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Original research

Toupet versus Dor as a procedure to prevent reflux after cardiomyotomy for achalasia: Results of a randomised clinical trial

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HIGHLIGHTS

- The optimal anti-reflux procedure after cardiomyotomy for achalasia remains unclear.
- The anterior (Dor) and the posterior (Toupet) fundoplication are commonly used.
- A randomised comparison was conducted between Toupet and Dor.
- Toupet seems to achieve more improvement in EORTC functional scale scores than Dor.
- Toupet also seems to achieve more improvement in oesophageal emptying than Dor.

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ABSTRACT

Background: The optimal anti-reflux procedure after Heller cardiomyotomy for oesophageal achalasia remains unclear. The most commonly used procedure is the anterior partial fundoplication according to Dor, although during recent years the posterior counterpart (Toupet) has become popular.
Methods: Patients with newly diagnosed achalasia and referred for cardiomyotomy were randomised to receive either an anterior or partial posterior fundoplication following a classical cardiomyotomy. The effect of surgery was assessed during the first postoperative year by Eckardt scores, EORTC QLQ-OES18 scores and HRQL questionnaires. Timed barium oesophagogram (TBO) and ambulatory 24-h pH monitoring were performed to determine oesophageal emptying and the degree of reflux control, respectively.
Results: Forty-two patients were randomised into Dor ($n = 20$) and Toupet ($n = 22$) groups. Eckardt scores improved dramatically with both procedures, but the EORTC QLQ-OES18 (functional scales) scores revealed significantly better relative improvements in the Toupet group compared to the Dor repair ($P = 0.044$). Corresponding advantages in favour of Toupet were observed postoperatively in the percentage of oesophageal emptying at TBO ($P = 0.011$ in height and $P = 0.018$ in area), an effect not observed in the Dor group. There were no other significant differences recorded between the study groups concerning HRQL evaluations and objective assessment of gastro-oesophageal acid reflux.
Conclusions: A partial posterior fundoplication after cardiomyotomy seems to achieve more improvement in oesophageal emptying and EORTC QLQ-OES18 functional scale scores than the anterior fundoplication. Otherwise no differences between the two anti-reflux repairs were noted.
Trial registration number: ClinicalTrials.gov Identifier: NCT01933373.

1. Introduction

Achalasia of the oesophagus is a rare primary motility disorder characterised by aperistalsis of the oesophageal body and failure of the lower oesophageal sphincter (LOS) to relax in response to swallowing. This results in dysphagia, regurgitation, weight loss,

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and chest pain. The goal of therapy for achalasia is symptom relief by eliminating the outflow resistance caused by the hypertensive and non-relaxing LOS. The results of pharmacological treatments for achalasia including injection of botulinum toxin have been generally disappointing and are only recommended to patients unfit for interventions under general anaesthesia [1–3]. According to the available evidence, pneumatic dilation of the LOS or a Heller cardiomyotomy constitutes standard care for the majority of patients with achalasia [4,5].

The major downside of cardiomyotomy is the substantial gastro-oesophageal reflux that follows a complete division of the entire LOS, including the gastric sling fibres. Therefore, a fundoplication to prevent debilitating reflux is required [6]. Available data suggest that a total fundoplication should be avoided, and instead a partial wrap of the oesophagus either dorsally (Toupet) or anteriorly (Dor) is generally recommended [7]. A potential disadvantage of the posterior approach is angulation of the gastro-oesophageal junction and the eventual obstruction of bolus passage. Advocates of the Dor procedure argue that disruption of the peri-oesophageal ligament and attachments during the posterior procedure might also induce reflux [8]. However, by extrapolating findings in gastro-oesophageal reflux disease (GORD) patients, the posterior partial fundoplication would better function as an anti-reflux repair [9].

The low incidence of achalasia makes it demanding and challenging to pursue randomised clinical trials in these patients. Accordingly, the evidence regarding differences between anterior and posterior fundoplication after cardiomyotomy is mainly based on prospective or retrospective single-institution series. Interestingly, data from a recent randomised trial showed no significant differences between the fundoplication alternatives [8]. Moreover, in a meta-regression analysis published thereafter, incorporating also non-randomised trials, more re-interventions were recorded after an anterior fundoplication [10].

Performing a complete cardiomyotomy in achalasia patients mandates the surgeon to follow a delicate balance between preventing reflux and maintaining the function and anatomy of the diaphragmatic hiatal region.

The aim of the present study was therefore to collect complementary data on the symptomatic and objective outcomes after Toupet and Dor fundoplications within a randomised clinical trial.

2. Patients and methods

The study was run as a prospective, randomised trial of patients with newly diagnosed achalasia. The patients were managed and operated on at Ersta Hospital Stockholm and Karolinska University Hospital, Huddinge.

The Local Ethics Committee approved the study and a signed informed consent was obtained from all patients. The study was registered in *ClinicalTrials.gov* with the register number of NCT01933373.

