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Current Opinion in Pharmacology

Interventional functional diagnostics in gastrointestinal endoscopy: Combining diagnostic and therapeutic tools in the endoscopy suite with the functional lumen imaging probe

Zuzana Vackova[1], Ian Levenfus[2] and Daniel Pohl[2]

Abstract

With technical progress of gastrointestinal functional testing, there has been a demand for more comprehensive examination of esophageal physiology and pathophysiology beyond high-resolution manometry. A new interventional technology based on impedance planimetry, the functional lumen imaging probe (FLIP), enables intraluminal measurement of distensibility and compliance of hollow organs. EndoFLIP uses balloon catheters to measure diameter and distension pressure to calculate cross-sectional area and distensibility in different organs (mostly esophagus, stomach, anorectal region) and can be used in wide variety of indications (diagnostics, pre- and post-treatment evaluation) and currently serves as a helpful adjunctive tool in ambiguous clinical cases. EsoFLIP is a therapeutic variation that uses a stiffer balloon catheter allowing for dilation. The trend to simplify the clinical process from diagnosis to treatment tends to a one-session procedure combining diagnostics and therapeutic interventions. In specified conditions like e.g. achalasia or gastroparesis, a combination of EndoFLIP and EsoFLIP procedures may therefore be useful. The aim of this narrative review is to introduce the clinical use of FLIP and its potential benefit in combined diagnostic-therapeutic procedures.

Addresses

[1] Department of Gastrointestinal Endoscopy, Department of Medicine, Military University Hospital Prague, Czech Republic

[2] Division of Gastroenterology and Hepatology, University Hospital Zurich, Switzerland

Corresponding author: Vackova, Zuzana (vackova.zuz@gmail.com)

Current Opinion in Pharmacology 2023, **73**:102414

This review comes from a themed issue on **Gastrointestinal (2022)**

Edited by **Tim Vanuystel** & **Daniel Pohl**

For complete overview about the section, refer Gastrointestinal (2022)

Available online 28 November 2023

https://doi.org/10.1016/j.coph.2023.102414

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Introduction

Over the past 20 years, significant changes have taken place in the field of functional gastrointestinal diagnostics, especially regarding motility testing. The introduction as well as the rapid establishment of high-resolution manometry (HRM) as the gold standard for esophageal motility testing followed by extensions using impedance measurements including impedance planimetry for evaluation of distensibility only reflected the demand for more precise and comprehensive diagnostic tools to assess esophageal physiology. The concept of using impedance testing for dynamic functional evaluation of luminal organs goes back to the 1980s, when a functional lumen imaging probe (FLIP) was initially developed by Hans Gregersen. The method was further elaborated and tested mostly in experiments predominantly in the area of the esophago-gastric junction (EGJ) [1–4]. Eventually, in 2009, the first commercially available device of the functional lumen imaging probe (EndoFLIP developed by Crospon, now Medtronic, Minneapolis, MN, USA) was introduced.

The functional lumen imaging probe constitutes an innovative functional diagnostics device that enables dynamic assessment of biomechanical properties of a sphincter or a tubular organ in the gastrointestinal (GI) tract. A balloon catheter equipped with impedance electrodes uses the principle of impedance planimetry to calculate luminal diameter, cross-sectional area and the distension pressure, which in turn allows to calculate luminal distensibility and compliance. These characteristics provide a more comprehensive evaluation of sphincter function compared to stationary manometry and can enhance our knowledge and understanding of the physiology and pathophysiology in different conditions.

The EndoFLIP was primarily used in the esophagus to evaluate the esophago-gastric junction in patients with gastroesophageal reflux disease and achalasia. Over the past decade, the spectrum extended not only to other esophageal conditions such as eosinophilic esophagitis but also to further locations of the GI tract, mostly to the

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stomach for pylorus measurements or to the pharyngeal and anorectal region. Moreover, an interesting perspective for the use of EndoFLIP seems to be prior to and/or after esophageal interventions and surgery to tailor the specific procedure (surgical myotomy, peroral endoscopic myotomy, fundoplication).

The EsoFLIP is a therapeutic modification of EndoFLIP that combines the advantage of both a diagnostic and a therapeutic tool. It is currently being evaluated as an alternative device for dilation of functional and structural stenoses in the GI tract.

