Received: 17 July 2020 | Revised: 3 August 2020 | Accepted: 5 August 2020

DOI: 10.1111/nmo.13980

REVIEW

Neurogastroenterology & Motility NGM WILEY

The use of impedance planimetry (Endoscopic Functional Lumen Imaging Probe, EndoFLIP®) in the gastrointestinal tract: A systematic review

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Abstract

Background and purpose: The EndoFLIP® system is a method of delineating impedance and was first designed to investigate the characteristics of the esophago-gastric junction. In the last decade, its use was widened to investigate other sphincteric and non-sphincteric systems of the gastrointestinal tract. The objective of the present systematic review was to summarize the available data in literature on the use of the EndoFLIP® system in the gastrointestinal tract, including sphincteric and non-sphincteric regions. We performed a systematic review in accordance with recommendations for systematic review using PRISMA guidelines without date restriction, until June 2020, using MEDLINE-PubMed, Cochrane Library, and Google Scholar databases. Only articles written in English were included in the present review. Five hundred and six unique citations were identified from all database combined. Of those, 95 met the inclusion criteria. There was a lack of standardization among studies in terms of anesthetic drugs use, probe placement, and inflation protocol. In most cases, only small cohorts of patients were included. Most studies investigated the EGJ, with a potential use of the EndoFLIP® to identify a subgroup of patients with achalasia and for intraoperative assessment of treatment efficacy in achalasia. However, the use of EndoFLIP® in the esophageal body (esophageal panometry), other esophageal diseases (gastro-esophageal reflux disease, eosinophilic esophagitis), and other sphincter regions (anal canal, pylorus) will need further confirmatory studies. The EndoFLIP® system provides detailed geometric data of the gastrointestinal lumen but further works are needed to determine its use in clinical practice.

KEYWORDS

anal canal, EndoFLIP® system, esophagus, gastrointestinal tract, pylorus, sphincter

1 | INTRODUCTION

Historically, gastrointestinal (GI) sphincters were investigated using pull-through and stationary manometry techniques, or with the more recent high-resolution manometry.[1,2] However, if manometry and Dent sleeve brought important physiological data such as the study of resting pressure and relaxation of the lower esophageal sphincter (LES) during and after swallowing, a poor correlation was found with the strength or sphincter competence.[3] The Endoscopic Functional Lumen Imaging Probe (EndoFLIP® system) was first developed to

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test the competence of GI sphincters using bag distension in the site of interest. The underlying principle for the EndoFLIP® is the use of "impedance planimetry" with the measurement of cross-sectional area (CSA) inside a distension bag obtained from electrical impedance measurements and from intrabag pressure. As several electrodes are positioned along the probe, the EndoFLIP® system is able to measure a longitudinal series of equally spaced 16 CSAs inside the bag, every 5 mm (EF325-N probe) or every 1 cm (EF322-N probe). Sphincter length CSA pooled acquisition and analysis allow the simulation of the sphincteric region as a three-dimensional profile of estimated diameters (Figure 1). One important result given by the EndoFLIP® is the possibility to investigate the distensibility of the sphincter, which is defined as the relationship between the minimum CSA in the narrow region and the bag pressure at the same point[4] (Table 1). Even if the EndoFLIP® was originally developed to investigate the esophago-gastric junction (EGJ), it is also used in other sphincteric and non-sphincteric regions of the GI tract.

The objectives of the present systematic review were to summarize the available data in literature on the use of the EndoFLIP® system in the GI tract, including sphincteric and non-sphincteric regions, and to determine the clinical utility of EndoFlip in the GI tract.

Key Points

- The objective of the present systematic review was to summarize the available data in literature on the use of the EndoFLIP system in the gastrointestinal tract, including sphincteric and non-sphincteric regions.
- The EndoFLIP system provides detailed geometric data of the gastrointestinal lumen but further works are needed to determine its use in clinical practice.

2 | METHODS

This systematic literature review was performed in accordance with recommendations for systematic review and meta-analysis using PRISMA guidelines.[5] The present review was not registered at PROSPERO. This systematic review was performed without temporal limitation using MEDLINE-PubMed, Cochrane Library, and Google Scholar databases. We completed our research by searching pertinent references from bibliography in all selected articles. The key words used were "endoflip," "flip," "functional lumen imaging probe," "impedance planimetry," and "functional luminal imaging probe."

All articles published until June 2020 were screened by identification of key words. Only articles written in English were included in the present review. The exclusion criteria were non-human studies, pediatric studies, case reports, animal studies, and impedance planimetry using other system than the EndoFLIP®. Two investigators (CD and AML) reviewed independently titles, abstract, and articles. All results were analyzed for MEDLINE-PubMed and Cochrane Library. Articles whose title did not refer to the subject were excluded from the present review. All the abstracts of the remaining articles were entirely read, and if potentially eligible, articles underwent full-text screening. Reasons for article exclusion are presented in Figure 2. Differences in screening decision were reviewed by a third investigator (GG). A level of evidence (LE) was set for each selected article.[6]

3 | RESULTS

Five hundred and six unique citations were identified, of which 95 studies met the inclusion criteria and were included in the present review (Figure 2).

3.1 | Part 1. Esophagus

3.1.1 | Methodology

There is currently no standardization of the EndoFLIP® protocol in the esophagus, representing a first limitation in the interpretation

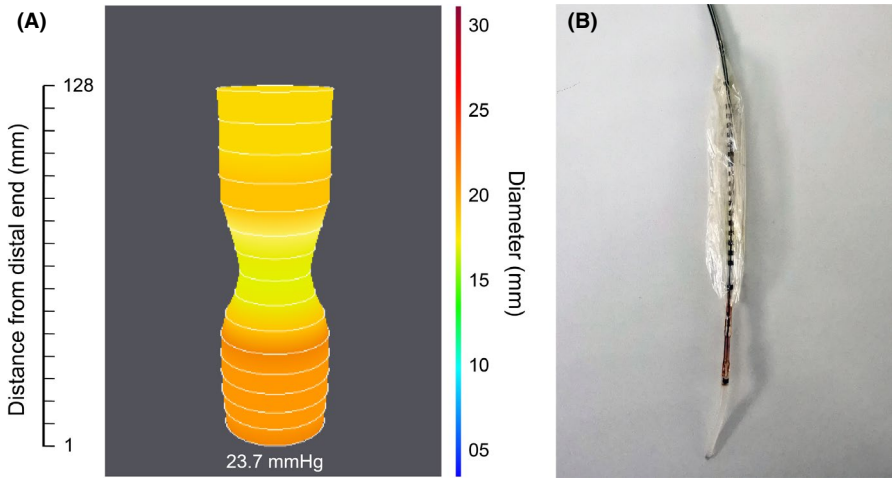

FIGURE 1 A, Traditional representation of the EndoFLIP of the EGJ with simulation of the sphincteric region as a three-dimensional profile of estimated diameters indicated by changes in color from blue (smaller diameter) to red (larger diameter). Oral direction is upward. Intrabag pressure (mm Hg) is indicated. B, Picture of the EndoFLIP catheter itself, showing the 8-cm balloon with 16 electrodes positioned each 5 mm along the probe

of data. The EF325-N probe was used in the EGJ and the EF322-N probe was used to assess the body of the esophagus. As the mode of anesthesia and the distension protocol differed among studies, these data are detailed below.

3.1.2 | Esophago-gastric junction

Healthy volunteers

Twenty studies investigated esophageal physiologic properties using the EndoFLIP® system in healthy volunteers (HV; Table 2). Results regarding intrabag pressure, narrowest CSA, and distensibility index (DI) (ie, narrowest CSA divided by intrabag pressure) at different volumes of inflation are given in Table 3 (LE 3). Using the 10th percentile in HV, two studies from Rohof et al, 2012[7] and Smeets et al, 2015[8] found a cutoff for the normality of the DI of, respectively, 2.9 mm^2/mm Hg and of 2.1 mm^2/mm Hg at 50 mL of inflation (LE 3). Both studies were prospectively performed in 15 HV without general anesthesia.

