ORIGINAL PAPER

Esophageal biomechanics assessed by impedance planimetry (EndoFLIP™) in healthy subjects and in patients with eosinophilic esophagitis. Normality values

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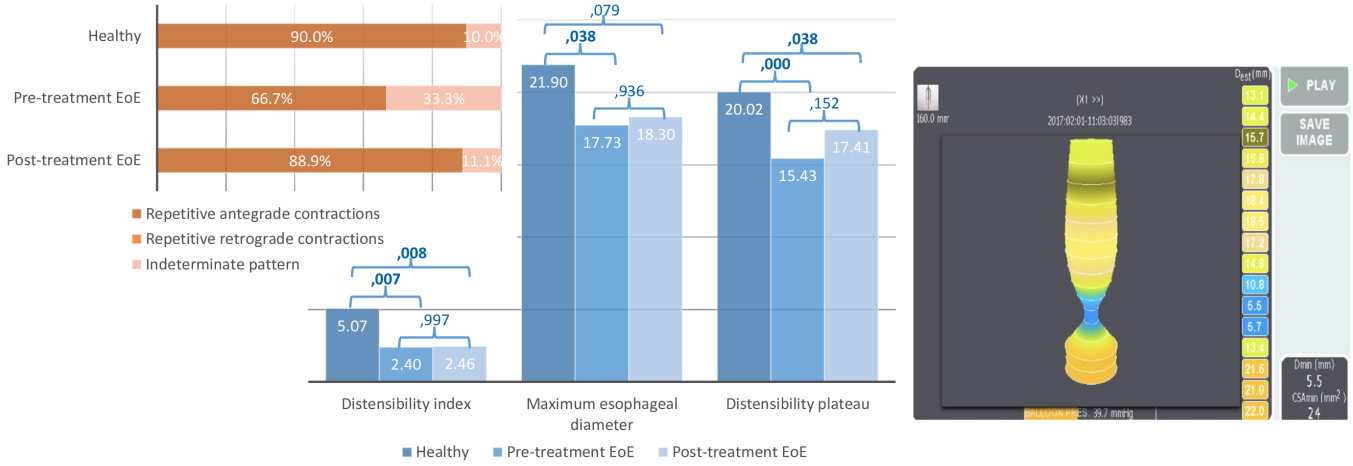
ESOPHAGEAL BIOMECHANICS ASSESSED BY IMPEDANCE PLANIMETRY (EndoFLIP™) IN HEALTHY SUBJECTS AND IN PATIENTS WITH EOSINOPHILIC ESOPHAGITIS. NORMALITY VALUES.



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Lay summary

Eosinophilic esophagitis is an inflammatory disease that affects the esophageal wall and prevents the patient from eating normally, and is reversible with appropriate treatment. In this study we analyzed and compared different properties of the esophageal wall using a device called EndoFLIP™ both in healthy people and in patients with eosinophilic esophagitis before and after a 6-week treatment with a swallowed topical corticosteroid. Ten healthy volunteers and 9 patients with eosinophilic esophagitis were included. We observed that esophageal contractions are the same in healthy subjects and in patients with eosinophilic esophagitis, while the ability of the esophagus to dilate and its diameter are decreased in patients, even after treatment, which may be due to the fact that 6 weeks is a short time. to see changes in this aspect. On the other hand, this is the first study in our environment that provides normal values for these esophageal measurements.

ABSTRACT

Background: active eosinophilic esophagitis is associated with esophageal caliber, distensibility and motility changes that may be reversed with treatment.

Objectives: to study esophageal diameter, distensibility and contractility in healthy subjects compared to patients with eosinophilic esophagitis, both before and after treatment.

Methods: a quasi-experimental study, EndoFLIP™, was used to analyze the esophageal body and esophago-gastric junction (EGJ) in all three groups, and a program was designed to obtain esophageal diameter, distensibility and contractility values.

Results: ten healthy volunteers (24-61 years, six men) and nine patients with eosinophilic esophagitis (21-52 years, seven men) were included. The esophagogastric junction distensibility index was 5.07 mm^2/Hg in the control subjects, 2.40 mm^2/Hg in the subjects with eosinophilic esophagitis before treatment and 2.46 mm^2/Hg after treatment. The distensibility plateau was 20.02 mm, 15.43 mm and 17.41 mm, respectively, and the diameter was 21.90 mm, 17.73 mm and 18.30 mm, showing significant differences ($p < 0.05$), except between control subjects and patients after treatment ($p = 0.079$). Repetitive antegrade contractions developed in 90 % of control subjects, 66.7 % of eosinophilic esophagitis patients before treatment and 88.9 % of the latter after treatment ($p > 0.05$).