Emerging evidence supports the use of distensibility testing with FLIP as a complementary method in numerous clinical scenarios, where standard functional testing fails to conclude the final diagnosis or direct the therapy. Together, EndoFLIP and EsoFLIP bring a new approach combining diagnostic and interventional measures in the endoscopy suite, which can be referred to as interventional functional diagnostics.

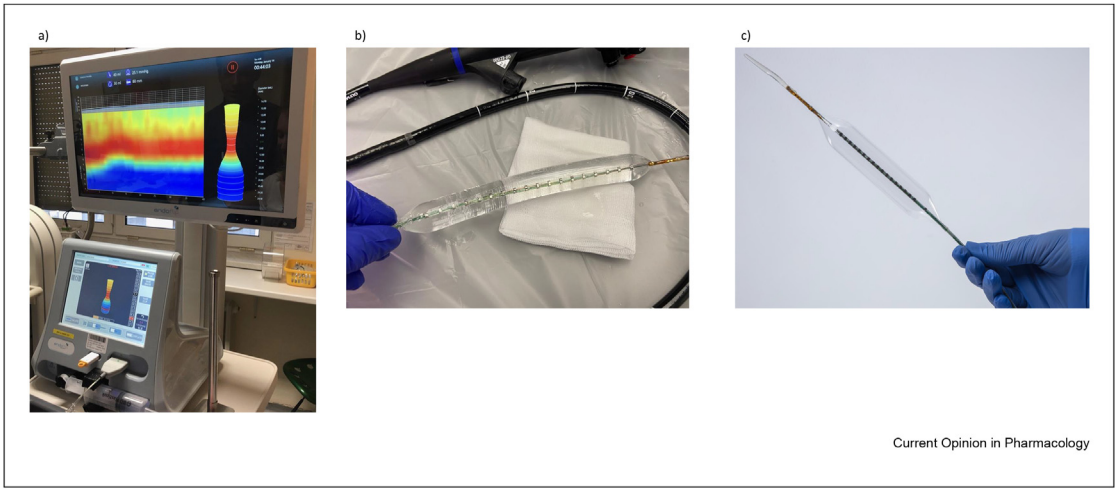
The aim of this narrative review is to introduce the current evidence and potential use of the FLIP technology in clinical practice.

Technology of impedance planimetry and distensibility measurements

Distensibility measurements are based on the principle of impedance planimetry. The EndoFLIP array consists of a 24 cm long 3 mm outer diameter catheter with a highly compliant balloon attached to its tip surrounding 16 paired impedance electrodes mounted on the catheter and a solid-state pressure transducer on the distal end of the catheter. The balloon catheters are available in 2 different lengths—the EF-322 (16 cm) and EF-325 (8 cm) (Figure 1). During examination, the balloon is filled with a conductive solution (0.3 % NaCl for EF-325 and 0.75 % NaCl for EF-322). Excitation electrodes at either end of the balloon emit a continuous low electric current and the voltage is measured across the paired impedance electrodes by leveraging Ohm's law (voltage is proportional to the impedance which is increasing with filling of the balloon) to provide luminal cross-sectional areas (CSA, mm^2) at intervals based on excitation electrode spacing [5–8]. The data from the pressure transducer, i.e. the intrabag pressure (mmHg), then allow for calculation of distensibility. Distensibility is represented by the main metric—distensibility index (DI, mm^2/mmHg) which refers to the ratio of the narrowest CSA to concurrent distension pressure at each distention volume [4]. The parameters provided or calculated by the EndoFLIP are: distensibility index [(DI), mm^2/mmHg], cross-sectional area [(CSA), mm^2], balloon diameter (mm), and intraballoon pressure (mmHg). The EndoFLIP screen image is presented as a 2D color-scale topographic map depicting the diameters throughout the measured area.

Prior to an upper GI FLIP study, a standard endoscopy usually with propofol sedation is performed for a visual examination of the mucosa and cleaning/emptying any esophageal or gastric content. After the endoscope has been withdrawn, the empty balloon catheter is introduced orally into the esophagus or further to the stomach and pylorus. Unlike in the esophagus, placing of the catheter to the pyloric sphincter requires endoscopic guidance and sometimes even the use of endoscopic forceps or snare to navigate the catheter through. The optimal position is reached when the balloon is

Figure 1



The EndoFLIP system with two different sizes of balloon catheters. **(a)** EndoFLIP system, **(b)** EF-322 catheter (16 cm), **(c)** EF-325 catheter (8 cm, electrodes spaced at shorter intervals than in EF-322).