Three publications investigated the effect of different drugs on the esophagus using the EndoFLIP® system.[9-11] No difference was found in regard to CSA and DI of the LES values before and after administration of oral acotiamide (peripheral inhibitor of acetylcholinesterase; LE 3) and intravenous metoclopramide (central dopamine D2 receptor agonist; LE 3). However, these studies were performed in a small number of HV and without placebo control. In contrast, EGJ DI at 40 and 50 mL of inflation was lower during the administration of mosapride (serotonin 5-HT4 agonist) in one study, but also without placebo control (LE 3).

Achalasia

Achalasia is a primary esophageal motor disorder classically diagnosed with esophageal manometry.[12] Thirty-two studies reported results regarding patients with achalasia in the literature (Table 4). All studies used the Chicago Classification[12] to determine achalasia subtypes among patients. However, there was also a lack of homogeneity in these studies regarding both distension protocols, probe placement methods, and the mode of anesthesia (Table 4). A recent prospective study performed in patients with achalasia[13] found lower values for both EGJ DI and CSA under endoscopic control of the EndoFLIP® in comparison with values after the withdrawal of the endoscope. Compared to HV, patients with untreated achalasia had lower EGJ DI at different distension volumes[7,8,14,15] (LE 3) and it correlated with the severity of symptoms assessed by Eckardt score (ES)[16] (LE 3). It was also found that 96% of patients with achalasia had an EGJ DI below the cutoff value set for HV[8] (LE 3).

Several studies used the EndoFLIP® to assess the response of treatment in achalasia. A significant decrease of the EGJ DI was found for Heller myotomy[7,14,17-22] and pneumatic dilation[7,8,14,23,24] (LE 3). Similar results were found regarding POEM (Per Oral Esophageal Myotomy), with a significant increase of the EGJ DI found in most studies immediately after POEM[16-20,25-28] or at 3 months[29] (LE 3). Intraoperative evaluation of EGJ during POEM showed that both submucosal tunnel creation and myotomy (6 cm proximal to the EGJ to 2-3 cm distal) caused an increase in EGJ DI[19,20,26] (LE 3). However, neither the addition of a proximal extension[20] nor final gastric extension[26] to the EGJ myotomy seemed to change EGJ DI (LE 3). Lastly, two studies[30,31] used a new EndoFLIP® device, the EsoFLIP 330, to perform dilation of the EGJ in patients with achalasia. Success defined by ES < 3 was obtained in, respectively, 63.8% (23/36) and

TABLE 1 Metrics that the EndoFLIP system can measure and what they mean

Cross-sectional area (CSA, mm^2): excitation electrodes positioned at either end of the balloon emit a continuous low electric current and the voltage is measured across the paired impedance planimetry electrodes by leveraging Ohm's law to provide a measurement of CSA and volume at intervals based on excitation electrode spacing.
Diameter (mm): diameter data from each impedance planimetry channel are scaled from 5 to 30 mm and are interpolated and color-coded on a hot/cold scale (small diameters are red/large diameters are blue).
Distensibility index (DI, mm^2/mm H): is the measure of sphincter distensibility and is calculated by dividing the median narrowest CSA (within the anatomical zone of interest) by the median intrabag pressure over a set timeframe (or distension volume).
Intrabag pressure (mm Hg): a solid-state pressure transducer is located at the distal end of the bag and allows the measure of the intrabag pressure.

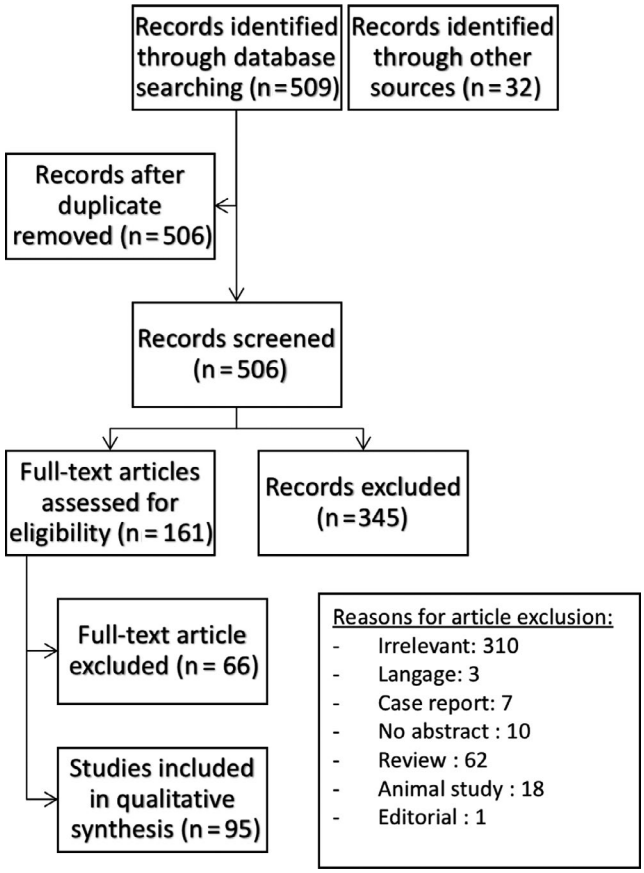

FIGURE 2 Flowchart of the study with reasons of exclusion

TABLE 2 Characteristics of studies performed in healthy volunteers

Reference	Method		Level of evidence/ Grade of recommendation	Probe	EndoFLIP measurement: time (s) and volumes of distension (mL)
	Number of HV (n)	Design of the study			
Healthy volunteers					
Carlson et al, 2019 (=Carlson et al, 2020)[57]	20	Prospective, case series study	3/C	EF322-N	30 s, 20-25-30-35-40-45-50-55-60-65-70 mL
Mikami et al, 2018[9]	8	Prospective, case-control study	3/C	EF325-N	30 s, 20-30-40 mL
Liao et al, 2018[107]	6	Prospective, case series study	3/C	EF325-N	20-30-40 mL
Carlson et al, 2016 (=Lin Z 2013 & Carlson 2015)[38]	10	Prospective, case-control study	3/C	EF322-N	20-30 s, 5-60 mL (by 5-mL step)
Mikami et al, 2016[10]	8	Prospective, case series study	3/C	EF325-N	30 s, 20-30-40 mL
Fynne et al, 2016[51]	11	Prospective, case-control study	3/C	EF325-N	30 s, 20-30-40-50 mL
Smeets et al, 2015[8]	15	Prospective, case-control study	3/C	EF325-N	30 s, 30-40-50 mL
Lottrup et al, 2015[49]	14	Prospective, case-control study	3/C	EF325-N	30 s, 20-30-40-50 mL
Fukazawa et al, 2013[11]	9	Prospective, case series study	3/C	EF325-N	30 s, 20-40-50 mL
Tucker et al, 2013[41]	21	Prospective, case-control study	3/C	EF325-N	30 s, 20-30 mL
Lin Z et al, 2013[56]	2	Prospective, case-control study	3/C	EF325-N	5-20 s, 5-40 mL (by 2-mL step)
Rieder et al, 2012[25]	4	Prospective, case series study	4/C	EF325-N	30 s; 30-40 mL
Rohof et al, 2012 (=Ponds 2016)[7]	15	Prospective, case-control study	3/C	EF325-N	30 s, 20-30-40-50 mL
Kwiatek et al, 2012[55]	15	Prospective, case-control study	3/C	EF325-N	30 s; 20-30 mL (EGJ); 2-40 mL by 2-mL step (body)
Kwiatek et al, 2011[91]	20	Prospective, case-control study	3/C	EF325-N	30 s, 10-20-30-40 mL
Nathanson et al, 2011[108]	50	Prospective, case series study	3/C	EF325-N	30 s; 30-40 mL
Kwiatek et al, 2010[40]	10	Prospective, case-control study	3/C	ND	30 s, 30-40-50 mL
Beaumont et al, 2009[54]	8	Prospective, case-control study	3/C	ND	ND; by 10-mL step
McMahon et al, 2007[4]	8	Prospective, case series study	3/C	ND	ND; 20-30-40-50-60 mL
McMahon et al, 2005[3]	3	Prospective, case series study	4/C	ND	ND; 0-40 mL

Abbreviations: EGJ, esophago-gastric junction; HV, healthy volunteers; ND, not detailed.