2.1. Inclusion/exclusion criteria

Inclusion criteria were symptoms rated as >3 by the Eckardt score [11], a diagnostic oesophageal manometry that demonstrated partial or complete absence of LOS relaxation as a response to repeated water swallows, and absence of oesophageal body peristalsis. Exclusion criteria were other severe illnesses liable to prevent anaesthesia and/or surgery, pseudo-achalasia due to oesophageal motility disorders associated with malignancy with extension into the lower oesophagus, or other factors expected to inhibit data retrieval.

2.2. Registration and randomisation of patients and blinding

Included patients were randomly assigned to treatment groups using computer-generated permutated blocks of random sizes. At inclusion each patient received a numeric code, and was thereafter blinded to the reconstructive procedure given, as were the care providers and assessors. Only the principal investigator (BH) could access patients through the codes. Patient data were collected separately from regular medical records in predefined case record forms.

2.3. 24-h pH monitoring

The pH recordings were performed using an antimony measurement electrode with a built-in reference electrode. The measurement electrode was placed 5 cm proximal to the LOS, as identified by the previous manometric examination. Patients were instructed to avoid acidic foods and drinks and to abstain from alcohol during the recording period. Technically unsatisfactory recordings, or recordings shorter than 18 h, were not included in the analysis.

The results of oesophageal pH monitoring were reported as percent time pH < 4.0 for the total duration of the recording, and for the time spent in upright and in supine positions, respectively. The total numbers of reflux episodes were also noted.

2.4. Timed barium oesophagogram (TBO)

Barium column height and width during TBO were measured at 1, 2, and 5 min after ingestion of 250 ml of low-density barium sulphate suspension according to standardised protocols [12]. Accordingly, a single radiologist (SG) calculated the area of the oesophageal barium column using the Sectra IDS7/DX (Sectra Imtec AB, Linköping, Sweden). The changes in area and height from the 1 min–5 min film formed the basis for analysing the degree of oesophageal emptying ("Percentage of oesophageal emptying"). The rate of reduction in the barium height or area from the preoperative to the postoperative study was calculated to evaluate the treatment effect ("Reduction rate").

2.5. Symptom assessments

Symptoms were measured using the HRQL questionnaire [13] and the Eckardt score [11]. Patients with symptoms rated as >3 by the Eckardt score at 12 months after operation were regarded as recurrences or treatment failures. In cases where the patient had experienced recurrent symptoms or relapse and appropriate treatment had been given, the symptoms proceeding additional treatment was analysed. Pre- and postoperative health-related quality of life was measured by the validated EORTC QLQ-OES18 form, an oesophageal cancer-specific module. This instrument consists of "functional scales" assessing the degree of dysphagia and "symptom scales" evaluating symptoms associated with eating, reflux, pain, swallowing, dry mouth, taste, coughing, and talking [14,15].

2.6. Surgical technique

In open surgery, an upper midline incision was made. For laparoscopy, patients were placed in the French position and five trocars were inserted in the upper abdominal region. In all patients, the phrenico-oesophageal ligament was then opened and the distal oesophagus was mobilised on the lateral and anterior sides. Myotomy was performed anteriorly with a length of at least 6 cm, extending no less than 1 cm below the gastro-oesophageal