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straddling either the esophago-gastric junction (if evaluating also the esophageal body with the EF-322, the EGJ pinch should be placed at the lower third of the balloon with the majority of sensors placed above the EGJ for motility assessment of the tubular esophagus) or the pylorus, which is graphically reflected in the EndoFLIP image as an hourglass shape (Figure 2). Exact positioning depends therefore on the balloon type and the area of interest. The image itself supports maintaining the correct balloon position during the whole procedure. The balloon is then automatically (but under direct supervision of the performing physician) filled via electro-hydraulic pump with conductive fluid to a baseline volume of 20–30 mL (depending on the balloon type) and, after stabilization of the image, a stepwise filling according to a proposed protocol is performed (the 16 cm balloon is filled initially to 30 mL and then by increments of 10 mL to 40, 50, 60 and if necessary to 70 mL, the 8 cm balloon is filled to 20 mL followed by stepwise filling to 30, 40 and 50 mL, at each volume a period of 30–60 s for observing should be included before proceeding or obtaining the measured values) [9]. Besides the diameter topography image, the monitor also displays the values of the measured and calculated parameters (diameter, CSA, distensibility index, pressure) at designated filling volumes. The additional time necessary for distensibility measurements of the distal esophagus and the EGJ to standard endoscopy is approximately 6 – 8 min [10]. Ideally, an assistant operates the FLIP and records the data allowing the endoscopist to focus on the scope and balloon placement adaptation as needed.

EndoFLIP: the diagnostic catheter

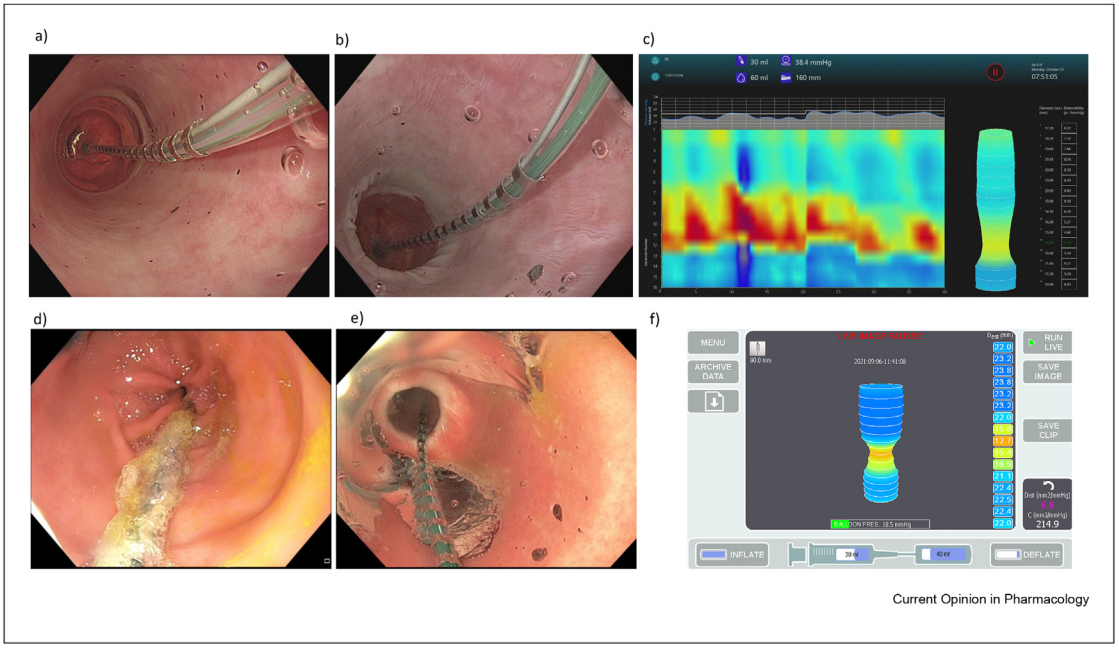
Use of the EndoFLIP in the esophagus

The pioneer studies of distensibility measurements in the esophagus were evaluating the esophago-gastric junction [3,4]. Since then, the spectrum of areas investigated in various esophageal pathologies expanded.

