

Effect of Vagus Nerve Injury on the Outcome of Antireflux Surgery: An Extensive Literature Review

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Key Words

Reflux disease · Upper GI surgery · Diaphragmatic hernias · Complications

Abstract

Background: Vagus nerve injury (VNI) is a feared complication of antireflux surgery (ARS). The impact of VNI on the functional outcomes of ARS has not yet been evaluated systematically. The aim of this review was to evaluate the impact of VNI on functional and clinical outcome of ARS. **Methods:** A systematic search was performed until March 2015, using the following online databases: MEDLINE, Embase and the Cochrane Register of Controlled Clinical Trials. Eight studies remained available for assessment. Articles were divided into 2 groups: (a) one with unintended, accidental VNI and (b) one group comparing ARS with and without intended vagotomy. **Results:** The prevalence of unintended, accidental VNI ranged from 10 to 42% after ARS. No clear differences were seen in outcome for reflux control between the VNI and vagus nerve intact group. A higher prevalence of diarrhea, nausea and vomiting was observed in the VNI group. **Conclusion:** VNI is a feared but neglected complication of ARS. Larger prospective studies that objectively assess vagus nerve integrity before and after ARS are needed.

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Introduction

In Western societies, the prevalence of gastroesophageal reflux disease (GERD) is known to be up to 10–20% [1, 2]. Changes in lifestyle and medical therapy, preferably with proton pump inhibitors (PPIs), are the first steps in the treatment of GERD [3]. Antireflux surgery (ARS) is considered an alternative treatment modality for patients who need increasing doses of PPI, for patients who require life-long medical treatment, or are refractory to medical treatment with PPIs. The most commonly employed techniques in ARS are Nissen fundoplication (NF) and Toupet fundoplication (TF) [4, 5]. With these procedures, excellent results have been obtained regarding symptomatic outcome and safety on both short- and long-term follow-up [6–11]. Despite these encouraging results, ARS is still accompanied by specific surgery-related peri- and postoperative complications and by unwanted postoperative symptoms [9, 12–14].

Vagus nerve injury (VNI) is a feared complication of ARS. The functional changes and consequences of this type of injury have not been investigated or evaluated systematically and the clinical consequences remain unclear for that reason. Earlier studies reporting the effect of intended vagotomy on gastric ulcer disease show that vagotomy is accompanied by gastric stasis (nausea 15%,

vomiting 4%), diarrhea (20–30%) and dumping syndrome (10%) [15–19]. Iatrogenic or accidental VNI during ARS may have effects similar to those after intended vagotomy and therefore, may contribute to newly developed postoperative symptoms and to impaired reflux control after ARS.

Accidental VNI is difficult to diagnose. In the clinical setting, no methods are available to directly evaluate vagus nerve (dys)function. The prevalence of VNI after ARS has been estimated in the past based on the onset of newly developed postoperative symptoms associated with VNI such as diarrhea, nausea and vomiting that have been associated with VNI [12, 17, 18, 20]. An objective but indirect method to measure abdominal vagus nerve function is based on the response of plasma pancreatic polypeptide (PP) secretion to insulin-induced hypoglycemia, the IH-PP test or on the response of plasma PP to modified sham feeding, a vagal-cholinergic stimulus [21, 22]. Up to now, the incidence and prevalence of VNI after ARS and its effect on the outcome of ARS have not been evaluated systematically.

The aim of this review is to systematically evaluate the impact of VNI on the clinical outcome of ARS. We hypothesize that VNI will have a negative impact on reflux control and GERD-related symptoms, on gastric emptying and on quality of life after both short- and long-term follow-up.

Methods

The guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement on identification and selection of individual studies were followed throughout the search of this extensive literature review [23].