Conclusions: esophago-gastric junction distensibility index, distensibility plateau and diameter values were higher in controls than in patients, although six weeks of treatment seems a short period to observe significant changes in esophageal biomechanics. Repetitive antegrade contractions are the predominant pattern in healthy subjects and eosinophilic esophagitis. We provide normality values for esophageal biomechanics, measured by impedance planimetry in our setting.

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Keywords: Esophagus. Esophagogastric junction. Dysphagia. Eosinophilic esophagitis. Motor activity. Distensibility. Diameter.

INTRODUCTION

The EndoFLIP™ (Medtronic, Minneapolis, USA) impedance planimetry system measures biometric parameters of the gastrointestinal lumen, which allows an increasing understanding of the biomechanical properties of gut segments from a different perspective than esophageal manometry (1-4).

In the esophageal setting, the most commonly used parameters include: distensibility index (DI), defined as the ratio of the mean cross-sectional area (CSA) at the narrowest point to the mean pressure (P) recorded by the balloon at that same point (ID = CSA in mm^2/P in mmHg); distensibility plateau (DP), defined as the value from which the lumen diameter no longer expands when increasing balloon volume, whereas intraluminal pressure does increase; esophageal diameter; and contractile response to esophageal distension (secondary peristalsis) (4), with contraction at the esophageal body being defined as the occurrence of a transient decrease in luminal diameter ≥ 5 mm on ≥ 3 consecutive channels. Contractions are categorized as: repetitive antegrade contractions (RACs) (≥ 3 consecutive antegrade contractions), and repetitive retrograde contractions (RRCs) (≥ 3 consecutive retrograde contractions).

The data collected by the EndoFLIP™ system must be appropriately processed using programs to filter the changes in diameter associated with esophageal contractions (1,3). Different methods and protocols are available for using EndoFLIP™ according to the condition under study and the data needed (1). Normality values are based on a small series of healthy control subjects, which are unavailable in our setting (2).

Eosinophilic esophagitis (EoE) is a chronic immune-mediated inflammatory disease characterized by a predominantly type-2 inflammatory response that favors eosinophil and mast cell recruitment towards the esophagus (5,6). It primarily affects younger males (7-9) and is characterized by increased eosinophils in the esophagus and esophageal dysfunction complaints (10-12). Treatment is based on proton-pump inhibitors (PPIs), oral topical corticosteroids (STCs) and empiric elimination diet (EED) (13-17). Active EoE is associated with changes in contractility and reduced caliber and distensibility in the esophagus and esophago-gastric junction (EGJ), which may regress or improve with effective treatment. We believe that these variations may be identified using impedance planimetry.

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This study analyzed the most relevant parameters of esophageal biomechanics (diameter, distensibility, contractile activity in response to distension) in both healthy subjects and patients with eosinophilic esophagitis, before and after treatment with STCs, to establish normality values by impedance planimetry, changes induced by eosinophilic esophagitis and the potential use thereof in the follow-up and objective assessment of treatment response.

MATERIAL AND METHODS

A quasi-experimental study was designed in patients consecutively diagnosed with EoE as per the established criteria (13), with active disease, at Hospital Universitario de La Princesa (Madrid, Spain) and Hospital General de Tomelloso (Ciudad Real, Spain). The study protocol was approved on December 29, 2017 by the Research Ethics Committee of Hospital Universitario de La Princesa (registration number 3301, certificate number 22/2017).

Patients were enrolled from January through December 2018. All the subjects included in the study provided informed consent. Data regarding the various variables were obtained from the available medical records, as well as from endoscopy findings, histological studies and impedance planimetry results. The research study was carried out in accordance with the tenets of the Declaration of Helsinki.

The inclusion criteria were as follows. Control group: volunteers older than 18 years, men and non-pregnant women, with no history of esophagogastric surgery or disease, willing to participate in the study, who underwent oral panendoscopy for reasons other than esophageal disease, where endoscopy showed a normal esophagus. EoE group: older than 18 years, men and non-pregnant women, with a verified diagnosis of EoE, with no other known conditions and no history of esophagogastric surgery. Symptoms were assessed using the Dysphagia Symptom Score (DSS) (18). Patient quality of life was measured with the Spanish adapted version of the quality of life questionnaire for patients with EoE (EoE-QoL-A) (19), administered at baseline (with active disease) and after six weeks of treatment with orodispersible budesonide tablets (1 mg twice a day). Endoscopic findings were graded according to endoscopic reference score (EREFS) for EoE (20).