Normal esophageal motility

The FLIP depicts the luminal dimensions of the esophagus including the opening characteristics of the EGJ as well as the secondary peristalsis induced by distension of the balloon in the so-called FLIP panometry. The normal EGJ distensibility values in healthy volunteers (or asymptomatic controls) have been evaluated in several but small and heterogenous case series. In 35 healthy volunteers, the median value for EGJ-DI (at 60 mL) was 5.8, and in all volunteers the DI was ≥3 and thus was classified as normal [11]. The lower cutoff for EGJ-DI is reported to be between 2.8 and 2.9 mm^2/mmHg [12–14], but the DI can be also affected by anesthesia and presence of the endoscope, making adherence to testing standards essential [15]. During esophageal measurements, the endoscope should be therefore retracted after balloon placement. Normal contractile response of the esophageal body to

Figure 2



EndoFLIP used for distensibility measurement in the esophagus and in the pylorus. **(a + b)** Filled EF-322 catheter in the esophagus, **(c)** Secondary peristaltic response and diameter topography image with corresponding distensibility index on the EndoFLIP monitor at 60 mL filling volume, **(d)** insertion of the balloon catheter into the pylorus, **(e)** balloon filled at 40 mL, **(f)** diameter topography image with corresponding DI on the EndoFLIP monitor at 40 mL balloon volume—an hourglass shape, DI 6.9 mm^2/mmHg (in patient with gastroparesis).

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distension is represented by repetitive antegrade contractions (RACs), whereas repetitive retrograde contractions (RRCs) have been found almost exclusively in pathological conditions [16,17]. A classification of secondary esophageal peristalsis based on FLIP panometry has been proposed recently ([18]; Figure 3). The FLIP panometry classification was confirmed to correlate well with the manometric Chicago Classification [19].

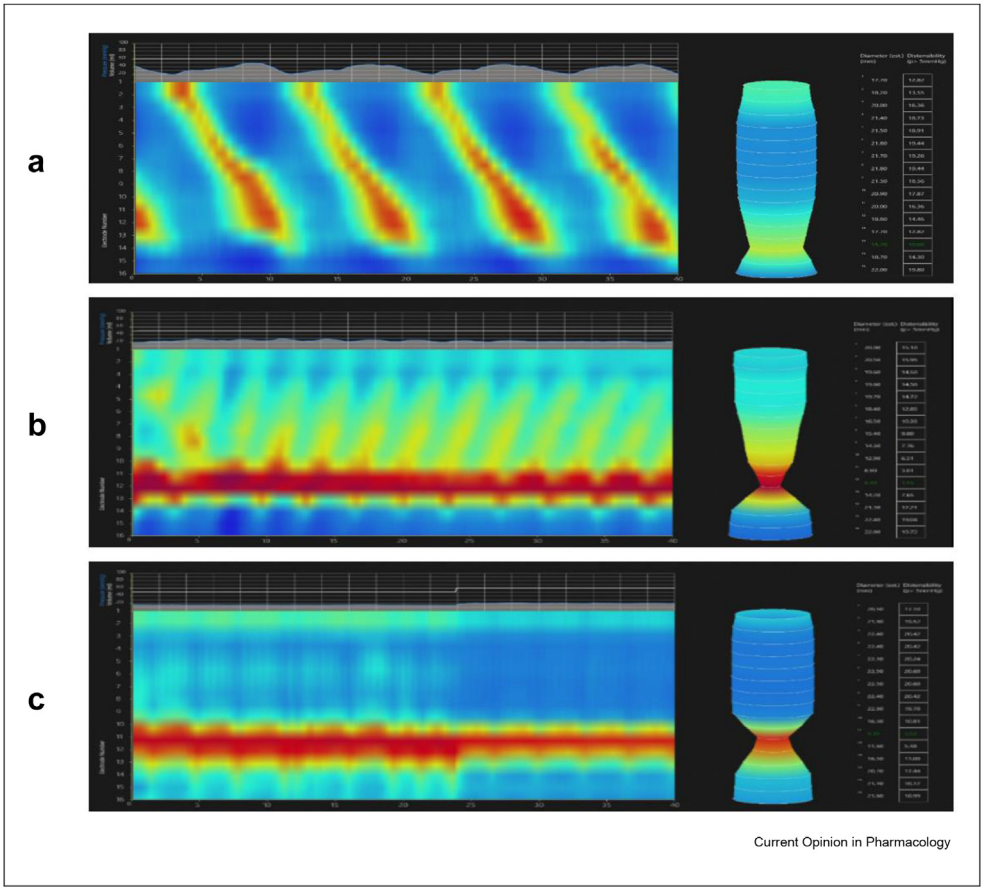
Gastroesophageal reflux disease (GERD)