85% (23/27) of patients at 6 months of dilatation without major adverse effect.

In addition, several studies found that patients with incomplete response (ie, ES > 3) had a lower EGJ DI than patients with success of treatment[7,14,16,18,23] (LE 3). Indeed, Pandolfino et al, 2013[14] showed prospectively (n = 54) that an EGJ DI of 2.8 mm^2/mmHg at 40 mL of inflation was predictive of early success with an AUC of 0.864 (LE 3). A prospective study (n = 58) from Teitelbaum et al (2015)[16] found an EGJ DI of 4.5-8.5 mm^2/mm Hg to predict 6-month efficacy of POEM (Eckardt score (ES) < 1 and gastro-esophageal reflux disease (GERD) score < 7) with a sensitivity of 68% and a specificity of 80% (LE 3). The assessment of EGJ during POEM could also help to predict incomplete response to POEM with different cutoff values found among studies.[14,16,27,28]

Moreover, previous reports identified a subgroup of patients with typical symptoms, radiological findings of achalasia using timed barium esophagogram (TBE), and normal relaxation of the LES with an integrated relaxation pressure (IRP) <15 mm Hg, but with a DI below the cutoff value of 2.9 mm^2/mm Hg set for HV[32] (LE 3). This subgroup represented 5.2% of patients with achalasia in this prospective case series and underlined a limitation of high-resolution manometry in the exploration of achalasia. Kim et al, 2020[33] showed that therapeutic outcomes measured with ES were not different between this subgroup of patients and patients with achalasia and abnormal IRP at distance from POEM. In parallel to these results, there was also a superiority of the DI of LES on IRP to identify patients with failure of treatment. One report[7] found that in patients with failure at 6 months of treatment (ie, ES ≥ 3), 92% had impaired EGJ DI whereas 42% had elevated LES (>15 mm Hg) pressure using high-resolution manometry (HRM) ($P < .01$; LE 3). These results were confirmed by a more recent study[34] (LE 3) with a higher AUC for EGJ metrics in association with pathological TBE for EGJ DI (0.90) than IRP at 3 months after treatment (0.64).

Two studies[16,18] investigated the postoperative risk of GERD. Su et al, 2020[18] found that patients with Reflux Symptom Index score of >13 at 2 years had a CSA > 96.0 mm^2 but the number of patients with GERD was small (n = 4). Teitelbaum et al, 2015[16] showed that

Calibration pressure	Procedure characteristics	Site of balloon inflation
Atmospheric	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & body
Intragastric	Transnasal, local anesthesia, without endoscopic control	EGJ
ND	Transoral, no sedation, without endoscopic control	EGJ
Atmospheric	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & body
Intragastric	Transnasal, local anesthesia, without endoscopic control	EGJ
ND	Transoral, midazolam or no sedation, without endoscopic control	EGJ
Atmospheric	Transorally, no sedation, without endoscopic control	EGJ
Atmospheric	Transoral, conscious sedation (midazolam), without endoscopic control	EGJ
Atmospheric	Transnasal, local anesthesia, without endoscopic control	EGJ
ND	Transoral, general anesthesia (midazolam, pethidine), under gastroscopic control	EGJ
Atmospheric	Transorally, no sedation, under endoscopic control	EGJ & body
Atmospheric	Transoral, general anesthesia, under endoscopic control	EGJ
Atmospheric	Transnasal, local anesthesia, without endoscopic control	EGJ
Atmospheric	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & body
Intragastric	Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control	EGJ
Atmospheric	Transoral, general anesthesia, without endoscopic control	EGJ
Atmospheric	Transnasal, local anesthesia, without endoscopic control	EGJ
Atmospheric	Transoral, local anesthesia, without endoscopic control	Body
Atmospheric	Transoral, local anesthesia, without endoscopic control	EGJ
Atmospheric	Transoral, local anesthesia, without endoscopic control	EGJ

patients with GERD had a higher EGJ DI with a maximal range value of 8.5 mm^2/mm Hg to predict optimal symptomatic results (GERD score < 1).

In summary, the EndoFLIP system demonstrated its relevance in the diagnosis of atypical achalasia, but also in the prediction of the treatment outcome in achalasia. However, the precise EGJ DI threshold associated with success and prolonged response remains to be determined in further studies.

Other esophageal dysmotility disorders

Seven studies (Table 4) included patients with other major motility disorders than achalasia (ie, esophago-gastric junction outflow obstruction: EGJOO).[13,30,35-39] One study[36] showed that patients with EGJOO on HRM and pathological TBE had a lower EGJ DI ($P = .03$) than patients with EGJOO on HRM and normal TBE (LE 3) with a cut-off value of 2.0 mm^2/mm Hg (NPV: 100% and PPV: 75%). These results suggest that EGJ DI could help to identify patients with EGJOO that could undergo achalasia-like therapy, but there is a need for confirmatory studies.

Gastro-esophageal reflux disease

Thirteen studies investigated EGJ in GERD patients using the EndoFLIP® system (Table 5). In all of these reports, patients were assessed with upper GI endoscopy and reflux monitoring (esophageal pH monitoring) in addition to symptomatic evaluation. Kwiatek et al, 2011[40] found that EGJ DI was about twofold higher at both 30 and 40 mL distension volumes in GERD patients (n = 20) in comparison with HV (n = 20; $P = .04$; LE 3), with a high variability of DI values in GERD patients. However, these findings were not confirmed in a more recent publication but with several limitations like the absence of matching between HV and GERD patients on demographic factors[41] (LE 3). No correlation was found between EGJ DI and reflux parameters including acid exposure time (AET), number of reflux episodes, and longest reflux episodes in one study.[42]

The EGJ changes following fundoplication (FP) were also evaluated in nine studies, but EndoFLIP® protocol varied among studies (Table 5), in particular regarding the timing of EGJ evaluation during FP: before, after pneumoperitoneum or after completion of the FP. Most studies showed a significant decrease of EGJ DI immediately

TABLE 3 Assessment of the esophago-gastric junction (CSA, DI, intrabag pressure) using the EndoFLIP® system at different volumes of inflation in healthy volunteers

Reference	Number of patients included (n)	Procedure characteristics	CSA 20 mL (mm^2)	CSA 30 mL (mm^2)	CSA 40 mL (mm^2)	CSA 50 mL (mm^2)
Healthy volunteers						
Carlson et al, 2016 (= Lin Z 2013 & Carlson 2015)[38]	10 HV	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control				
Mikami et al, 2018[9]	8 HV	Transnasal, local anesthesia, without endoscopic control	40.4 ± 9.0	89.4 ± 10.4	150.3 ± 12.2	
Liao et al, 2018[107]	6 HV	Transoral, no sedation, without endoscopic control				
Mikami et al, 2016[10]	8 HV	Transnasal, local anesthesia, without endoscopic control	32.9 ± 10.0	84.5 ± 33.2	152.4 ± 34.2	
Smeets et al, 2015[8]	15 HV	Transorally, no sedation, without endoscopic control		50.4 (41.7-69.1)	99.5 (79.5-138.0)	169.4 (131.7-187.9)
Fukazawa et al, 2013[11]	9 HV	Transnasal, local anesthesia, without endoscopic control	25.2 ± 2.5		163.0 ± 5.9	259.6 ± 12.0
Rohof et al, 2012 (=Ponds 2016)[7]	15 HV	Transnasal, local anesthesia, without endoscopic control				
Kwiatek et al, 2012[55]	15 HV	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control				
Rieder et al, 2012[25]	4 HV	Transoral, general anesthesia, under endoscopic control			122.3 (72.9-170.9)	
Kwiatek et al, 2011[91]	20 HV	Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control	38 (13-94)	94 (27-225)	264 (99-496)	
Kwiatek et al, 2010[40]	10 HV	Transnasal, local anesthesia, without endoscopic control		50 (50-68)	50 (50-50)	50 (50-52)

