophagus: prevalence and risk factors in patients with chronic GERD in Upper Egypt. World J Gastroenterol 15:3511–3515
13. Katz PO, Zavala S (2010) Proton pump inhibitors in the management of GERD. J Gastrointest Surg 14:S62–S66
14. Salminen PT, Hiekkanen HI, Rantala AP, Ovaska JT (2007) Comparison of long-term outcome of laparoscopic and conventional Nissen fundoplication: a prospective randomized study with an 11-year follow-up. Ann Surg 246:201–206
15. Engstrom C, Lonroth H, Mardani J, Lundell L (2007) An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 31:1221–1225

16. Wijnhoven BP, Watson DI, Devitt PG, Game PA, Jamieson GG (2008) Laparoscopic Nissen fundoplication with anterior versus posterior hiatal repair: long-term results of a randomized trial. Am J Surg 195:61–65
17. Shaw JM, Bornman PC, Callanan MD, Beckingham IJ, Metz DC (2010) Long-term outcome of laparoscopic Nissen and laparoscopic Toupet fundoplication for gastroesophageal reflux disease: a prospective, randomized trial. Surg Endosc 24:924–932
18. Horvath KD, Jobe BA, Herron DM, Swanstrom LL (1999) Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg 3:583–591
19. Oleynikov D, Eubanks TR, Oelschlager BK, Pellegrini CA (2002) Total fundoplication is the operation of choice for patients with gastroesophageal reflux and defective peristalsis. Surg Endosc 16:909–913
20. Broeders JA, Mauritz FA, Ahmed AU, Draaisma WA, Ruurda JP, Gooszen HG, Smout AJ, Broeders IA, Hazebroek EJ (2010) Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. Br J Surg 97:1318–1330
21. Freys SM, Fuchs KH, Heimbucher J, Thiede A (1997) Tailored augmentation of the lower esophageal sphincter in experimental antireflux operations. Surg Endosc 11:1183–1188
22. Watson DI, Mathew G, Pike GK, Baigrie RJ, Jamieson GG (1998) Efficacy of anterior, posterior, and total fundoplication in an experimental model. Br J Surg 85:1006–1009
23. Siewert R, Jennewein HM, Waldeck F, Peiper HJ (1973) Experimental and clinical tests on the mechanism of fundoplication. Langenbecks Arch Chir 333:5–22
24. Chrysos E, Tsiaoussis J, Athanasakis E, Zoras O, Vassilakis JS, Xynos E (2002) Laparoscopic vs open approach for Nissen fundoplication: a comparative study. Surg Endosc 16:1679–1684
25. Bowrey DJ, Peters JH (1999) Current state, techniques, and results of laparoscopic antireflux surgery. Semin Laparosc Surg 6:194–212
26. Broeders JA, Rijnhart-de Jong HG, Draaisma WA, Bredenoord AJ, Smout AJ, Gooszen HG (2009) Ten-year outcome of laparoscopic and conventional Nissen fundoplication: randomized clinical trial. Ann Surg 250:698–706
27. Peters MJ, Mukhtar A, Yunus RM, Khan S, Pappalardo J, Memon B, Memon MA (2009) Metaanalysis of randomized clinical trials comparing open and laparoscopic antireflux surgery. Am J Gastroenterol 104:1548–1561
28. Granderath FA, Kamolz T, Schweiger UM, Pasiut M, Haas CF, Wykypiel H, Pointner R (2002) Long-term results of laparoscopic antireflux surgery. Surg Endosc 16:753–757
29. Rosenthal R, Peterli R, Guenin MO, von Flüe M, Ackermann C (2006) Laparoscopic antireflux surgery: long-term outcomes and quality of life. J Laparoendosc Adv Surg Tech A 16:557–561
30. Anvari M, Allen C, Marshall J, Armstrong D, Goeree R, Ungar W, Goldsmith C (2006) A randomized controlled trial of laparoscopic Nissen fundoplication versus proton pump inhibitors for treatment of patients with chronic gastroesophageal reflux disease: one-year follow-up. Surg Innov 13:238–249
31. Balci D, Turkcapar AG (2007) Assessment of quality of life after laparoscopic Nissen fundoplication in patients with gastroesophageal reflux disease. World J Surg 31:116–121
32. Booth MI, Stratford J, Jones L, Dehn TC (2008) Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 95: 57–63
33. Cuschieri A, Hunter J, Wolfe B, Swanstrom LL, Hutson W (1993) Multicenter prospective evaluation of laparoscopic antireflux surgery: preliminary report. Surg Endosc 7:505–510
34. Munro A (2000) Laparoscopic anterior fundoplication. J R Coll Surg Edinb 45:93–98
35. Nijjar RS, Watson DI, Jamieson GG, Archer S, Bessell JR, Booth M, Cade R, Cullingford GL, Devitt PG, Fletcher DR, Hurley J, Kiroff G, Martin IJ, Nathanson LK, Windsor JA (2010) Five-year follow-up of a multicenter, double-blind randomized clinical trial of laparoscopic Nissen vs anterior 90 degrees partial fundoplication. Arch Surg 145:552–557
36. Fry LC, Monkemuller K, Malfertheiner P (2007) Systematic review: endoluminal therapy for gastro-oesophageal reflux disease: evidence from clinical trials. Eur J Gastroenterol Hepatol 19:1125–1139
37. Schiefke I, Zabel-Langhennig A, Neumann S, Feisthammel J, Moessner J, Caca K (2005) Long-term failure of endoscopic gastroplication (EndoCinch). Gut 54:752–758
38. Pearl JP, Marks JM (2007) Endolumenal therapies for gastroesophageal reflux disease: are they dead? Surg Endosc 21:1–4
39. Watson DI (1999) Tailored augmentation of the lower esophageal sphincter in experimental antireflux operations. Surg Endosc 13:92–93
40. Huttl TP, Huttl TK, Lang RA, Meyer G, Wichmann MW (2006) Laparoscopic partial myectomy: an experimental reflux model. Surg Endosc 20:665–672
41. Yau P, Watson DI, Ascott N, Lafullarde T, Jamieson GG (2000) Efficacy of a 90-degree anterior fundoplication vs a total fundoplication in an experimental model. Surg Endosc 14:830–833