Endoscopy and EndoFLIP™

Endoscopies were performed with high-resolution gastroscopes under sedation with propofol, and biopsy samples were taken from both the distal and proximal esophagus. Prior to collecting these biopsy samples, measurements were made with EndoFLIP™, using a 16-cm probe (EF-322N), as previously described (3,21-25). After calibration at atmospheric pressure (Fig. 1), the catheter was orally inserted into the esophagus, ensuring that it advanced past the EGJ (Fig. 2). After filling the balloon with 20 ml of conductive solution, the catheter was fixed in place, leaving 2-3 electrodes inside the gastric cavity, and the balloon was further progressively filled in 5-ml steps, remaining for 20-30 seconds in each step. The procedure ended when 60 ml was infused or the balloon pressure reached 45 mmHg (whatever occurred first). The balloon was then emptied and removed. All recordings were then saved for subsequent analysis.

The data obtained by EndoFLIP™ were analyzed by a program developed by the data analysis unit of Hospital Universitario de La Princesa based on the method by Carlson et al. (3) with the modifications that were deemed appropriate (Fig. 3).

One patient was withdrawn from the study because of an unstable recording, which prevented a proper DP from being obtained. This may happen when pressure changes occur that do no match volume changes, when catheter mobility precludes establishing which electrodes should be analyzed, or when the balloon is advanced too far into the stomach with very few channels remaining in the esophagus.

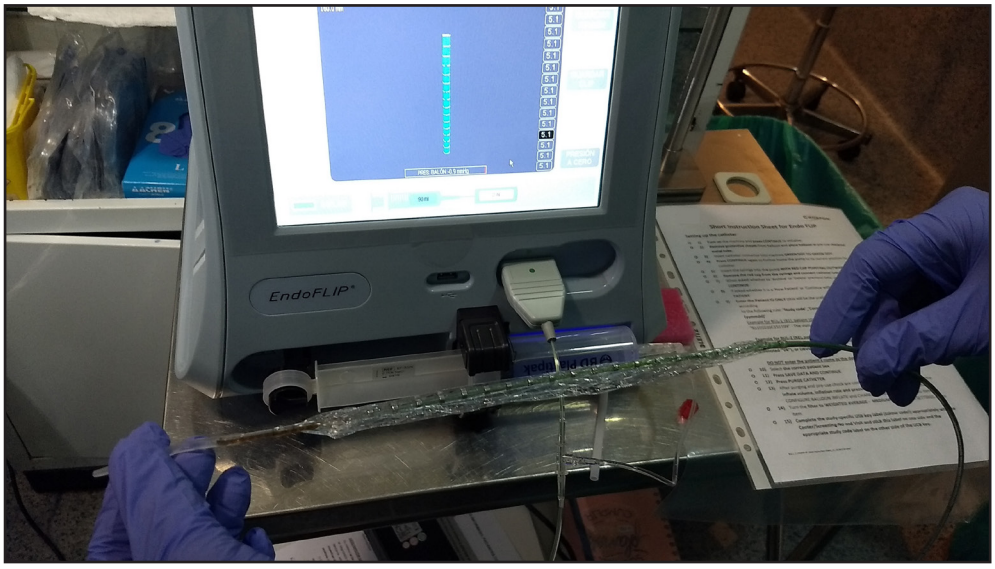

Fig. 1. *EndoFLIP™ device (catheter and monitor with calibration image prior to the study).*