A comprehensive systematic search was performed until March 2015, using the following online databases: MEDLINE, Embase and the Cochrane Register of Controlled Clinical Trials. The search terms and Boolean operators that were used are ('fundoplication'[mesh] OR fundoplication OR Nissen OR Toupet OR (hernia AND repair) OR (wrap AND (stomach OR fundic OR esophageal OR esophagus))) OR (('general urgency'[mesh] OR 'surgical procedures, operative'[mesh] OR 'surgery'[mesh] OR operation OR procedure) AND ('gastroesophageal reflux'[mesh] OR (gastroesophageal reflux) OR GERD OR GORD OR reflux OR anti-reflux OR antireflux))) AND ('vagotomy'[mesh] OR 'vagotomy, truncal'[Mesh] OR 'vagotomy, proximal gastric'[Mesh] OR (vagus nerve) OR (vagal nerve) OR vagotomy OR (vagal damage) OR (vagal injury)) AND (English (lang)). All abstracts were screened for eligibility by 2 independent reviewers (Y.G.M.R. and S.R.).

Study Selection

Only studies that were conducted in human subjects undergoing surgical treatment for gastroesophageal reflux were included. Articles comparing ARS solely to ARS combined with vagotomy

were included, as well as articles diagnosing unintended VNI after ARS and reporting on associated outcomes. ARS was defined as any procedure primarily developed for GERD (e.g. NF, TF, anterior fundoplication (AF), hiatal gastropexy, hiatal hernia repair (HHR)). Articles were included only if they were reporting on the type of vagotomy accompanying the ARS, since only truncal and selective vagotomy can be assumed to mimic the type of unintended VNI during ARS. In the case of iatrogenic VNI, the injury needs to be diagnosed by PP-testing both before surgery (intact) and after surgery (impaired). Furthermore, studies assessing the effect of VNI after re-operations were included only when VNI was objectively measured prior to the re-operation, since VNI could be present after the primary antireflux procedure.

Surgical procedures for acid reflux that remove part(s) of the stomach, esophagus or duodenum were not included in this review. In addition, the following exclusion criteria were used: only reporting on ARS without vagotomy (no intervention group); only reporting on ARS with vagotomy (no control group); vagotomy without ARS; surgical procedures because of malignancy; ARS in patients with malignancy; pediatric study; article reporting only on patients with recurrent symptoms after surgery (no systematic follow-up); animal study; review; meta-analysis; case report; (conference) abstract; comment.

In addition to the online search, the references of the selected articles were screened for eligibility following the same selection process. After exclusion of the abstracts not meeting our criteria, full articles were assessed for eligibility using the exclusion criteria mentioned earlier (fig. 1). Discrepancies in the selection of studies were sorted out through discussions with the senior authors (N.D.B. and A.A.M.).

Results

Search Strategy and Study Selection

During the initial systematic search, 1,328 potentially useful articles were identified. After exclusion of 78 duplicates, 1,250 potentially eligible articles remained. Two authors (S.R. and Y.G.M.R.) screened all abstracts separately, thereby excluding 1,191 articles. A total of 59 articles were read in detail for further eligibility assessment. The full text of these remaining articles was read and assessed for applicability. In this phase, another 51 articles were excluded and 8 studies were incorporated for final analysis in this systematic review (fig. 1).

General Study Characteristics

In the 8 studies selected for this review, data were reported on a total of 893 patients [24–31]. In all studies, 2 groups were compared: one in which vagus nerve integrity was maintained and one with VNI. In total, the vagus nerve intact group consisted of 559 patients and the VNI group of 331 patients. Six studies reported on the outcome between both groups comparing ARS alone with ARS combined with an intended vagotomy [26–31].