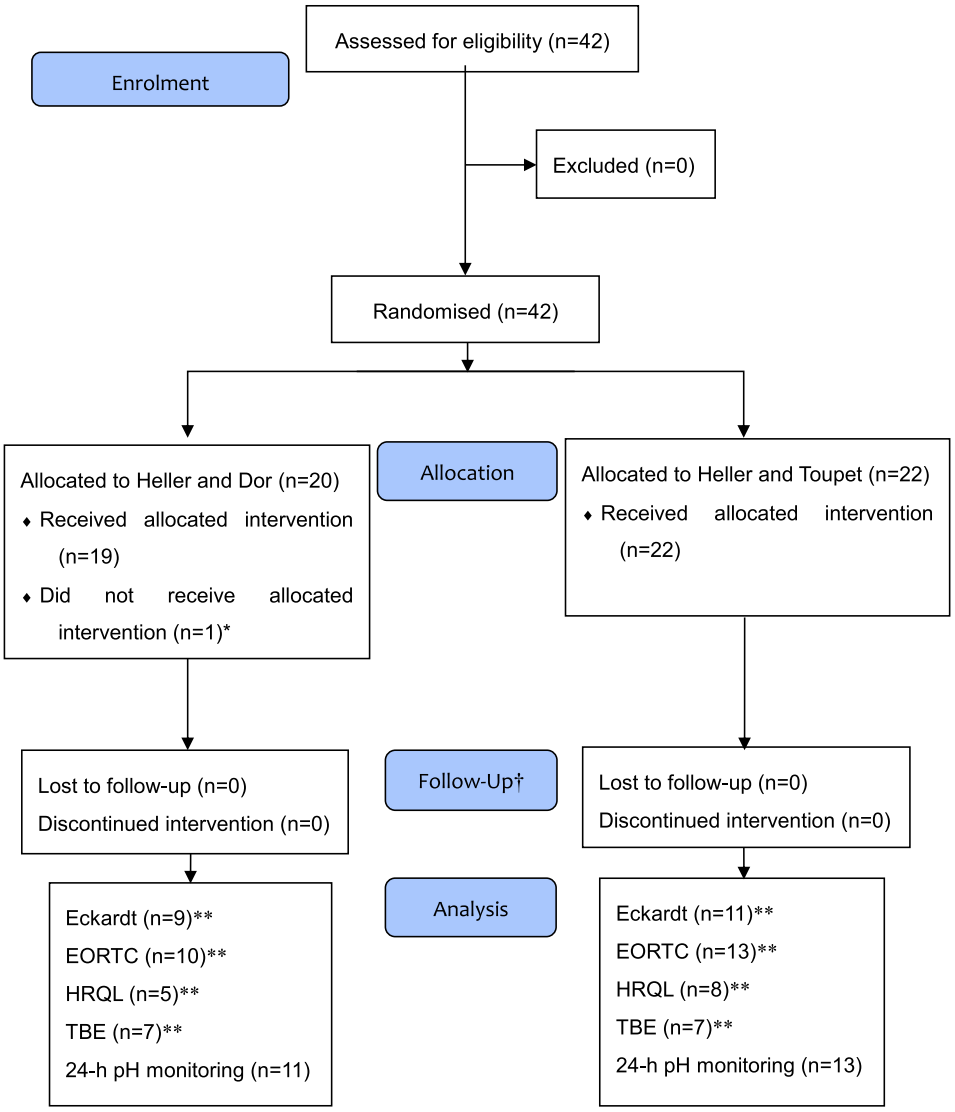

Fig. 1. CONSORT Flow diagram. *One patient desired to have pneumatic dilatation after randomisation and refused surgery. †There were no patients who were lost to follow up or discontinued intervention, but data were not available from all the patients. Analyses were performed using all available data. **Number of the patients analysed in repeated measures.

junction. In the Dor group, the proximal short gastric vessels were divided only if the fundus was insufficiently mobile and the fundus was then sutured to each end of the myotomy and to the right hiatal crus using non-absorbable sutures. In the Toupet group, the mobilised fundus was pulled posteriorly to the oesophagus creating a wrap that was sutured to the right and left edges of the myotomy using non-absorbable sutures. Finally, the posterior aspect of the wrap was sutured to the diaphragmatic crura.

Table 1
Patient characteristics.

	Dor ($n = 19$)	Toupet ($n = 22$)	P value
General characteristics			
Age (years)	45 (19–82)	44 (20–76)	0.666
Sex (male/female)	8/11	11/11	0.756
BMI (kg/m^2)	22.9 ± 4.2	23.8 ± 3.3	0.879
Previous treatment			
Medical treatment (yes/no)	2/17	0/21	0.219
Botox (yes/no)	0/19	1/20	1.000
Dilatation (yes/no)	1/17	1/20	1.000

BMI, Body mass index. Data are presented as means ± SD, median (range) or the number of patients. A Mann–Whitney U test was used to test the equality between the two medians of the variables. The Fisher's exact test was used to test the independence between the two groups.

Table 2
Operative data.

	Dor ($n = 19$)	Toupet ($n = 22$)	P value
Operation time (min)	103 (83–151)	95 (83–135)	0.537
Blood loss (ml)	0 (0–20)	0 (0–20)	0.758
Postoperative complication			
Grade IIIb			
Leakage	0	1	0.941
Grade II			
Pneumonia	0	1	0.941
Postoperative hospital stay (days)	2 (1–12)	2 (1–16)	0.743
Sick leave (days)	14 (0–21)	14 (0–30)	0.789

Data are presented as median (range) or the number of patients. The severity of complications was graded using the Clavien–Dindo classification of surgical complications. Mann–Whitney U tests were used to test the equality between the two medians of the variables. The Fisher's exact test was used to test the independence between the two groups.

Table 3
Pre- and postoperative Eckardt score.

	Pre			Post (12 months)		
	Dor ($n = 15$)	Toupet ($n = 19$)	*P* value	Dor ($n = 11$)	Toupet ($n = 14$)	*P* value
Weight loss						
0, None	5	8	0.288	11	12	0.487
1, <5 kg	6	3		0	2	
2, 5–10 kg	1	5		0	0	
3, >10 kg	3	3		0	0	
Dysphagia						
0, None	1	1	0.200	5	5	0.846
1, Occasional	0	3		2	5	
2, Daily	5	2		2	2	
3, Each meal	9	13		2	2	
Retrosternal pain						
0, None	2	2	0.443	6	7	0.369
1, Occasional	5	10		3	6	
2, Daily	6	3		2	0	
3, Each meal	2	4		0	1	
Regurgitation						
0, None	2	5	0.802	10	11	0.604
1, Occasional	4	5		1	3	
2, Daily	3	4		0	0	
3, Each meal	6	5		0	0	

Data are presented as the number of patients. The Fisher's exact test was used to test the independence between the two groups.