Note: Results are given as median (25th-75th percentile) or as mean ± SD

Abbreviations: CSA, cross-sectional area; DI, distensibility index; EGJ, esophago-gastric junction; HV, healthy volunteers.

after completion of FP[17,40,43-45] (LE 3) and this despite the type of FP (ie, Nissen or Toupet FP) in one study[43] (LE 3) but not in another study[44] (LE 4). Moreover, the importance of the timing of EGJ evaluation during FP was also demonstrated. In fact, it was shown that EGJ DI was decreased after pneumoperitoneum in comparison with initial measurements after induction of anesthesia[44,45] (LE 3 & 4). Nevertheless, the clinical implication of post-FP EndoFLIP® findings remains controversial. Turner et al[46] found that EGJ pressure and DI variations following FP did not correlate with symptomatic outcomes at 6 months contrary to CSA and Dmin variations (LE 3). However, only 7 patients had a failure of FP in this cohort. Another recent study[43] showed that there was no correlation between post-FP EGJ DI and both dysphagia score and GERD-HRQL score at 1 year from FP (LE 3). In addition, transoral incisionless FP using the EsophyX-2 device was evaluated in two reports (n = 15 and n = 42)[47,48] (LE 3) using EndoFLIP®. A lower EGJ DI and CSA were found after FP in both studies and patients with lower AET at 6 months had a lower preoperative EGJ DI.[47] No association was found between postoperative EGJ DI and AET.

In summary, patients with GERD seem to have a higher EGJ DI than HV among studies, but the relevance of the EndoFLIP system in the prediction of the efficacy of fundoplication remains undemonstrated.

Hiatal hernia

Two studies[49,50] specifically assessed patients with hiatal hernia (HH) using the EndoFLIP® system. In a prospective controlled study[49] (sliding HH n = 30; HV n = 14; LE 3), a specific profile was visible with EndoFLIP® a double-diameter zone (LES and crural diaphragm components) permitting the diagnosis of HH with a sensitivity of 100% and a specificity of 77.8% using endoscopic findings as gold standard. Patients with sliding HH had a lower LES pressure ($P < .001$) and a higher LES DI ($P < .001$) compared to HV. The crural diaphragm (CD) component had a lower pressure and a higher DI than the LES ($P < .001$). Interestingly, higher symptom scores were associated with lowest LES pressure and highest LES DI ($P < .01$), but not with pressure or DI of the CD. However, there is to date no confirmatory study available.

DI 20 mL (mm^2/mm Hg)	DI 30 mL (mm^2/mm Hg)	DI 40 mL (mm^2/mm Hg)	DI 50 mL (mm^2/mm Hg)	Intrabag pressure 20 mL (mm Hg)	Intrabag pressure 30 mL (mm Hg)	Intrabag pressure 40 mL (mm Hg)	Intrabag pressure 50 mL (mm Hg)
	3.2 (1.0-11.6)	5.7 (1.4-15.8)	5.9 (1.6-9.3)				
2.2 ± 0.5	3.4 ± 0.5	3.5 ± 0.4		14.7 ± 0.8	23.4 ± 2.1	40.8 ± 2.0	
				16.3 ± 0.5	27.4 ± 1.2	40.2 ± 1.5	
1.8 ± 0.2	3.5 ± 0.6	4.5 ± 0.5		15.5 ± 5.1	22.0 ± 6.0	31.2 ± 6.8	
	2.0 (1.6-3.0)	3.0 (2.2-4.2)	3.4 (2.7-4.2)		25.9 (21.4-30.0)	34.5 (29.0-40.2)	45.8 (41.9-53.4)
2.9 ± 0.6		7.1 ± 0.9	8.2 ± 0.8	10.3 ± 1.4		25.9 ± 3.2	33.1 ± 2.3
			6.3 ± 0.7				
0.9 (0.3 - 1.4)	0.8 (0.4 - 2.8)						
		2.7 (2.4-8.3)				36.8 (20.7-45.8	
2 [1-9]	4 [1-14]			9 (2-20)	25 (6-47)	39 (17-60)	
					16 (13-19)	17 (11-21)	

Another retrospective report (n = 40; LE 4)[50] used the EndoFLIP® device to determine how tight to create the fundoplication with an arbitrary set final EGJ DI near 1 mm^2/mm Hg at 30 mL of inflation. If the use of EndoFLIP® eliminated the need for a bougie in this study without dysphagia or GERD symptoms at 1 month, there is a need to confirm these findings in further large prospective studies with a longer time of follow-up. Lastly, some studies on fundoplication in GERD patients included a low number of patients with HH, but without particular analysis of this subgroup of patients.[17,42,45,47,48]

Systemic sclerosis

Only one prospective report (LE 3)[51] investigated EGJ parameters in patients with diffuse systemic scleroderma (SSc, n = 11) in comparison with HV (n = 10). All patients had mild-to-moderate digestive symptoms with hypomotility on HRM in 7/11 patients. The authors did not use the DI in this study but the pressure strain elastic modulus (defined as the change in the diameter at the narrowest point of the EGJ divided by change in the bag pressure relative to a reference diameter), which was lower in patients with SSc, indicating reduced resistance to distension. However, due to the small and heterogenic cohort of patients, these results need confirmatory studies.

Sleeve gastrectomy

One prospective study[52] (n = 15; LE 3) showed an increase in EGJ DI during per operatory evaluation but no correlation was found between EGJ DI and GERD-HRQL score at 3 and 6 months of follow-up. However, the number of patients who developed postoperative GERD was small in this cohort (n = 4), with a need for other confirmatory studies.

Esophageal stenosis

One retrospective study[53] (n = 56; LE 4) compared videofluoroscopy including a tablet test (placebo sugar tablets of spherical shape, 14 mm diameter) to EndoFLIP® for the evaluation of esophageal stenosis in patients with dysphagia. A significant correlation was found between tablet impaction with a delay of more

TABLE 4 Characteristics of studies performed in patients with achalasia or other esophageal dysmotility disorders

Reference	Method		Level of evidence/ Grade of recommendation	EndoFLIP measurement: time (s) and volumes of distension (mL)	Procedure characteristics	Site of balloon inflation
	Number of patients included (n)	Design of the study				
Achalasia						
Sloan et al, 2020[30]	37 Achalasia, 14 EGJOO	Retrospective, case series study	4/C	ND; 30 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Schnurre et al, 2020[31]	28 Achalasia	Retrospective, case series study	4/C	30 s, 30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Kim et al, 2020[33]	89 Achalasia	Retrospective, case series study	4/C	30 s; ND	ND	EGJ
Su et al, 2020[18]	94 POEM	Prospective, case series study	3/C	30 s; 30-40 mL	Transoral, general anesthesia, ±under endoscopic control	EGJ
Su et al, 2020[17]	77 Achalasia (71 POEM & 6 HM)	Prospective, case series study	3/C	30 s, 30 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Bianca et al, 2020[13]	18 Achalasia, 43 EGJOO	Prospective, case series study	3/C	30 s; 30-40-50 mL	Transoral, general anesthesia, ±under endoscopic control	EGJ
Carlson et al, 2020[58]	20 HV, 140 Achalasia	Prospective, case series study	3/C	30 s, 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	Body
Campagna et al, 2019[37]	27 Achalasia, 7 EGJOO	Prospective, case series study	3/C	30-60 s; 30-40-50-60-70 mL	Preoperative: Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control/Intraoperative: transoral, general anesthesia, under endoscopic control	EGJ & Body
Jain et al, 2019[34]	79 Achalasia (not naive of treatment)	Prospective, case series study	3/C	10-30 s, 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, general anesthesia, ±under endoscopic control	EGJ & Body
Yoo et al, 2019[28]	52 Achalasia (POEM)	Retrospective, case series study	4/C	ND; 30-40 mL	Transoral, general anesthesia, ± under endoscopic control	EGJ
Carlson et al, 2019[39]	9 Achalasia, 10 EGJOO, 1 DES, 2 Jackhammer esophagus	Prospective, case series study	3/C	30-60 s; 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl)±propofol, without endoscopic control	EGJ & body
Wu et al, 2017[23]	54 PD, 15 HV	Prospective, case-control study	3/C	30 s, 10-20-30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Carlson et al, 2017[38]	32 Fundoplication, 25 Achalasia	Prospective, case series study	3/C	30 s, 20-30-40-50-60-70 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	
Ahuja et al, 2017[109]	24 Achalasia	Retrospective, case series study	4/C	30 s, 20-30-40-50 mL	Transoral, general anesthesia, under endoscopic control	EGJ & body