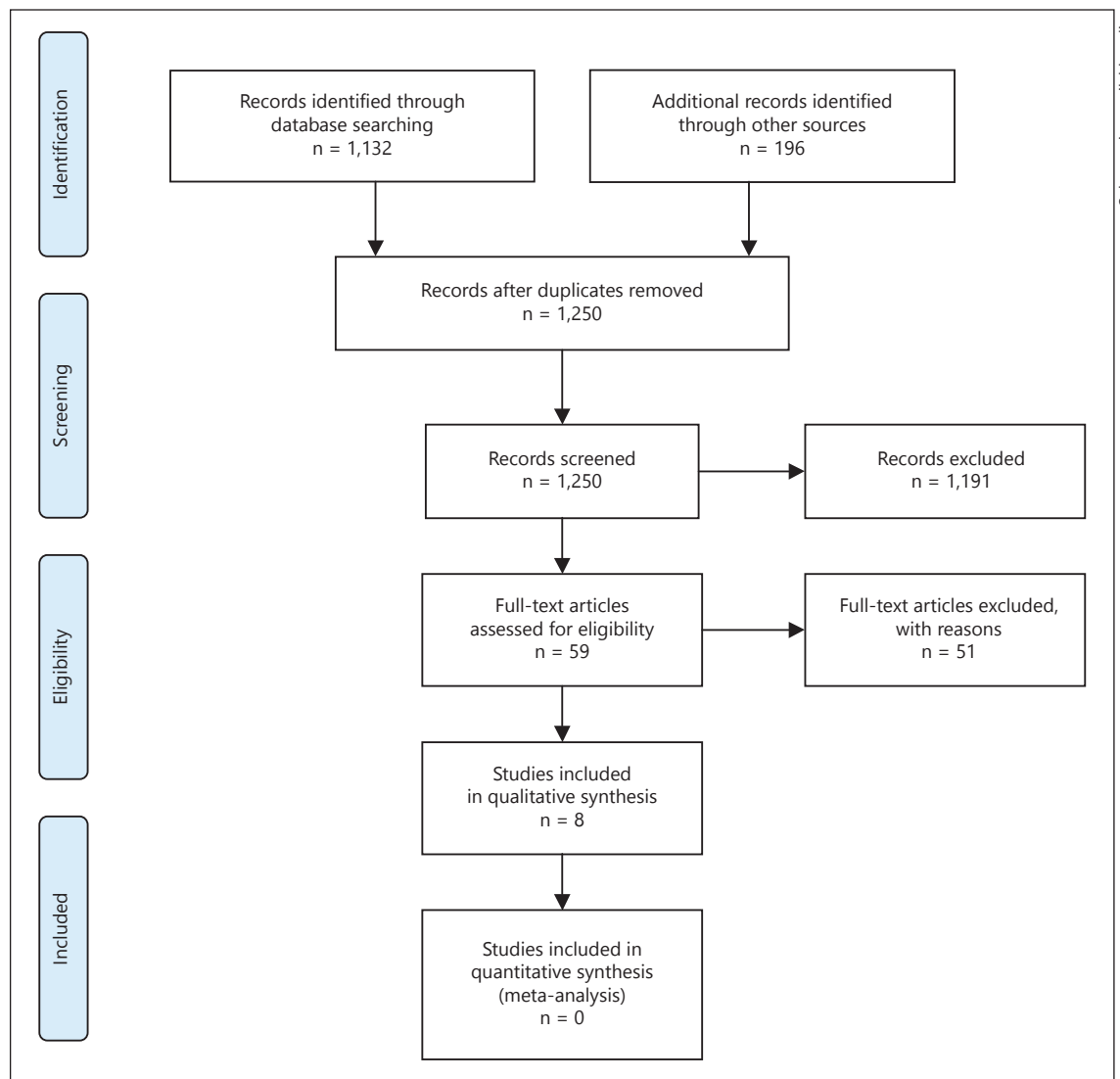


Fig. 1. Flowchart.

In 3 of these 6 studies, vagotomy was added to the antireflux procedure because of acid hypersecretion, severe esophagitis or peptic ulcer disease. The 2 remaining studies reported on unintended, accidental VNI objectively measured by the response of pancreas polypeptide to insulin-induced hypoglycemia (PP-IH) or to sham feeding PP-SF) [21, 22, 24, 25]. Different operative techniques were used in the 8 selected studies: laparoscopic TF (LTF), TF, laparoscopic NF (LNF), NF, AF, hill posterior gastropexy (HPG), HHR and Lortat Jacobs fundopexia (LJF). In addition, the vagotomy procedure was not uniform: different techniques have been employed from truncal vagotomy combined with pyloroplasty or pyloromyotomy to proximal gastric vagotomy (PGV) alone. Overall fol-

low-up of patients ranged from 6 months to 12 years post-surgery. A detailed overview of all study characteristics is given in tables 1–4.