2.7. Power calculation

The primary endpoint in the study was postoperative oesophageal acid exposure at one year postoperatively. Based on previous studies of partial posterior and anterior fundoplications in GORD patients, we estimated that a partial posterior fundoplication would result in a total time oesophageal pH < 4 of 2% [9,16]. To detect an increase in acid exposure time to 5% after partial anterior fundoplication, it was calculated that 20 patients would have to be randomised into each arm, ($P < 0.050$) with a power of 0.80.

2.8. Statistical analysis

The Mann–Whitney *U* test was used to test the equality of medians between the groups for each variable. The Fisher's exact test was used to test the independence between groups. A general linear model (two-way repeated measures ANOVA) was used to analyse repeated measures. A *P* value <0.05 was considered statistically significant. All analyses were performed on the per-protocol set, using SPSS version 11.0 (SPSS, Chicago, IL, USA).

3. Results

From September 2005 to June 2011, a total of 42 patients consented to participate in the study and were accordingly randomised (20 into the Dor arm and 22 to have a Toupet). The enrolment ended in June 2011 when sufficient number of patients had been included and the study ended in June 2012 when the follow-up of the last patient was completed. One patient allocated to a Dor fundoplication, ultimately decided to have pneumatic dilatation after randomisation, thus refusing surgery and was excluded from the trial. Therefore, the study analyses were based on 41 randomised patients (Dor, $n = 19$; Toupet, $n = 22$). For details of the enrolment procedure, see Fig. 1.

3.1. Preoperative and perioperative data

All but one of the Heller myotomies was performed by laparoscopy. As seen in Tables 1 and 3, there were no differences in patient characteristics or symptom severity between the study groups preoperatively, nor were differences observed in operation time or estimated blood loss (Table 2). The postoperative course was basically uneventful after both procedures, although one patient in the Toupet group developed a leakage from a perforation in the myotomy that was sealed by a covered self-expanding metal stent.

3.2. Eckardt score

As a response to therapy, significant improvements were observed in repeated measures of the Eckardt score in the Dor group ($P < 0.001$) as well as in the Toupet group ($P < 0.001$, Fig. 2). We were unable to reveal a difference in the Eckardt score at any time point neither between the groups (Table 3) nor in the magnitude of improvement (Fig. 2). According to the Eckardt score, 1 out of 11 patients (9.1%) in the Dor group and 2 out of the 14 patients (14.3%) in the Toupet group had recurrences or treatment failures 12 months after operation ($P = 1.000$).

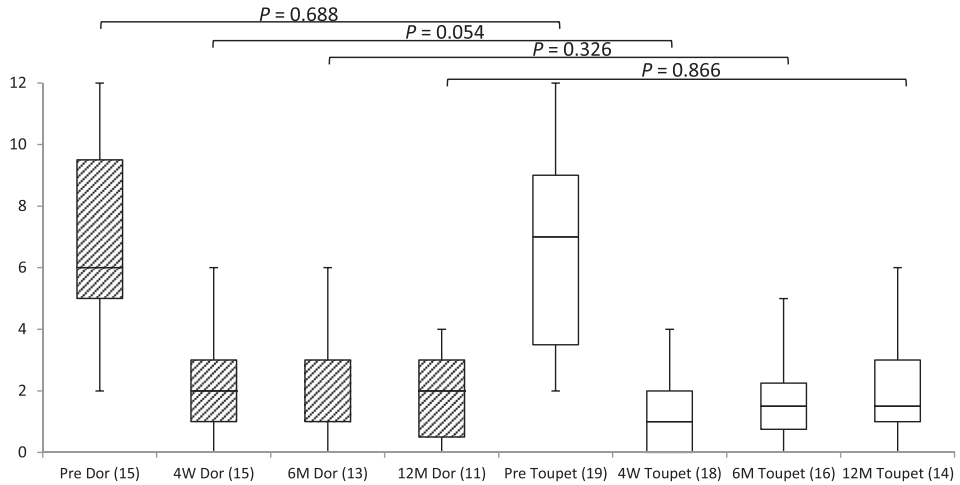

Fig. 2. Time course of Eckardt scores from baseline and during the postoperative follow up after cardiomyotomy and either Toupet or Dor fundoplication. The corresponding *P*-values are also given. The bottom and top of the box are the first and third quartiles, and the band inside the box is the median. The ends of the whiskers represent the minimum and maximum of all of the data. Data in parenthesis are number of the patients analysed.