(Continues)

TABLE 4 (Continued)

Reference	Method		Level of evidence/ Grade of recommendation	EndoFLIP measurement: time (s) and volumes of distension (mL)	Procedure characteristics	Site of balloon inflation
	Number of patients included (n)	Design of the study				
Ponds et al, 2016[32]	13 Achalasia	Prospective, case-control study	3/C	30 s, 20-30-40-50 mL	Transnasal, local anesthesia, without endoscopic control	EGJ
Carlson et al, 2016[15]	70 Achalasia, 38 EGJOO, 3 Jackhammer	Prospective, case series study	3/C	10-30 s, 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl) or general anesthesia, without endoscopic control	Body
Dehaan et al, 2016[22]	14 Achalasia (HM)	Retrospective, case series study	4/C	ND; 30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Teitelbaum et al, 2016[26]	16 Achalasia (POEM)	Prospective, case series study	3/C	ND; 40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Ngamruengphong et al, 2015[27]	63 Achalasia (POEM)	Retrospective, case series study	4/C	30 s; 30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Carlson et al, 2015[59]	51 Achalasia, 10 HV	Prospective, case-control study	3/C	5-20 s; 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl) or general anesthesia, without endoscopic control	Body
Smeets et al, 2015[8]	26 Achalasia, 15 HV	Prospective, case-control study	3/C	30 s; 30-40-50 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ
Ilczyszyn et al, 2015[21]	38 Achalasia (HM)	Retrospective (8 patients) and prospective (30 patients), case-control study	4/C	30 s; 30-40 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Teitelbaum et al, 2015[16]	58 Achalasia (20 LHM, 38 POEM)	Prospective, case series study	3/C	ND; 40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Kappelle et al, 2015[24]	10 Achalasia (PD)	Prospective, case series study	3/C	ND; 30 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Familiari et al, 2014[110]	21 Achalasia (POEM)	Prospective, case series study	3/C	ND; 30 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Teitelbaum et al, 2014[20]	31 Achalasia (12 HM, 19 POEM)	Prospective, case series study	3/C	ND; 30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Teitelbaum et al, 2013[19]	25 Achalasia (11 HM, 14 POEM)	Prospective, case series study	3/C	ND; 30-40-50 mL	Transoral, general anesthesia, under endoscopic control	EGJ

(Continues)

TABLE 4 (Continued)

Reference	Method		Level of evidence/ Grade of recommendation	EndoFLIP measurement: time (s) and volumes of distension (mL)	Procedure characteristics	Site of balloon inflation
	Number of patients included (n)	Design of the study				
Pandolfino et al, 2013[14]	54 Achalasia (17 PD, 10 HM, 4 POEM)	Prospective, case-control study	3/C	30 s; 40 mL	Transoral, conscious sedation (midazolam, fentanyl)±under endoscopic control	EGJ
Verlaan et al, 2013[29]	10 Achalasia (POEM)	Prospective, case series study	3/C	30 s; 20-30-40-50 s	Transorally, no sedation, without endoscopic control	EGJ
Rieder et al, 2012[25]	4 Achalasia (POEM), 4 HV	Prospective, case series study	4/C	30 s; 30-40 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Rohof et al, 2012[7]	15 HV, 30 Achalasia	Prospective, case-control study	3/C	30 s, 20-30-40-50 mL	Transnasal, local anesthesia, without endoscopic control	EGJ
McMahon et al, 2007[4]	8 HV, 2 Achalasia	Prospective, case-control study	3/C	ND; 20-30-40-50-60 mL	Transoral, local anesthesia, without endoscopic control	EGJ
Other dysmotility disorders						
Sloan et al, 2020[30]	37 Achalasia, 14 EGJOO	Retrospective, case series study	4/C	ND; 30 mL	Transoral, general anesthesia, under endoscopic control	EGJ
Baumann et al, 2020[35]	10 IEM, 20 EGJOO	Retrospective, case series study	4/C	30-60 s; 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	Body
Bianca et al, 2020[13]	18 Achalasia, 43 EGJOO	Prospective, case series study	3/C	30 s; 30-40-50 mL	Transoral, general anesthesia, with and without endoscopic control	EGJ
Triggs et al, 2019[36]	34 EGJOO	Retrospective, case series	3/C	30-60 s; 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control	EGJ & body
Carlson et al, 2019[39]	9 Achalasia, 10 EGJOO, 1 DES, 2 jackhammer esophagus	Prospective, case series study	3/C	30-60 s; 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl)±propofol, without endoscopic control	EGJ & body
Campagna et al, 2019[37]	27 Achalasia, 7 EGJOO	Prospective, case series study	3/C	30-60 s; 30-40-50-60-70 mL	Preoperative: Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control/Intraoperative: transoral, general anesthesia, under endoscopic control	EGJ & Body
Carlson et al, 2016[15]	70 Achalasia, 38 EGJOO, 3 Jackhammer	Prospective, case series study	3/C	10-30 s, 20-25-30-35-40-45-50-55-60-65-70 mL	Transoral, conscious sedation (midazolam, fentanyl) or general anesthesia, without endoscopic control	Body

Note: Abbreviations: DES, distal esophageal spasm; EGJ, esogastric junction; EGJOO, esophago-gastric junction outflow obstruction; HM, Heller myotomy; HV, healthy volunteers; ND, not detailed; PD, pneumatic dilation; PD, pneumatic dilation; POEM, per oral endoscopic myotomy.

than 15 seconds and an EndoFLIP® esophageal diameter of less than 15.1 mm ($P = .035$). However, the etiologies of esophageal stenosis were heterogeneous in this population and some patients had an impaction of videofluoroscopy proximally to EndoFLIP® placement.

3.1.3 | Body of the esophagus

Healthy volunteers

The body of the esophagus was studied in 6 reports in healthy volunteers (n = 2-20) using[54-56] the classical 8 cm probe or a more recent 16-cm probe (EF322-N).[38,57,58] These publications introduced the concept of *distension plateau (DP)*, which was defined as the reflection of the fixed luminal diameter that would fail to expand despite increasing intraballoon pressures.[38,57] Moreover, the contractility response of the esophagus to distension (ie, secondary peristalsis) could be identified in these studies, with the introduction of new parameters: 1/esophageal body contractions (transient decrease of ≥5 mm in the luminal diameter in ≥3 adjacent impedance planimetry channels); 2/repetitive anterograde contractions (RACs; ≥3 antegrade contractions consecutively); and 3/repetitive retrograde contractions (RRCs; ≥3 retrograde contractions consecutively).[38,57-59] The RAC pattern, occurring every 6-10 seconds, was found to be the normal contractile response to sustained volume distension in 95% of HV (LE 3)[58,59] mostly at 40 and 50 mL fill volume and was assimilated to secondary peristalsis (Figure 3). Table S1 (Supplemental material) summarizes results regarding esophageal body studies in HV.