Intended Vagus Nerve Injury

A majority of selected studies investigated the influence of intended VNI on the outcome of ARS [26–31] (tables 1 and 2).

Symptomatic Outcome: Overall

Overall symptomatic outcome between ARS alone and ARS + vagotomy was assessed in 5 of the 6 articles [26–29, 31]. Since each study used different methods of assessment on specific clinical outcomes, and each study inves-

Table 1. Characteristics of studies reporting on intended vagotomy

Author	Year	Procedure			
		ARS	type of vagotomy	patients, n	
				with vagotomy	without vagotomy
Woodward et al. [30]	1971	CR; NF	VP	98	133
Wilson et al. [29]	1974	SR; NF	VP	25	56
Mokka et al. [27]	1976	NF; HHR; APF; LJF	VP	17	69
Vansant and Baker [28]	1976	HP	VP	118	152
O'Rourke and Baker [31]	1985	(N)F; HP	VP	19	37
Jamieson et al. [26]	1991	NF	PGV	34	20

CR = Crural repair; SR = simple repair; APF = anterior partial fundoplication.

tigated a different subset of clinical outcomes, a large heterogeneity exists among the overall symptomatic outcomes.

Already in the early seventies of the past century, Wilson et al. [29] compared the symptomatic outcome between 'simple repair' (n = 23) and 'simple repair + vagotomy and pyloroplasty' (n = 21). The simple repair technique consisted of closure of the hiatus hernia, followed by the suturing of the fundus to esophagus in order to re-create a steep angle of this. Recurrence of reflux symptoms was scored and categorized in 4 groups: (1) no symptoms, (2) minimal symptoms, (3) improved but still with symptoms, and (4) no improvement in symptoms. Grades 1 and 2 were defined as 'good overall outcome' and grades 3 and 4 as 'poor overall outcome'. Sixteen percent of the patients that underwent simple repair + vagotomy and pyloroplasty (VP) scored poor overall outcome, compared to 0% of the patients with simple repair only.

Mokka et al. [27] compared outcomes after various ARS techniques (NF, HHR, LJF, AF) without vagotomy to one ARS technique NF combined with VP. These authors categorized the overall symptomatic outcome into 3 grades: excellent, good and poor. These grades were assigned according to the severity of complaints including heartburn, regurgitation, fullness, dysphagia and inability to vomit [27]. Poor outcome was seen in 17% (12/69) of the patients after ARS alone, compared to 53% (9/17) after NF + VP.

In the study conducted by Vansant and Baker [28], the overall symptomatic outcome was assessed between HPG only (n = 152) vs. HPG + VP (n = 118). Symptomatic out-

come was evaluated according to the duration of symptoms: <3 or >3 months. Diarrhea, bloating, nausea, vomiting and dumping were taken into account in this overall outcome. Within the first 3 months, symptoms were reported by 39.5% (60/152) of the HPG only group, compared to 22% (26/118) in the HPG + VP group. After 3 months, only 1.3% (2/152) of the HPG only group reported symptoms compared to 33% (33/118) in the HPG + VP group.

O'Rourke [31] assessed a total of 56 patients who underwent a standard fundoplication similar to NF (Nissen like fundoplication, NLF). Thirty-seven patients underwent fundoplication only, 19 patients underwent NLF with additional VP. Severity of heartburn, regurgitation and dysphagia were scored on a 0–3 point scale with 0 indicating no symptoms and 3 indicating daily presence with a maximum total score for the questionnaire of 9 points. A decrease in mean score from 5.39 to 0.41 was seen after ARS for the whole group. Postoperative comparison between the various operations showed no difference regarding postoperative symptoms.

Jamieson et al. [26], categorized patients in 4 grades assessing reflux specific symptoms: (1) no or minor symptoms, (2) moderate symptoms, (3) marked symptoms, (4) symptoms as bad as or worse than preoperatively. Thirty-one patients were analyzed at 3 years follow-up; 20 patients with NF and 11 with NF + PGV. Considering grades 3 and 4 as unfavorable, 30% of patients with fundoplication only had unfavorable results compared to 9% of patients with fundoplication + PGV group.