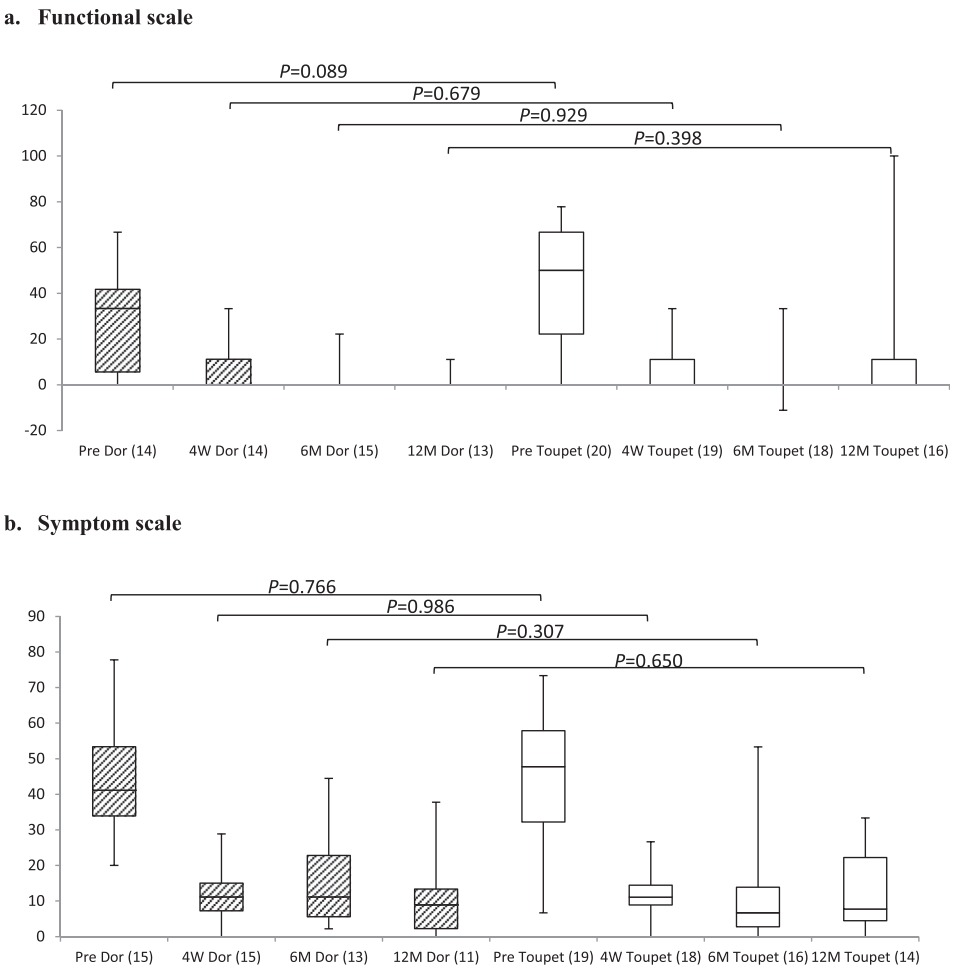

Fig. 3. Time course of EORTC QLQ-OES18 scores from baseline and during the postoperative follow up after cardiomyotomy and either Toupet or Dor fundoplication. (a) Functional scale between the groups at any time point. (b) Symptom scale in the two groups at any time point. The corresponding *P*-values are shown. The bottom and top of each box represent the first and third quartiles, respectively, and the horizontal band inside the box represents the median. The ends of the whiskers represent the minimum and maximum of all data points. Data in parenthesis are number of the patients analysed.

3.3. EORTC QLQ-OES18

Significant improvements were also observed in repeated measures of functional scales of the QLQ-OES18 both in the Dor ($P = 0.022$) and Toupet groups ($P < 0.001$, Fig. 3). There were no significant differences between the groups, at any time point after surgery, in neither of these scales. However, the improvement after surgery was significantly larger in the Toupet group than in the Dor group when the functional scales ($P = 0.044$) were compared, although no corresponding difference could be noted in the