Several studies addressed the use of EndoFLIP in patients with GERD to assess the impairment of the physiologic anti-reflux barrier. Although one of the studies showed increased EGJ distensibility in GERD patients compared to healthy volunteers [20], the results of the studies were inconsistent and there was a significant variability within the EGJ-DI values. Thus far, the EGJ-DI has not been found to be associated with objective parameters of pathological gastroesophageal reflux (acid exposure time, number of reflux episodes) [21] and the role of EndoFLIP in diagnosis and management of GERD patients is unclear.

Achalasia and esophago-gastric junction outflow obstruction (EGJOO)

FLIP has been shown to be highly sensitive in recognizing motility abnormalities in patients with an established diagnosis of achalasia [9]. Moreover, patients with clinically suspected achalasia but not meeting the HRM criteria of the Chicago Classification v 4.0 (integrated relaxation pressure, IRP >15 mmHg in supine position) [22] can be recognized by the FLIP by decreased EGJ-DI or abnormal esophageal contractions [16,23]. It has been suggested that the diagnosis of achalasia can be made reliably by the FLIP during the endoscopy without further need for high-resolution manometry [24].

Figure 3



Different secondary contractile response patterns during FLIP panometry. **(a)** Normal contractile response (NCR) with repetitive antegrade contractions (RACs) with normal EGJ opening (NEO). **(b)** Spastic-reactive contractile response (SRCR) with repetitive retrograde contractions (RRCs) with reduced EGJ opening (REO). **(c)** Absent contractile response (ACR) with aperistalsis and reduced EGJ opening (REO).

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Nevertheless, the HRM still remains gold standard diagnostic tool in assessing achalasia, with EndoFLIP providing additional information.

The role of EndoFLIP in evaluating the non-achalasia esophago-gastric junction outflow obstruction (EGJOO) in the single-procedure scenario has not been established yet. EGJOO is a manometric diagnosis with elevated IRP (and intrabolus pressure, IBP) and normal esophageal peristalsis harboring heterogenous clinical situations and requiring prove of EGJ obstruction by another functional method such as fluorosocopy or EndoFLIP to be considered clinically significant [21]. EndoFLIP can thus be crucial in clinical decision-making when combination of endoscopy and HRM is not conclusive whether the elevated IRP is the true cause of patients' obstructive symptoms. In the validation study of the EGJ-DI thresholds for clinically relevant EGJOO, 93 % (229/245) of patients with conclusive EGJOO had an EGJ-DI with maximum EGJ diameter 3.0 mm^2/mmHg or EGJ-DI 2−3 mm^2/mmHg with maximum EGJ-diameter >12 mm [11].

EndoFLIP can be also used to predict and assess the effect of treatment (dilation, endoscopic or laparoscopic myotomy) [14,25−29]. Besides that, it can be potentially combined with a therapeutic intervention within the index endoscopic procedure using the therapeutical dilation catheter EsoFLIP [30].

Eosinophilic esophagitis

In eosinophilic esophagitis (EoE), the chronic inflammation may lead to fibrous changes causing stiffening of the esophageal wall and formation of strictures. Localization of esophageal narrowing and dominant strictures can be illustratively detected with the FLIP. It has been demonstrated, that compared to healthy controls, patients with eosinophilic esophagitis have decreased esophageal compliance [31]. Moreover, the value of 225 mm^2 of the distensibility plateau (a calculated parameter reflecting the lowest CSA within the esophagus) was associated with lower risk of food impaction and need for dilation [32]. Therefore, a patient with suspected EoE stricture is another clinical scenario in which diagnostics and therapeutic intervention (dilation of the detected narrowest areas using the EsoFLIP) could be combined within one endoscopic session.