Table 2. Overview of results of intended vagotomy

Author	Year	Follow-up, months	Outcome								
			diarrhea, n (%)	dumping, n (%)	gas bloat, n (%)	nausea and vomiting, n (%)	reflux, n (%)	clinical symptoms overall, n (%)	esophagitis, gastric emptying for pH monitoring solids at 6 months (A); 3 years (B) n (%)		
Woodward et al. [30]	1971	3–6	R 8 (13) R no VT (n = 65) 0 (0)	16 (26) 0 (0)	0 (0) 0 (0)	-	-	-	9 (15) 14 (20)	-	35 (56) 35 (54)
			F 2 (6) F no VT (n = 68) 0 (0)	9 (25) 2 (3)	16 (44) 37 (54)	-	-	-	2 (6) 6 (9)	-	14 (39) 33 (49)
Wilson et al. [29]	1974	-	VT (n = 25) No VT (n = 56)	Poor: 0% Poor: 16%	-	-	-	-	-	-	-
Mokka et al. [27]	1976	12–132	VT (n = 17) No VT (n = 69)	- -	- -	-	-	-	Poor score: 9 (53) Poor score: 12 (17)	-	-
Vansant and Baker [28]	1976	>3	VT (n = 118) No VT (n = 152)	44 (37) 26 (17)	9 (8) 55 (36)	50 (42) 2 (1)	20 (17)	-	26 (22) 60 (39)	-	-
O'Rourke and Baker [31]	1985	6–60	VT (n = 19) No VT (n = 37)	6 (32) 0 (0)	4 (20) 1 (3)	7 (37) 7 (19)	-	-	4 (21) 8 (22)	-	-
Jamieson et al. [26]	1991	4–47	VT (n = 34) No VT (n = 20)	- -	- -	-	-	Poor score, 3–4: 1 (9) ^a Poor score, 3–4: 6 (30)	- -	A: not improved B: not improved A: improved* B: improved*	-

R = Hiatal hernia repair; F = fundocoplication; VT = vagotomy; - = not reported.

^a Only 11 patients were available for this outcome parameter.* Statistically significant $p < 0.05$ compared to preoperative result.**Table 3.** Characteristics of studies reporting on accidental VNI

Author	Year	Procedure		
		ARS	diagnostics for VNI	VNI, n
DeVault et al. [25]	2004	LNF	Sham-feeding	5
Lindeboom et al. [24]	2004	LTF	PP-IH test	4
				12
				41

Table 4. Overview of results of accidental VNI

Author	Year	Follow-up, months	Outcome		gastric emptying rate, 50% emptying time, min (SEM)		24 h pH monitoring, mean % pH <4 (range)		
			clinical symptoms overall, n		preoperative	postoperative	preoperative	postoperative	
			worse	same or better					
DeVault et al. [25]	2004	12	VNI (n = 5)	2	3	-	-	-	-
			No VNI (n = 7)	3	4	-	-	-	-
Lindeboom et al. [24]	2004	3-6	VNI (n = 4)	-	-	141 (63)	92 (23)	9.2 (4.2-12.7)	3.2 (1.8-7.4)
			No VNI (n = 37)	-	-	114 (8)	79 (4)*	8.7 (2.5-20.2)	1.1* (0-14.4)

Clinical symptoms overall: bowel habit questionnaire; - = not reported.
* Statistically significant p < 0.05 compared to preoperative result.

Symptomatic Outcomes: Specific Symptoms

Specific symptomatic outcomes with respect to diarrhea, nausea and vomiting, dumping syndrome, dysphagia and gas bloat syndrome have been described only in 3 articles of Woodward et al. [30], Vansant and Baker [28] and O'Rourke [31] (table 2). None of the selected articles has specifically described the criteria they used to define the presence of each symptom.