Eosinophilic esophagitis

Six reports assessed esophageal properties in eosinophilic esophagitis (EoE) using the EndoFLIP® system (Table 4). The DI of the distal esophageal body was significantly reduced in patients with EoE (n = 33) in comparison with HV (n = 15) in a prospective report (LE 3),[55] with a DP of the distal esophageal body of <300 m^2 in 73% of EoE patients whereas it was >400 m^2 in 67% of HV. These findings were confirmed by another group (LE 3).[60] The EGJ DI was also lower at different inflation volumes in patients with EoE than in HV ($P = .01$). No correlation was found between the DP and mucosal eosinophilic count from proximal or distal biopsies, age, gender, and proton pump inhibitors use.[55] However, the symptomatic relevance or association with endoscopic patterns of EoE was not assessed in this study. Another prospective study[61] (n = 70, LE 3) showed that the association between the DP and the follow-up symptom score at 12 months was stronger than the association between the follow-up symptom score and eosinophilic density. In addition, patients with a history of food impaction had a significantly lower DP, but there was no difference in eosinophilic density, compared to those without food impaction in the same study. The association between endoscopic severity of EoE (rings, strictures, exudates) using the EoE Endoscopic Reference Score and esophageal distensibility was assessed in a retrospective study (n = 72; LE 4).[62] The main findings were that higher ring scores were associated with lower DP ($P < .001$) but not with mucosal eosinophilic density. On the contrary, the severity of exudates and furrows were not associated with distensibility parameters, in contrary to mucosal eosinophilic density ($P < .001$). Lastly, an analysis of a small retrospective cohort of patients with EoE (n = 18; LE 4) suggested that the median esophageal DP was higher more than 3 months after initiation of therapy (including PPI, topical steroids, or elimination diet) in comparison with baseline. Moreover, the improvement in DP was associated to an improvement in ring scores and not mucosal eosinophilic density or inflammatory endoscopic changes.

All these results suggest that there is a disconnect between the degree of tissue remodeling and inflammation. Thus, the fibrostenotic changes could be independent of the inflammatory influence of activated eosinophils. In fact, previous reports showed a disconnection between symptomatic outcome and eosinophilic density,[63] with a relevant place for an endoscopic evaluation in patients with EoE. However, the place of EndoFLIP® in the evaluation of patients with EoE will need further evaluation studies, as its superiority to esophageal biopsies evaluation and its use to guide treatment remains still unclear.

Achalasia

The body of the esophagus was also investigated in patients with achalasia in six reports (ie, panometry).[37-39,58,59,64] Contrary to 95% (19/20) of HV, less than 1% (1/140) of patients with achalasia exhibited the RAC pattern as response to distension in a large cohort of patients[58] (LE 3). Moreover, type I and type II achalasia patients demonstrated absent contractility or non-RAC contractility pattern, whereas patients with type III achalasia showed RRC pattern, which was not observed in HV[38,59,64] (LE 3). Discrepancy between HRM and EndoFLIP® was also demonstrated in one study[38] (LE 3). All (106/106) patients with achalasia on HRM had abnormal FLIP topography (ie, abnormal EGJ DI, RRCs, absent contractility) but 50% (17/34) of patients with dysphagia and without major motility disorder on HRM had abnormal FLIP topography. One report showed that there was a modification of these abnormal contractility patterns following myotomy of the LES[37] (LE 3). Lastly, one recent report showed an excellent agreement ($\kappa = 0.939$; $P < .01$) between new real-time panometry (FLIP 2.0) interpretation and classical post hoc panometry interpretation (MATLAB) for detecting major contractility disorders of the esophagus.[39]

Other motility disorders than achalasia

Abnormal FLIP topography (ie, abnormal EGJ DI, RRCs, absent contractility) was found in 33/38 (87%) patients with EGJOO on HRM (defined by LES IRP > 15 mm Hg) in one study[38] and the remaining five patients had normal TBE in majority and were managed without invasive therapy (LE 3). However, the time of follow-up after FLIP assessments was short in this cohort. Another report[35] investigated patients with normal FLIP panometry and EGJOO diagnosed on HRM. 17/20 (85%) of these patients had normal bolus transit on

TABLE 5 Characteristics of studies performed in patients with gastro-esophageal reflux disease or hiatal hernia or eosinophilic esophagitis

Reference	Method		Level of evidence/ Grade of recommendation	EndoFLIP measurement: time (s) and volumes of distension (mL)	Procedure characteristics	Site of balloon inflation
	Number of patients included (n)	Design of the study				
GERD						
Su et al, 2020[17]	226 Fundoplication	Prospective, case series study	3/C	30 s, 30-40 mL	Transoral, general anesthesia, ±under endoscopic control	EGJ
Turner et al, 2019[46]	43 Fundoplication	Retrospective, case series study	4/C	20 s, 30 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Su et al, 2019[43]	175 Fundoplication	Prospective, case series study	3/C	30 s, 20-30-40 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Mikami et al, 2018[9]	8 HV, 3 GERD	Prospective, case-control study	3/C	30 s, 20-30-40 mL	Transnasal, local anesthesia, without endoscopic control	EGJ
Carlson et al, 2018[42]	25 GERD	Prospective, case series study	3/C	30 s, 20-30-40-50-60-70 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & Body
Carlson et al, 2017[64]	32 Fundoplication, 25 Achalasia	Prospective, case series study	3/C	30 s, 20-30-40-50-60-70 mL	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & Body
Dehaan et al, 2016[44]	75 Fundoplication	Retrospective, case series study	4/C	20 s, 30-40 mL	Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control	EGJ
Smeets et al, 2015[47]	42 Fundoplication	Prospective, case series study	3/C	30 s, 20-30 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Tucker et al, 2013[41]	21 HV, 18 GERD	Prospective, case-control study	3/C	30 s, 20 and 30 mL	Transoral, general anesthesia (midazolam, pethidine), under endoscopic control	EGJ
Rinsma et al, 2013[48]	15 Fundoplication	Prospective, case series study	3/C	30 s, 30 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Ilczyszyn et al, 2013[45]	17 Fundoplication	Prospective, case series study	3/C	30 s, 30-40 mL	Transoral, general anesthesia, without endoscopic control	EGJ
Kwiatek et al, 2011[40]	20 HV, 20 GERD	Prospective, case-control study	3/C	30 s, 10-20-30-40 mL	Transoral, conscious sedation (midazolam, fentanyl), under endoscopic control	EGJ
Kwiatek et al, 2010[91]	8 HV, 7 post-FP	Prospective, case-control study	3/C	30 s, 30-40-50 mL	Transnasal, local anesthesia, without endoscopic control	EGJ
Hiatal hernia						
Kim et al, 2018[50]	40 Fundoplication	Retrospective, case series study	4/C	30 s, 30 mL	Transoral, general anesthesia, without endoscopic control	EGJ

(Continues)

TABLE 5 (Continued)

Reference	Method		Level of evidence/ Grade of recommendation	EndoFLIP measurement: time (s) and volumes of distension (mL)	Procedure characteristics	Site of balloon inflation
	Number of patients included (n)	Design of the study				
Lottrup et al, 2015[49]	30 HH, 14 HV	Prospective, case-control study	3/C	30 s, 20-30-40-50 mL	Transoral, conscious sedation (midazolam), without endoscopic control	EGJ
Eosinophilic esophagitis						
Carlson et al, 2017[111]	18 EoE	Retrospective, case series study	4/C	20-30 s, 5-60 mL (by 5-mL step)	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & Body
Chen et al, 2016[62]	72 EoE	Retrospective, case series study	4/C	5-20 s, 2-40 mL (by 2-mL step)	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	Body
Carlson et al, 2016[60]	9 HV, 20 EoE	Prospective, case-control study	3/C	20-30 s, 5-60 mL (by 5-mL step)	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & body
Lin Z et al, 2013[112]	2 HV, 6 EoE	Prospective, case-control study	3/C	5-20 s, 5-40 mL (by 2-mL step)	Transorally, no sedation, under endoscopic control	EGJ & body
Nicodème et al, 2013[61]	10 HV, 70 EoE	Prospective, case-control study	3/C	5-20 s, 2-40 mL (by 2-mL step)	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	Body
Kwiatek et al, 2012[55]	15 HV, 33 EoE	Prospective, case-control study	3/C	30 s; 20-30 mL (EGJ); 2-40 mL by 2-mL step (body)	Transoral, conscious sedation (midazolam, fentanyl), without endoscopic control	EGJ & Body

Abbreviations: EGJ, esogastric junction; EoE, eosinophilic esophagitis; FP, fundoplication; GERD, gastro-esophageal reflux disease; HH, hiatal hernia; HV, healthy volunteers; ND, not detailed.

supine swallows and 10/20 (50%) had normal TBE, with therefore conservative therapy in all patients (LE 4).