Esophageal surgery

EndoFLIP has been used during esophageal surgical procedures such as laparoscopic Heller myotomy in achalasia or anti-reflux surgery (fundoplication) to intraoperatively assess the distensibility of the esophago-gastric junction. This has been argued to adjust the length of the myotomy or tightness of the wrap to achieve the optimal clinical outcome, although very little outcome data are currently available. In fundoplication, the EGJ distensibility objectively decreases after the surgery with different values reflecting the type of wrap [33,34]. One study suggested, that an intraoperative EGJ-DI value between 2 and 3.5 mm^2/mmHg is associated with lower frequency of post-fundoplication dysphagia and less reflux symptom burden at follow up [35]. On the contrary, postoperative EGJ-DI < 2 mm^2/mmHg was associated with development of post-fundoplication dysphagia and the need for intervention [36−38]. A relevant issue is the standardization of data gathering in these patients, especially the role of pneumoperitoneum and use of opioids in analgosedation. All in all, the role of EndoFLIP as an intraoperative sizing tool is still in development.

Use of EndoFLIP in the stomach

Throughout the last decade increasing attention was brought to the distensibility testing of the pylorus as pylorospasm (decreased pyloric distensibility) seems to play a role in the pathophysiology in a relevant subset of patients with gastroparesis [39]. Thus, if identified, a pylorus-targeted treatment (such as dilation or G-POEM—(gastric peroral endoscopic myotomy) could help reduce patients' symptoms as well as the frustration from otherwise efficacy-limited therapeutical options available. The limitation that remains is the lack of an objective measurement method and definition for pylorospasm. Although the pyloric distensibility assessment with EndoFLIP seems to be promising for this purpose, so far available data on pyloric distensibility in gastroparesis as well as correlation with gastric emptying and symptoms vary significantly among published studies and thus EndoFLIP has not been advised by European Society of Gastrointestinal Endoscopy to select patients for pylorus-targeted therapy yet [40].

In the first published study evaluating the pyloric compliance in 21 healthy volunteers using an EF-325 catheter, the mean pyloric compliance was 25 ± 2.4 mm^2/mmHg at 40 mL filling volume vs 16.9 ± 2.1 mm^2/mmHg in patients with gastroparesis; $P < 0.05$ and vs 10.9 ± 2.9 mm^2/mmHg in patients after esophagectomy; $P < 0.05$, with 10 mm^2/mmHg set as a lower cutoff for the normal value [41]. Malik et al. assessed pyloric distensibility in 54 patients with mostly idiopathic and diabetic gastroparesis, the mean distensibility index was 10.7 ± 2.57 mm^2/mmHg, but a wide range of values for both distensibility (1−55 mm^2/mmHg) and diameter (5.6−22.1 mm) was observed [42]. A more recent study from India reported median pylorus distensibility index 8.37 mm^2/mmHg (interquartile range, 4.22−13.04 mm^2/mmHg) at 40 mL balloon volume in 20 healthy volunteers [43].

Snape et al. demonstrated that patients presenting with nausea and vomiting and confirmed delayed gastric emptying had decreased pyloric distensibility compared

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to patients with normal gastric emptying (8 mm^2/mmHg vs 12.4 mm^2/mmHg) [44]. Several other studies, including limited number of patients, reported the use of EndoFLIP to assess pyloric distensibility in patients with gastroparesis before and/or after treatment with balloon dilation, botulinum toxin injection or G-POEM [45–53]. For the purposes of the study, most of the authors used an upper cut-off of 9–10 mm^2/mmHg to define pylorospasm. The reported mean pre-treatment DI ranged between 5.3 and 16.9 mm^2/mmHg [39,49] and most of the studies confirmed significant increase in DI after the G-POEM and correlation with improved symptom score or clinical success [46,52–54]. Some results suggest that lower pre-treatment DI in patients with gastroparesis might be associated with better clinical outcome after G-POEM or dilation [55].