Diarrhea

Woodward et al. [30] compared 4 groups: (1) HHR only (n = 65), (2) HHR + VP (n = 62), (3) NF only (n = 68), and (4) NF + VP (n = 36). The authors reported diarrhea solely in the groups where VP was added to the ARS with percentages of 13 and 6 respectively in groups 2 and 4 [30].

In the study by O'Rourke [31], diarrhea was seen in 6 out of the 19 patients (31.6%) that underwent NLF + VP, whereas none of the patients of the NLF only group reported diarrhea (p < 0.005). Vansant and Baker [28] reported a prevalence of diarrhea of 17% (26/152) in the HPG group compared to 37% (44/118) in the HPG + VP group.

Dumping Syndrome

O'Rourke [31] reported a prevalence of 2.7% (1/37) in the NLF only group vs. 20% (4/19) in the NLF + VP group (difference: ns). Woodward et al. [30] and Vansant and Baker [28] report dumping syndrome only in the groups with added VP, with prevalences of 25.5% (25/98) and 8% (9/118) respectively. In addition, Vansant and Baker [28] also differentiated between the severity of mild 6% (7/118) and severe 2% (2/118) dumping.

Gas Bloat Syndrome

Within the study of Woodward et al. [30], no gas bloat syndrome was reported after HHR. On the contrary, after NF, the patients reported gas bloating in 54% (37/68). In the group where VP was added to the NF, 44% (16/36) reported gas bloating. O'Rourke [31] reported gas bloat syndrome in 18.9% (7/37) after NLF, vs. 36.8% (7/19) when VP was added. In the study of Vansant and Baker [28], 55 patients (36.2%) suffered from gas bloat syndrome after HPG only, whereas 50 patients (42.4%) reported these complaints after HPG + VP.

Nausea and Vomiting

Nausea and vomiting have been described only by Vansant and Baker [28]. A prevalence of 1.3% (2/152) was seen in the HPG only group vs. 17% (20/118) in the group with additional vagotomy + pyloromyotomy.

Dysphagia

Woodward et al. [30] also reported on the prevalence of dysphagia between the 4 groups. Dysphagia occurred in almost a quarter of the patients after NF (16/68), compared to only 9% (6/65) after HHR. In the groups where VP was added, 16% (10/62) of the HHR-VP patients suffered from dysphagia, compared to 14% (5/36) of the NF-VP patients.

Esophagitis

Additionally, in the report by Woodward et al. [30] endoscopic esophagitis was present in 20% after HHR and 9% after NF and was less frequent when these procedures were combined with VP: 15 and 6% respectively.

Satisfaction Rate

O'Rourke [31] also evaluated the outcome with respect to patient satisfaction between the various groups. A significantly worse outcome was noted in the group where VP was added to NLF ($p < 0.01$).

Gastric Emptying

Jamieson et al. [26] have assessed gastric emptying both for solids and liquids using a dual isotope radionuclide technique. Patients were evaluated at 6 months and 3 years after NF alone ($n = 20$) and after NF with added PGV ($n = 34$). In patients with NF alone, a significant acceleration ($p < 0.05$) of gastric emptying for solids was seen at 6 months and 3 years after surgery compared to the condition before surgery. In contrast, gastric emptying for solids did not change after the operation in patients with NF + PGV. Both groups showed a significant acceleration of liquid gastric emptying 6 months after the operation ($p < 0.05$). At 3 years follow-up, a significant acceleration for liquids was seen only in the NF group ($p < 0.05$). The authors evaluated the relation between symptomatic outcome and gastric emptying: no correlation was found. Of the 10 patients with troublesome complaints of postprandial epigastric fullness, only 3 patients had delayed gastric emptying of solids.

Unintended, Accidental Vagus Nerve Injury

Only 2 studies assessed unintended VNI objectively by the response of PP-SF or PP-IH [24, 25] (table 3).

As described by Schwartz et al. [21, 22], the secretion of pancreas polypeptide by the pancreas is mediated through the efferent vagal activity. Stimulation of PP secretion through the vagus nerve activity can be evoked either by sham feeding or by insulin-induced hypoglycemia.

An absent or minimal response in PP secretion to one of both stimuli is considered to be compatible with vagus nerve dysfunction.