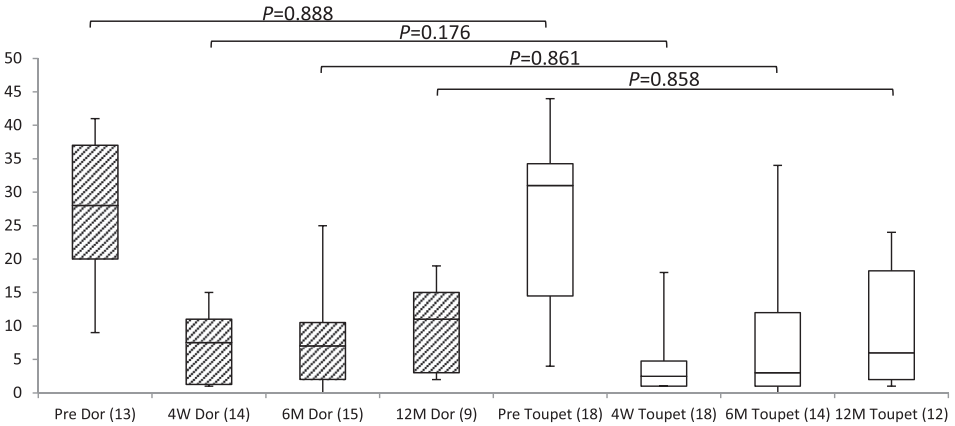

Fig. 4. Time course of HRQL scores in achalasia patients before and after cardiomyotomy and either Toupet or Dor fundoplication. The corresponding *P*-values are shown. The bottom and top of each box represent the first and third quartiles, respectively, and the horizontal band inside the box represents the median. The ends of the whiskers represent the minimum and maximum of all data points. Data in parenthesis are number of the patients analysed.

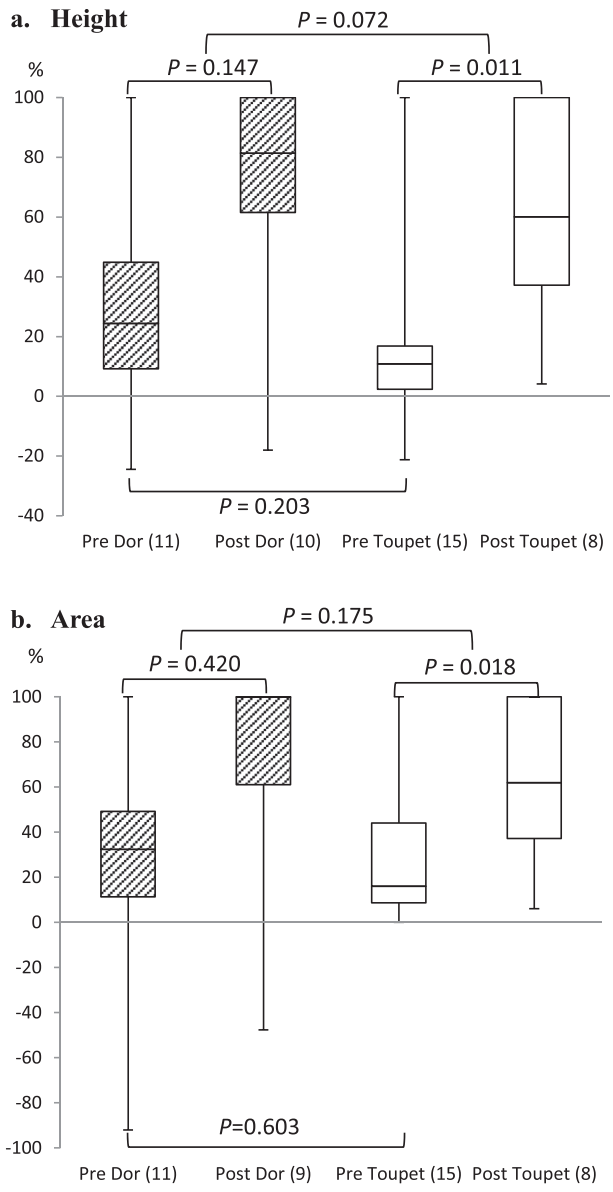

Fig. 5. Percentage of oesophageal emptying (%) = (1 − height or area 5 min after ingestion/height or area 1 min after ingestion)*100(%). The corresponding *P*-values are shown. The bottom and top of each box represent the first and third quartiles, respectively, and the horizontal band inside the box represents the median. The ends of the whiskers represent the minimum and maximum. Data in parenthesis are number of the patients analysed.

repeated measures of respective symptom scales ($P = 0.252$). When comparing the two reflux items within the QLQ-OES18 ("heartburn" and "acid or bile coming up to the mouth"), we could not demonstrate significant differences between the two groups at any time point (data not shown).

3.4. HRQL

HRQL scores at 4 weeks, 6 months, and 12 months after the operations were similar across the groups. There was no significant difference between the groups at any time point (Fig. 4). Significant improvements were observed in repeated measures in the Dor group ($P = 0.001$) and in the Toupet group ($P < 0.001$), respectively, while no significant difference was observed in the magnitude of improvements between the two groups ($P = 0.359$).

3.5. Endoscopy

Postoperative endoscopy was performed 12 months after surgery in 17 patients (7 in the Dor group and 10 in the Toupet group). Apart from one patient in the Toupet group who had LA grade A oesophagitis, no signs of gastro-oesophageal reflux could be found in any of the patients.

3.6. Timed barium oesophagogram (TBO)

Statistically significant improvements after the operation were observed in percentage of the oesophageal emptying both in height ($P = 0.011$) and area ($P = 0.018$) in those having a Toupet fundoplication (Fig. 5). However, no significant improvement in height ($P = 0.147$) or area ($P = 0.420$) was found in those patients allocated to a Dor fundoplication (Fig. 5). However, when the magnitude of the improvements were compared no differences in height ($P = 0.072$) or area ($P = 0.175$) were recorded between the groups (Fig. 5). There was also no significant difference in the reduction rate at any time point (Fig. 6).