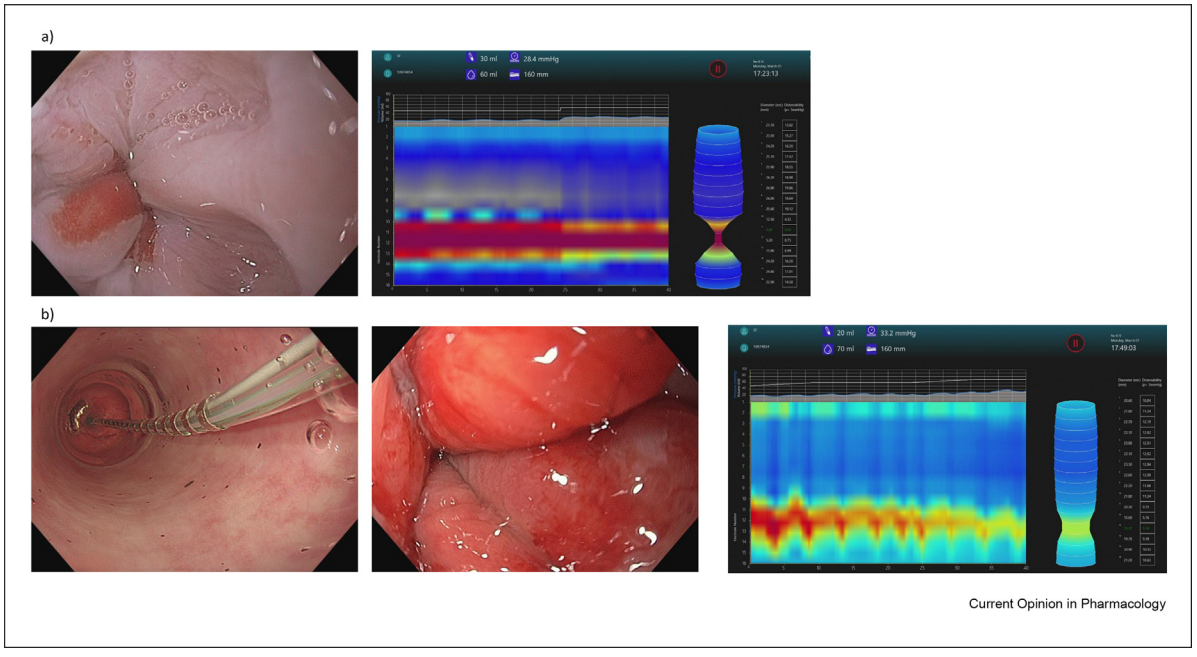
The inconclusive results from heterogenous studies only affirm the need of a prospective validation of the current cut-off values (either distensibility or CSA) to be conducted as the normative values of distensibility for the pylorus neither in healthy population nor in patients with gastroparesis have been established yet.

EsoFLIP: the therapeutic dilation catheter

Dilatation using bougie or balloon dilators is a widely used method for treatment of benign strictures throughout the gastrointestinal lumen with favorable efficacy and safety [56–58]. On the other hand, although the dilation is performed under fluoroscopic or endoscopic control, there is no control over the immediate impact on the luminal physical characteristics, and both visualizations have their limits. The EsoFLIP (Medtronic, Minnesota, USA) is a more recently developed therapeutic device for esophageal hydraulic balloon dilation. EsoFLIP uses the same hardware system and technology platform as EndoFLIP but comes with a stiffer, more robust balloon to generate sufficient pressure for dilation. This tool combines the advantage of direct visual control through the balloon during dilation and visualization of the shape of the dilated area with information on diameter of the stricture. Since the EsoFLIP balloon is rigid (to be able to achieve effective dilation), it does not allow real-time distensibility measurements and has no internal pressure control built in (can be attached via 3-way stopcock). Three sizes of the EsoFLIP catheters are now available – a 10 mm (ES-310) and 20 mm (ES-320) balloon for esophageal stricture dilation and a 30 mm (ES-330) balloon predominantly used in achalasia and esophago-gastric junction outflow obstruction (Figure 4).

Beyond the esophagus, EsoFLIP can be also used to dilate the pylorus or in theory any upper GI (e.g. anastomotic) strictures within its technical reach. The size of the catheter refers to the dilation balloon diameter

Figure 4



EsoFLIP used for dilation in patient with achalasia. **(a)** Endoscopic image of spastic EGJ prior to dilation with corresponding topographic image of diameters on EndoFLIP (EGJ-DI 0.64 mm^2/mmHg, diameter 4.8 mm). **(b)** Dilation with EsoFLIP, endoscopic image of EGJ after dilation, EGJ-DI increased to 5.54 mm^2/mmHg, diameter to 15.3 mm.