PP-IH Test

Within the study by Lindeboom et al. [24] the PP-IH test was performed on fasted patients at the outpatient department where at $t = 0$ min, 0.1 U/kg of insulin bolus was administered intravenously. During a period of 90 min, blood was drawn at 10 min intervals for measurement of PP and glucose. The nadir blood glucose response was < 2.5 mmol/l in all patients (adequate stimulus). A peak increment response in plasma PP < 47 pmol/l was considered to be compatible with truncal vagotomy based on data obtained in a large group of patients with previous intended truncal vagotomy.

PP-SF Test

DeVault et al. [25] assessed VNI using the PP-SF test. After an overnight fast, 2 baseline blood samples were obtained from the patients. Next, patients were given a meal with the instruction to chew the food but not to swallow it. Blood samples were taken during a period of 30 min with 5 min time intervals. A peak increment of < 25 pg/ml was considered compatible with VNI.

Prevalence

The prevalence of VNI after ARS can be assessed only by objectively measuring vagus nerve integrity both pre- and postoperatively. Lindeboom et al. [24] reported a VNI prevalence of 10% (4/41) 6 months after LTF in a prospective cohort. In the study by DeVault et al. [25], 20 patients were assessed prior to and 1 week after LNF. Among the patients with a normal PP response in the preoperative state ($n = 12$), an abnormal postoperative test result was seen in 5 patients (42%; table 4).

Symptoms

Heartburn, fullness and nausea were assessed prior to and 6 months after LTF by Lindeboom et al. [24]. A grading system was used to combine severity and frequency per symptom, resulting in a minimum score of 0 and a maximum score of 3 for each symptom. Both the LTF group and the LTF + VNI group showed a significant decrease for heartburn and nausea. The LTF + VNI group did not show a reduction of fullness compared to preoperative scores, whereas the LTF group decreased significantly in fullness postoperatively.

DeVault et al. [25] assessed symptoms only at 12 months after operation. Symptoms of diarrhea, constipation,

tion, abdominal pain, bloating or distention and frequency of bowel movements were assessed before and after LNF. Six out of 15 patients developed new symptoms or had worse symptoms consisting of flatus ($n = 2$) and diarrhea ($n = 4$) postoperatively. Three of these 6 patients were considered to have VNI; however, the distribution of new symptoms or worsening of symptoms among groups was not reported. No correlation was found between symptoms and PP test results.

Gastric Emptying and 24-Hour pH Monitoring

Additionally, Lindeboom et al. [24] also reported the outcome of gastric emptying and 24-hour pH monitoring between patients after LTF. Patients with VNI did not differ in gastric emptying or 24-hour pH monitoring results compared to the vagus nerve intact group (table 4).

Discussion

ARS can be accompanied by VNI, a complication that may negatively affect the overall outcome of the procedure [9, 12–14]. Because little is known on the prevalence of VNI after ARS, an extensive review of the existing literature was performed. The effects of both intended and unintended, accidental VNI on outcome of ARS were assessed. A total of 8 published articles were evaluated after careful systematic selection [24–31].

Only 2 of the 8 studies objectively assessed vagus nerve integrity: one study measured the response of PP-IH before and after LTF, the other measured PP response to sham feeding before and after LNF [24, 25]. The prevalence of VNI (defined as an absent or reduced PP response to IH or SF) after LTF appeared to be 10%, whereas LNF resulted in 42% absent or reduced PP response to SF, indicating the presence of VNI. It is well known that about 10% of healthy controls in the population will have an absent or reduced PP response to sham feeding without any evidence for VNI or dysfunction [21, 22]. This should be taken into consideration when interpreting the high percentage of patients with an abnormal SF-PP test result. Symptomatic outcomes after ARS did not differ between groups with and without VNI according to both studies. Lindeboom et al. [24] reported no significant differences in postoperative gastric emptying or 24-hour pH monitoring between the groups with and without VNI.