Gastro-esophageal reflux disease

The body of the esophagus was investigated in 2 studies using panometry. Carlson et al, 2018[42] found that total esophageal acid exposure time was lower in GERD patients exhibiting RAC pattern (6.1%) than in those that did not generate RACs (14.9%; $P = .009$; LE 3), but this cohort included patients with typical and atypical GERD symptoms. In patients with dysphagia post-Nissen FP, it was found that RRC pattern could occur in these patients, but in a lesser degree than in patients with type III achalasia ($P < .001$), and these abnormalities were in mainly cases associated with HRM findings of neural imbalance favoring excitation[64] (LE 3).

3.1.4 | Pharyngoesophageal junction

Pharyngoesophageal junction motility during swallowing is traditionally difficult to explore, even using the most recent technology, including videofluoroscopy and HRM coupled with intraluminal impedance recording manometry. This relies on the lack of reliable objective measures and/or limited interrater reliability to assess upper esophageal sphincter resting pressure and opening.[65,66] The recent development of FLIP measurement provided a new tool to assess dynamic change of pharyngoesophageal junction geometry and distensibility, especially during swallowing. Two studies from the same group in 11 and 14 HV demonstrated the feasibility of this investigation with the balloon inflated up to 20 mL.[67,68] CSA increased during swallowing compared to the resting period, while intraballon pressure dropped. A third study showed similar data in seven patients with total laryngectomy.[69] Unfortunately, no comparison with values obtained from HV was carried out. A last report investigated 60 patients with head and neck cancer treated either with chemotherapy or laryngectomy + radiotherapy.[70] Pharyngoesophageal junction distensibility was found to be decreased in patients with strictures compared to patients free of strictures with a diagnostic performance of 100%. Additionally, endoscopic dilation of pharyngoesophageal junction strictures resulted in an increase in pharyngoesophageal junction distensibility. Altogether, these data suggest that the measurement of the pharyngoesophageal junction distensibility provides additional information on swallowing dynamics and may be of use in the future in patients with dysphagia, especially after head-neck cancer.

3.2 | Part 2. Pyloric distensibility measurement in gastroparesis

Clinical diagnosis of gastroparesis may be challenging as symptoms patterns and severity are poorly correlated with gastric emptying.[71-73] Historically, the role of pylorus in gastric emptying delay and symptom generation has been highlighted. In fact, a first report published in 1986 by Mearin et al[74] identified pyloric dysfunction as unusually prolonged and named intermittent pyloric contractions "pylorospasms." However, this study required a specific manometric assembly which limited its spread among specialized centers. More recently, pyloric distensibility measurement using EndoFLIP® technology has been validated as a complementary measurement to sphincter pressure in gastroparesis. Pyloric distensibility measurement can be easily achieved using probe placement either by radiofluoroscopy guidance[75] or through the endoscope.[76,77] Whether anesthetics impact or not pyloric distensibility measurement has however not yet been investigated.

An initial study (LE 3) in HV (n = 21) reported mean pyloric distensibility at 25.2 mm^2/mm Hg using a 40-mL inflated bag while the normal lower range was set at 10 mm^2/mm Hg.[75] Subsequent studies performed in 27,[75] 20,[76] and 54[77] gastroparetic patients reported mean pyloric distensibility at 16.9, 12.4, and 10.7 mm^2/mm Hg, respectively (LE 3). Using the threshold of 10 mm^2/mm Hg, nearly one third of patients with idiopathic or diabetic gastroparesis had decreased pyloric distensibility[75,77] (LE 3). Altered pyloric distensibility is even more likely to be found in patients with suspected or confirmed vagotomy, namely postfundoplication gastroparesis and esophagectomy, with decreased pyloric distensibility found in 61% and 75%, respectively[78] (LE 4). Another study performed in patients with nausea and/or vomiting, either associated with delayed or normal gastric emptying, found decreased pyloric distensibility (mean = 8.0 mm^2/mm Hg) in patients with gastric retention compared with patients with normal gastric emptying (mean = 12.4 mm^2/mm Hg)[79] (LE 3). Interestingly, in these studies, pyloric pressure measured either using EndoFLIP® system or manometry was not different between subjects with or without delayed gastric emptying.[75,79] In all studies, pyloric distensibility was inversely correlated with gastric emptying[75,77,79] (LE 3). In addition, pyloric distensibility correlated negatively with gastroparesis symptoms, including nausea,[75,79] gastric fullness,[75,77] early satiety,[75,77] and quality of life.[75,77] This contrasts with gastric emptying measurement which is poorly correlated with symptoms or quality of life[71-73] (LE 3). This suggests therefore that pyloric distensibility may be a clinically relevant tool in a subset of gastroparetic patients to better identify precisely one of the underlying mechanisms involved in gastric retention.[17,80]

Based on these results, subsequent studies investigated whether pyloric distensibility measurement could predict clinical outcome of pyloric targeted therapies, including pyloric dilation, intrapyloric botulinum toxin injection, or gastric POEM (G-POEM).[80] Proof-of-concept studies identified that prokinetics,[81] pyloric dilation,[75] and G-POEM[76,82,83] increased pyloric distensibility, but not pyloric pressure (LE 3). Likewise, patients with decreased pyloric distensibility at baseline were more likely to normalize gastric emptying rate after botulinum toxin compared with patients with normal pyloric distensibility[84] (LE 4). Cohort studies showed that pyloric distensibility lower than 8-10 mm^2/mm Hg could predict favorable outcome after pyloric dilation,[75] intrapyloric botulinum toxin injection,[84,85] and G-POEM[76,86] (LE 3). This remains, however, to be further confirmed by randomized controlled trials.

3.3 | Part 3. SPHINCTER OF ODDI

Manometry of the sphincter of Oddi is currently the gold standard for assessment of SO physiology. This technique is used to diagnose sphincter of Oddi dysfunction characterized by elevated basal SO pressure that may lead to sphincterotomy operations.[87] A pilot study evaluated the feasibility of an alternative technique based on sphincter distensibility measurement[88] (LE 4). This was achieved using a custom-made miniaturized probe inserted into the SO during an endoscopic retrograde cholangiopancreatography in four subjects. However, such a probe has since never been marketed and is therefore not currently available for clinical use.