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with maximal filling, but it can also be used for smaller diameters as the filling volume is manually controlled via an electro-hydraulic pump and can be adjusted according to target diameter and intraprocedural behavior of the stricture. After initial measurement of the diameter and/or CSA at partial filling volume (20 mL for ES-320 and 30 mL for ES-330), we suggest gradual stepwise filling by 3 mL (ES-320) or 5 mL (ES-330) to approximately 30 mL/50 mL. It is then followed by additional filling of 1−3 mL at a time to reach the target diameter. The maximum possible filling volume of 42 mL/75 mL (ES-320/ES-330) is used if a maximum target diameter of 20/30 mm is aimed for. During the procedure the stricture and surrounding mucosa can be visually assessed by placing the tip of the endoscope gently on top of the balloon. After holding the target volume for 1−2 min, the balloon is then emptied, and post-dilation diameter and CSA can be measured to assess the treatment response. EndoFLIP distensibility measurement can be performed in addition prior to and directly after treatment during the same sitting.

There are several advantages to the dilation using the EsoFLIP system. Lumen assessment with EndoFLIP before dilation and/or with EsoFLIP during dilation can be used to objectively measure the diameter of the stricture. The planimetric assessment after dilation may prove useful to evaluate treatment response in the future; currently data are sparse [59]. The precisely controlled filling of the balloon enables dilation to a desirable diameter with usually one balloon only. Also, with the continuous control of the balloon position during dilation via visualization of the lumen and localization of the stricture on the EndoFLIP monitor, there is no need for fluoroscopy, thus reducing the radiation burden and need for such equipment.

Studies evaluating the clinical outcomes of the use of EsoFLIP for therapeutic dilatation are currently limited, but several small series (mostly in the esophagus, one in pylorus) showed technical feasibility, safety and at least good short-term efficacy [30,60−62]. The limitation for dilation in achalasia patients is the 30 mm maximum size of the balloon.

Summary

The EndoFLIP is a promising device for evaluation of sphincters and hollow organs, extending the functional assessment beyond the simple measurement of pressure by providing real-time dynamic monitoring of distensibility, luminal geometry and biomechanical properties to enhance our knowledge of both, physiology and pathophysiology of these structures. The EndoFLIP was originally utilized as a diagnostic tool in the esophagogastric junction, but the application spread to other locations including the esophageal body, upper esophageal sphincter, pylorus and the anal sphincter. Recently, the proposed classification of esophageal FLIP panometry showed good correlation with the manometric Chicago Classification [19] which could, in certain cases, simplify the diagnostic process where diagnosis is made during the initial endoscopy or moreover to combine the diagnostic and treatment procedure into a single session when dilation is the treatment of choice. The distensibility measurement can also guide tailoring of specific endoscopic and surgical therapies (dilation, fundoplication, myotomy etc.) to reach optimal clinical outcomes. The EsoFLIP is a therapeutic modification of the catheter enabling hydraulic balloon dilation that showed to be safe and effective in preliminary studies.

Although research is progressing, the published data lack proper prospective validation studies and together with the relatively high costs of the EndoFLIP system as well as related catheters plus a lack of dedicated analysis software, its use in daily clinical practice is limited to mostly highly specialized centers. So far, the international guidelines do not recommend standard use of distensibility measurements as a part of the diagnostics or treatment yet, but it can be considered in ambiguous cases (i.e. achalasia with low IRP) and to assess pylorospasm in gastroparesis [61]. The future direction should primarily aim to standardize the measurement protocol, to determine and validate the normative values in health and disease (also with respect to sedation used) and to focus on the utilization in the therapeutic setting. After all, such interventional functional diagnostics is a promising new field allowing patient-friendly diagnostic measures and therapeutic procedures in single session.

Editorial disclosure statement

Guest Editor, Daniel Pohl had no involvement in the peer review of the article and has no access to information regarding its peer-review. Full responsibility for the editorial process of this article was delegated to Tim Vanuystel.

Declaration of competing interest

Zuzana Vackova - none.
Ian Levenfus - none.
Daniel Pohl − consultant for Medtronic.

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* of special interest
** of outstanding interest

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