In summary, unintended VNI was observed in at least 10% of patients undergoing ARS, a percentage that is higher than previously has been assumed. On short-term follow-up, the outcome of ARS with respect to reflux con-

trol, overall symptoms, gastric emptying and 24-hour pH monitoring appeared not to be negatively affected by unintended, accidental VNI. Results on longer-term follow-up after ARS related to VNI have not been published up to now.

Six of the 8 studies compared ARS procedures with and without intended vagotomy [26–31]. Overall symptomatic outcome has been assessed in 5 studies; 3 of these studies used a composite score. Outcome was poor (with symptoms still present) in 16–53% of the patients after ARS with added VP, vs. 0–17% of the patients after ARS alone. It should be noted that the composite score after ARS with VP was negatively affected by newly developed postoperative symptoms such as diarrhea and dumping.

With respect to reflux control, the symptomatic outcome was slightly in favor of ARS with added vagotomy or VP. O'Rourke [31] found a significant improvement of reflux control in the patients after ARS, independent of VP. In contrast, Jamieson et al. [26] found that 9% of patients scored worse (or did not improve) in reflux control after ARS + PGV, compared to 30% in the ARS only group. In addition, Woodward et al. [30] reported fewer cases of esophagitis after ARS with added VP.

Three studies reported specifically on diarrhea, dumping syndrome, nausea, vomiting and gas bloat after ARS. All 3 studies combined vagotomy with pyloromyotomy or pyloroplasty. Also, the degree of vagotomy differed between studies. Diarrhea, nausea and vomiting occurred more often in the ARS + VP group compared to ARS alone. However, the symptoms of gas bloat and dysphagia were equally prevalent in both groups and dumping syndrome was present only when VP was added to ARS.

Certain limitations of the present review have to be taken into account. The methodological quality of the studies on which we based our review is relatively poor. Five of the articles were prospective in design and 3 were retrospective cohort studies. Randomized clinical trials were not available. The surgical details have been described poorly, which is also true for the statistical analyses. Five out of the 8 articles did not specifically describe at what time point data were assessed. A majority of studies did not use standardized questionnaires or specified criteria to assess the prevalence of symptoms. In addition to the vagotomy, pyloromyotomy or pyloroplasty may have a significant impact on diarrhea and dumping syndrome [32–35]. Therefore, no straightforward conclusions on the impact of VNI on dumping syndrome and diarrhea can be drawn, since in a majority of studies, either pyloromyotomy or pyloroplasty has been added to vagotomy.

With respect to the outcome of ARS after unintended, accidental VNI, it should be acknowledged that patient groups were small and that only one study reported extensively with respect to symptomatic outcome. Therefore, definite conclusions about the prevalence and impact of accidental VNI on the outcome of ARS have to be drawn with caution.

How should we deal with these findings in daily clinical practice? VNI should be considered in patients after ARS who either have a poor outcome with respect to reflux control or who postoperatively develop new symptoms such as diarrhea, dumping, nausea and/or vomiting. Confirmation of VNI by nerve function testing through the PP secretory response to insulin-induced hypoglycemia or to sham feeding should be undertaken, when test facilities are available. Therapy should be directed at controlling the major symptoms. Redo ARS is not advised in case of (suspected) VNI because of significantly lower success rates. In case of documented delayed gastric emptying, treatment with prokinetics, pyloric botulin toxin injections or pyloromyotomy should be considered [36]. Dumping syndrome usually does respond to dietary measures, with or without motility reducing drugs. In severe

and invalidating cases, somatostatin analog therapy should be considered [37].

In summary, the prevalence of accidental VNI after ARS, measured by indirect tests, is much higher than previously assumed. With respect to intended vagotomy added to the antireflux procedure, the symptomatic outcome of diarrhea, dumping and nausea is worse, while reflux control is equal or slightly better.

However, the level of evidence of the studies we have evaluated is low and larger prospective studies are necessary.

In conclusion, VNI is a feared but generally neglected complication of ARS. Recognition of the clinical impact of unintended VNI and strategies to prevent vagus nerve damage should be encouraged. Larger, prospective studies are needed to assess the prevalence and impact of objectively determined VNI on the outcome of ARS.

Disclosure Statement

None.

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