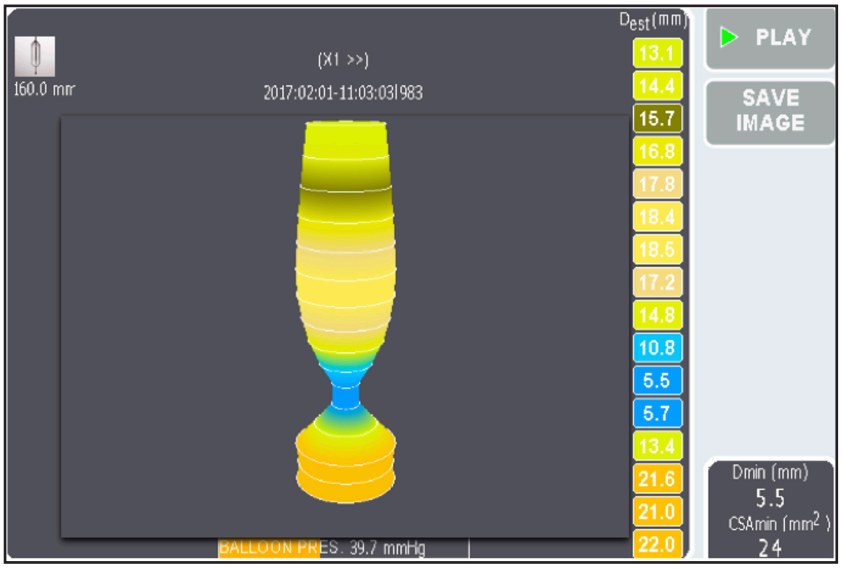

Fig. 2. *EGJ identification at 30 ml, represented as the narrowest region, in blue, in the display.*

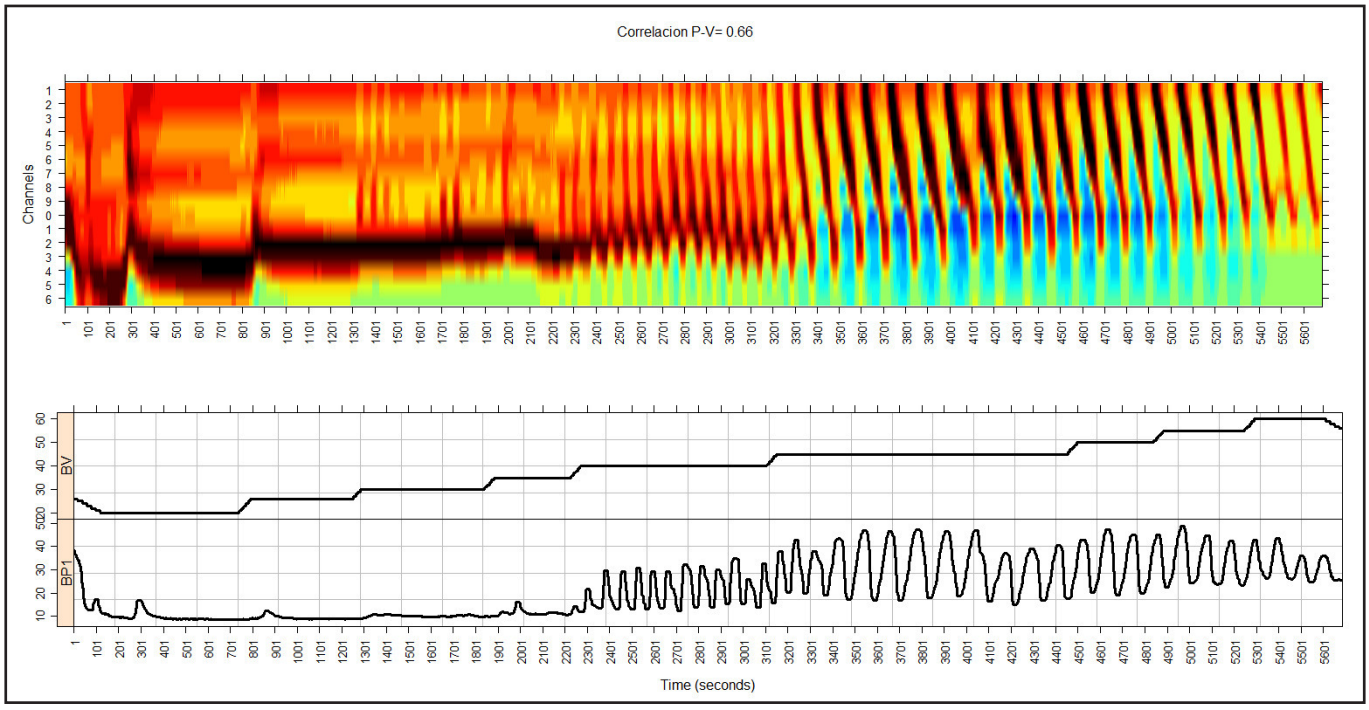

Fig. 3. *Heatmap and pressure and volume curves obtained via the analysis of the data collected by EndoFLIP™ by the Data Unit at the Hospital Universitario de La Princesa.*

Statistical analysis

Using the Epidat 3.1 system, in order to assess differences in esophageal distensibility between patients with EoE and control subjects with a power of 80 %, ten patients and ten controls are required, based on the 2013 study by Nicodeme et al. (21). Categorical variables were expressed as number of cases and percentage; continuous variables were expressed as median and interquartile range. Total sample characterization (controls *vs* cases), treatment effect on each variable, and differences between patients with reduced and normal distensibility were compared using the Mann-Whitney U-test or the Chi-squared test when necessary. A *p*-value < 0.05 was considered as statistically significant. The statistical analysis was performed using the SPSS version 20.0 software.