3.4 | Part 4. Anal sphincter evaluation

Several methods can be used to investigate the anal sphincter. Magnetic resonance imaging or transanal ultrasound is commonly used to determine the morphology of the anal sphincters while electrophysiological tests are used to assess the innervation of the external anal sphincter.[89] Most often, anal sphincter function is assessed by measuring anal resting and voluntary contraction pressures by manometry.[90] While manometric techniques, including 3D-HRM, provide direct measurements of closure forces of the anal canal using a fixed diameter, non-collapsible probe, they cannot be used to quantify the opening dimension, which is a major variable for determining trans sphincteric flow.[91] Indeed, it has been suggested that the ability of sphincter muscles to withstand distension is more important for continence than their contraction capabilities.[92]

Several studies have evaluated anal canal resistance to distension with the FLIP technique in HV and patients with fecal incontinence. While the methodology used was quite similar among all studies, there is until now, no consensus about the best parameters to record with FLIP technology. Several parameters have been suggested from the most complexes (anal canal stiffness defined on the basis of the pressure and diameter changes when the volume increased from 1 to 50 mL,[93-95] flow resistance of the anal canal defined from the anal canal length, the middle part diameter of the anal canal and the dynamic viscosity of the inflated bag[96] or mechanical work of the anal sphincter muscle,[97] to the most simple (wall tension (T = P.r),[98] anal DI (CSA/P),[99,100] anal compliance (D/P),[97] yield pressure when the most resistant (middle) part of the sphincter begins to distend.[93-95] More recently, Zifan et al described the use of area-pressure and area-tension-loop analysis of the anal sphincters and puborectalis muscles in normal subjects and fecal incontinent patients, assessing the relationship between changes in muscle length (secondary to anal distension) and muscle function.[101,102] Thus, although 10 studies have reported results of FLIP measurements in the anal canal in HV,[93,95,97-99,101,103-105] no reliable normal values are yet available because of the absence of standardized protocols for assessing and analyzing FLIP measurements. However, some of these studies have demonstrated that the geometry of the lumen and the biomechanical properties of the anal canal are not uniform during distension. Luft et al[98] attribute the least compliant position to the mid-anal

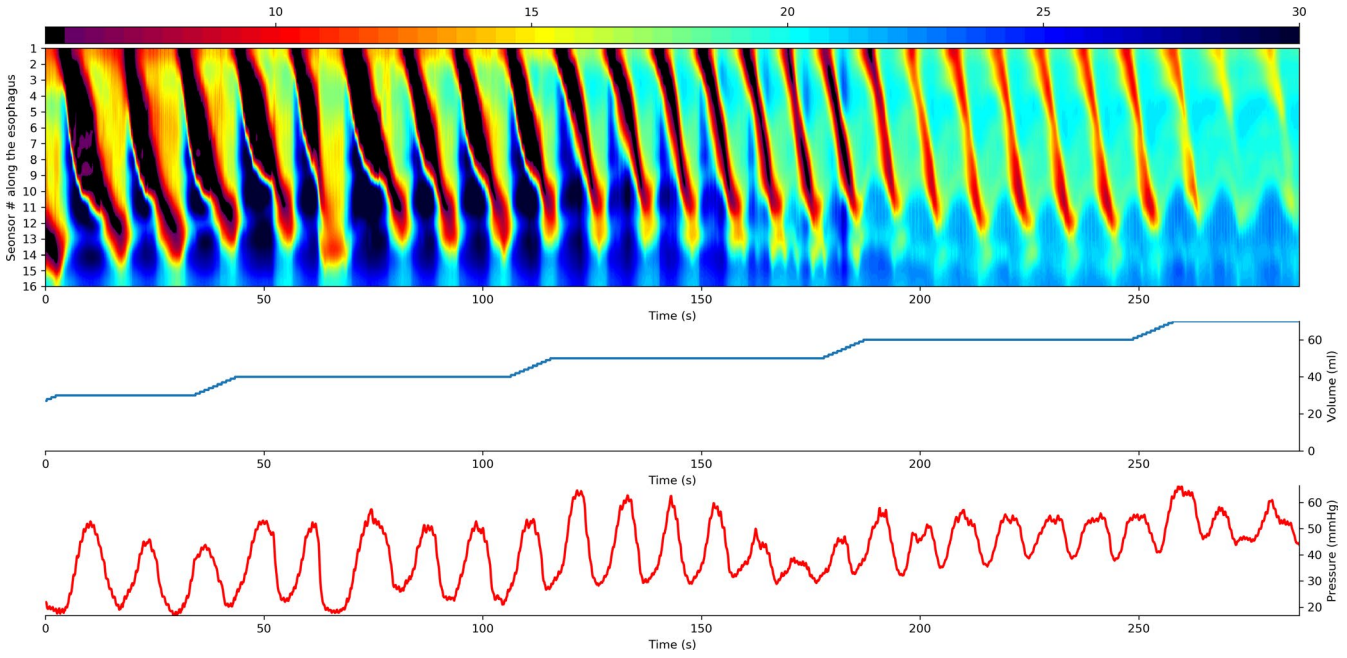

FIGURE 3 Example of FLIP topography in a HV. The EF322-N probe was used in this patient, with 16 electrodes positioned every 1 cm along the probe (vertical axis). Topographic representation of interpolar diameter changes over time using a color scale (blue: largest diameter; red narrowest diameter) from 5 to 30 mm. The blue curve illustrates the different inflation volumes used in the study over time: from 40 to 70 mL by 5 mL levels. The red curve illustrates the variation of intrabag pressure (mm Hg) over time. The figure shows the RAC pattern in a HV subject, with repetitive anterograde contractions occurring every 6-10 s. Courtesy of the Esophageal Center of Northwestern University, Chicago, IL, USA

canal, where the extern anal sphincter (EAS) and intern anal sphincter (IAS) overlap.

Regardless of the endpoints used, significantly higher anal distensibility was found in patients with fecal incontinence than in HV in all clinical studies'.[93,96,99,102,104] This has been demonstrated in patients with poor internal anal sphincter function resulting from systemic sclerosis,[104] in patients treated with sphincter-sparing radiotherapy or chemoradiation for anal cancer[96] and whatever the cause of fecal incontinence.[99,100] It has been suggested that FLIP assessment would be a more selective tool to discriminate between patients with fecal incontinence and HV[99] but not confirmed by others.[106] However, because there is substantial diagnostic agreement about the anal sphincter weakness between high-resolution anorectal manometry and FLIP in patients with fecal incontinence,[99,100,106] the usefulness and the place of FLIP in diagnosing and managing fecal incontinence need to be identified. Some suggest that the resistance of the anal canal to distension evaluated with FLIP would be a better criterion than anal pressure to assess treatment effectiveness[94,102] but other larger studies may shed light on this issue.

4 | CONCLUSION

Most studies investigated the esophago-gastric junction, with a promising role of the EndoFLIP® in the diagnosis of atypical achalasia or EGJOO and in the prediction of treatment outcome in achalasia using EGJ DI threshold. However, the application of the use of EndoFLIP® in the body of the esophagus (esophageal panometry), other esophageal diseases (GERD, eosinophilic esophagitis), and other sphincter regions (anal canal, pylorus) will need further confirmatory studies. Moreover, the cost and the availability of the EndoFLIP system could be an important limitation to the application of this interesting tool in daily practice. In conclusion, the EndoFLIP® system provides detailed geometric data of the gastrointestinal lumen and further works are needed to determine its use in clinical practice.

ACKNOWLEDGMENTS

We are grateful to Nikki Sabourin-Gibbs, Rouen University Hospital, for her help in editing the manuscript. The authors are grateful to the Esophageal Center of Northwestern University, Chicago, IL, USA.

CONFLICT OF INTEREST

Guillaume Gourcerol has received consulting fees from Allergan. Sabine Roman served as consultant for Medtronic and received research grants from Medtronic and Diversatek Healthcare. Anne-Marie Leroi is a member of scientific board for the Medtronic Company. The other authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

All authors have approved the final version of the article, including the authorship list. CD conceived and designed the study; and GG, CD, AML, and SR wrote the article and edited the manuscript.

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SUPPORTING INFORMATION

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

How to cite this article: Desprez C, Roman S, Leroi AM, Gourcerol G. The use of impedance planimetry (Endoscopic Functional Lumen Imaging Probe, EndoFLIP®) in the gastrointestinal tract: A systematic review. *Neurogastroenterol Motil*. 2020;32:e13980. https://doi.org/10.1111/nmo.13980