3.7. 24-h pH monitoring

Postoperative ambulatory pH data were obtained from 24 patients. Median interval between surgery and postoperative pH monitoring was 189 days (range; 159–371). We found no significant differences in neither median % total time with pH < 4 between the groups nor when acid reflux was related to body position (upright or supine) (Table 4). Similarly, no differences between the groups were observed in the number of reflux episodes represented by total, upright and supine positions (Table 4). Abnormal acid reflux, defined as the patient with more than 4% total time with pH < 4, was observed in 2 patients in the Dor group and 5 patients in the Toupet group (Table 4).

4. Discussion

The present study aimed to determine the efficacy of a partial fundus wrap in preventing significant gastro-oesophageal reflux after cardiomyotomy in achalasia patients. Comparing ambulatory 24-h pH variables, recorded about 6 months after a Toupet (posterior) or a Dor (anterior) wrap, revealed no differences between the groups. These data suggest that the partial anterior wrap equally well controls reflux after myotomy compared to the partial posterior fundoplication. Apparently these findings in achalasia patients do deviate to a certain degree from the published experiences in GORD patients [9].

Another important finding of the present study was the prompt improvement in TBO variables after a Toupet fundoplication, while a corresponding effect in those patients having a Dor reconstruction was not equally apparent. Previous studies of TBO as a surrogate marker of the functional–clinical outcome after cardiomyotomy indicate that these operations induce changes in these markers that relate well to the clinical course [17,18]. Moreover, Vaezi et al. [19] reported that patients with poor oesophageal emptying at the TBO after pneumatic dilatation, soon returned with incomplete symptom relief and required complementary treatment within a year. Previous studies have also used the criterion of "50% or more reduction in post-treatment height compared to pre-treatment height on 5-min films" to define TBO response. This is possibly due to the reported better reproducibility of the static TBO variables such as height and width compared to the percentage emptying calculated using the area or height of the barium column [19,20]. Therefore, both the percentage of oesophageal emptying