RESULTS

The reference group for EndoFLIP™ values comprised ten volunteers without esophageal disease (60 % male) with a mean age of 31.9 years (range: 24-61 years) and a mean body mass index (BMI) of 23.08 kg/cm^2 (range: 17.51-27.07 kg/cm^2). Nine patients with EoE (seven male) were included, with a mean age of 36.22 years (range: 21-52 years) and a BMI of 22.2 kg/cm^2 (range: 18.42-25.62 kg/cm^2). Mean symptom duration was 73.25 months.

No significant differences were reported between both groups in terms of age or BMI. Regarding their past history, 1 control and 6 patients had previously had rhinitis (p = 0.017), 0 and 4 asthma (p = 0.033), 0 and 3 dermatitis (p = 0.087) and 1 and 3 food allergies (p = 0.249), respectively. No cases or controls had a family history of EoE. Table 1 lists the symptoms, quality of life, endoscopic characteristics, eosinophil infiltration and EndoFLIP™ findings in controls and patients with EoE both before and after treatment.

Differences were obtained between control subjects and EoE cases (both before and after treatment) in EGJ DI (5.07 mm^2/Hg *vs* 2.40 mm^2/Hg and 2.46 mm^2/Hg), DP (20.02 mm *vs* 15.43 mm and 17.41 mm) and esophageal diameter (21.90 mm *vs* 17.73 mm and 18.30 mm). The values of all parameters were higher among normal controls. Differences in DP between controls and patients in remission achieved statistical significance (p = 0.038) whereas differences in maximum diameter did not (p = 0.079).

Regarding, esophageal contractile activity, RAC patterns were seen in nine of ten controls (90 %), with no RRCs reported in any of them. At least two distinct patterns may seemingly be perceived regarding the shape of this motor activity. A predominant form is observed, where antegrade waves are seen with increases in volume, with a tendency towards higher baseline pressures in the esophageal body and a lower rate of contractions with greater EGJ diameters in most studies. Albeit, this behavior disappears with the highest volumes at the end. The other pattern is less common, with predominant simultaneous waves, where increases in baseline pressure at the esophageal body are more irregular, a lower EGJ response is observed and the highest volumes for the final recordings elicit a disjointed response.

Regarding esophageal motor activity in patients with EoE, RACs were seen in six of nine patients with EoE during the activity phase (66.7 %), and eight of nine patients with EoE after treatment (88.9 %) (p > 0.05). Furthermore, no RRCs were observed in any of the patients with EoE. When considering the shape of this motor activity in this case, it is more irregular than in controls. On the one hand, a similar pattern to that predominant in the control group was seen, but the number of triggered waves was lower at high volumes and their amplitude was greater. A pattern consisting of simultaneous waves with a highly variable response at higher volumes may also be seen. No complications were recorded in association with the use of EndoFLIP™ in any of the procedures performed.

Table 1. *Symptoms, endoscopic characteristics, eosinophil infiltration and data collected by EndoFLIP™ in control subjects and in patients with eosinophil esophagitis (EoE) both before and after treatment*