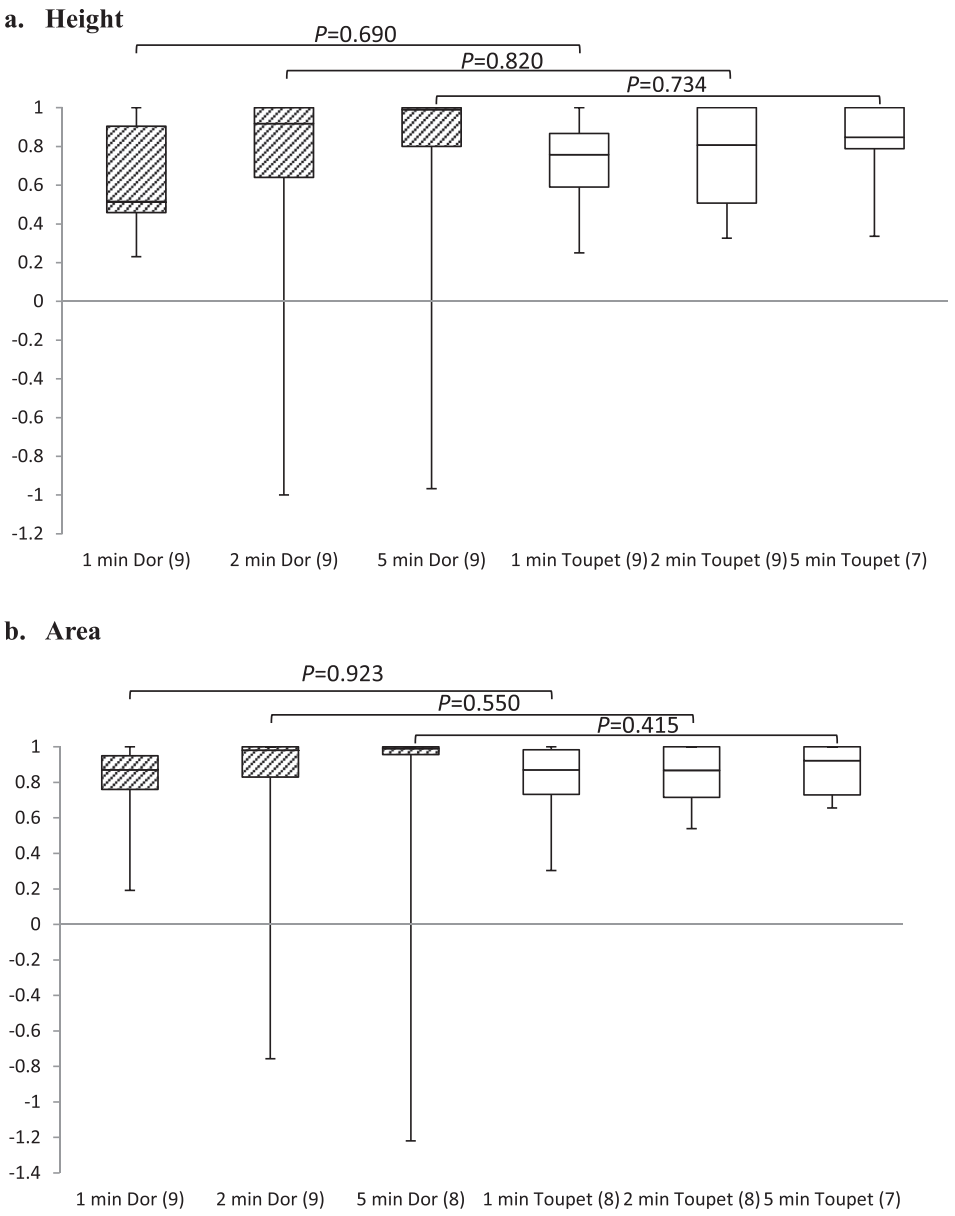

Fig. 6. Reduction rate in height and area for the timed barium oesophagogram. Corresponding *P*-values are shown. The bottom and top of each box represent the first and third quartiles, respectively, and the horizontal band inside the box represents the median. The ends of the whiskers represent the minimum and maximum. Data in parenthesis are number of the patients analysed.

and reduction rate were evaluated and compared between the groups in the present study.

The question then arises of how relevant these radiological observations are for the clinical outcome. When symptoms were longitudinally evaluated within each study group, we observed that the relative improvement in functional scales, on the OES18 instrument, separated the two procedures from each other in advantage of the Toupet alternative. Originally, it was hypothesised that the anterior angulation of the gastro-oesophageal junction induced by the posterior fundic wrap if anything might elicit a relative obstacle to food transit over the area. Indeed, this might be of particular relevance for achalasia patients with non-existent propulsive motor function of the oesophageal body. However, our present data do not support such an argument. On the contrary, we propose that the coverage of the entire length of the cardiomyotomy afforded by the anterior wrap may in fact partially counteract the functional outcome of the complete division of the sphincter musculature. It therefore seems relevant to reiterate the argument in favour of the Toupet reconstruction, the construction of which basically supports the separation of the divided muscle components from each other. Whether this is an effect that will become even more apparent over time remains to be studied.

It is difficult to conduct single-institution trials for patients with achalasia and the current study suffered from slow recruitment of patients and a small sample size. This background introduces, by necessity, the risk for type I as well as type II errors. However, it should be recognised that until now TBO has not been used in a controlled clinical trial within this field, whereby the results correlate nicely and plausibly with the clinical outcomes. To date, there has only been one randomised controlled trial comparing the Dor

Table 4
Postoperative 24-h pH monitoring.

	Dor ($n = 11$)	Toupet ($n = 13$)	P value
Percent time pH < 4 in 24-h pH monitoring			
Total (%)	0.8 (0–21.0)	1.9 (0–12.2)	0.267
Upright (%)	1.1 (0–15.4)	2.9 (0–19.8)	0.483
Supine (%)	0 (0–35.2)	0 (0–12.3)	0.571
Number of reflux episode			
Total	3.5 (0–77)	1 (0–44)	0.682
Upright	3 (0–77)	1 (0–44)	0.772
Supine	0 (0–9)	0 (0–3)	0.427
Abnormal acid reflux			
Total	2	5	0.386

Data are presented as median (range) or the number of patients. Mann–Whitney U tests were used to test the equality between the two medians of the variables. The Fisher's exact test was used to test the independence between the two groups.

and Toupet fundoplication after Heller cardiomyotomy, wherein the authors found no statistical difference in the degree of postoperative dysphagia or reflux symptoms between the groups, although there was a trend towards more reflux in the Dor group [8].

In conclusion the results of the present study imply that a partial posterior fundoplication after cardiomyotomy achieves better improvement in oesophageal emptying and EORTC QLQ-OES18 functional scale scores compared to an anterior anti-reflux procedure. Otherwise no differences between the anti-reflux repairs were noted.

Ethical approval

Ethical approval was given by the Regional Ethics committee in Stockholm (Dnr 2007/595-32).

Author contribution

Conception and design: Ann Kjellin, Anders Thorell, Lars Lundell and Bengt Håkanson.

Collection and assembly of data: Ann Kjellin, Anders Thorell, Staffan Granqvist, Lars Lundell and Bengt Håkanson.

Data analysis and interpretation: Koshi Kumagai, Jon A Tsai and Lars Lundell.

Manuscript writing: All authors.

Final approval of manuscript: All authors.

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Conflict of interest

None.

Declaration

KK and AK equally contributed to the conduct and completion of the study.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ijsu.2014.05.077.

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