	Control	Pre-treatment EoE	Post-treatment EoE	*p* control *vs* pre	*p* control *vs* post	*p pre vs post*
DSS	NA	10.56	3.00	NA	NA	NA
EoEQoL	NA	2.53	3.24	NA	NA	NA
EREFS	NA	3.78	0.78	NA	NA	NA
Eos/hpf, proximal	NA	21.78	0	NA	NA	NA
Eos/hpf, distal	NA	47.22	0	NA	NA	NA
Maximum EGJ diameter	28.90	24.51	24.22	0.317	0.274	0.995
EGJ DI 60 ml	5.07	2.40	2.46	0.007	0.008	0.997
Plateau	20.02	15.43	17.41	0.000	0.038	0.152
Mean diameter 60 ml	16.07	14.89	14.79	0.412	0.353	0.993
Minimum diameter 60 ml	8.16	8.01	8.72	0.998	0.978	0.967
Maximum diameter 60 ml	21.90	17.73	18.30	0.038	0.079	0.936
Occlusive contractions onset	31.00	27.14	31.00	0.825	1	0.872
Occlusive contractions end	53.50	42.14	55.00	0.098	0.963	0.118
Volume at RAC onset	36.11	36.67	43.12	0.764	0.464	0.205
Volume at RAC end	58.00	49.37	56.87	0.138	0.964	0.250
Minimum pressure change	11.48	22.46	17.72	0.093	0.438	0.645
Maximum pressure change	16.73	28.76	25.05	0.097	0.307	0.802

DSS: Dysphagia Symptom Score; EoEQoL: Eosinophilic Esophagitis Quality of Life; EREFS: eosinophilic esophagitis endoscopic reference score; Eos/hpf: number of eosinophils per high-power field; EGJ: esophago-gastric junction; EGJ DI: EGJ distensibility index; RACs: repetitive antegrade contractions; NA: not applicable.

DISCUSSION

We provide the first normality values for esophageal biomechanics as measured by impedance planimetry in our setting. EGJ DI, DP and maximum esophageal diameter values were as previously described or higher (2,4), and esophageal diameter and distensibility values at the EGJ were higher in healthy subjects than in patients with EoE, the latter improving with treatment.

Among our patients with EoE, male sex, age 20 to 50 years and atopic comorbidities were more common (rhinitis, asthma, dermatitis, food allergies) than among controls, as described in other studies (7,26). In patients with EoE, treatment improved symptoms, quality of life and endoscopic scores, and reduced eosinophil count. In fact, endoscopic findings went back to normal, as reported in other studies (27-29).

A lower DP has been associated with more endoscopic findings that are characteristic of the fibrostenotic pattern of EoE (33), more esophageal impaction events in the past, the need for more endoscopic dilations and the use of corticosteroids. Prior studies indicate that patients with active EoE have an EGJ DI similar to that of patients with esophageal motor disorders (3,4,30,31). Hence, it may be claimed that not only the esophageal body but also the EGJ are involved in EoE (32,33). Confirming this characteristic is highly relevant for gaining insight into the pathophysiology of dysphagia in this group of patients, and for considering alternative therapies in patients with persisting dysphagia, despite histological response (21), including endoscopic EGJ dilation.

In patients with EoE, DP increases with therapy; this DP improvement is associated with improvement of the endoscopically observed fibrostenotic pattern (1,30) and clinical improvement (23), as reported by other studies. Therefore, distensibility offers a clinically relevant, quantitative assessment of disease activity (34). In our study, in patients with EoE EGJ DI, DP and esophageal diameter improved with STC treatment within six weeks. However, such improvement lacked significance and scores remained nowhere near those of control subjects. This can be interpreted as treatment for such a short period cannot reverse the deeper, chronic changes undergone by the esophageal wall, and treatment should be maintained longer to induce further regression, as described in studies where corticosteroids were administered long-term (29).

Regarding esophageal contractility, our study confirmed that a normal contractile response to esophageal distension in healthy subjects and patients with EoE will show a RAC pattern every 6-10 seconds (30), which in most cases will persist for over ten seconds (2). A "rule of sixes" has been described, with a normal response to esophageal distension defined as the presence of > 6 antegrade contractions that extend for at least 6 cm with a frequency of 6 ± 3 per minute. This contractile response was exceptional in patients with esophageal conditions such as achalasia, where contractility and RACs are absent, and even RRCs are seen that are not observed in controls (3,30,35).

Regarding study limitations, a small sample size must be highlighted, which is justifiable because of the inherent difficulties when using a technique outside the scope of routine clinical practice, and because EoE is an uncommon disease. Other potential biases include the unknown effect that propofol and the various doses used for sedation may have had on EndoFLIP™ results, as described in other studies (3), and the potential for uncontrolled catheter drifting. Another study limitation is that enrolled patients had no esophageal manometry recordings, either before or after treatment. Hence, we cannot relate EndoFLIP™ findings to potential esophageal motility changes as measured using manometry.

To conclude, esophageal examination with the EndoFLIP™ system is a safe technique that provides information on the esophagus, both at the functional and mechanical levels. Our study is the first one to provide normality values for esophageal biomechanics with this technique in our setting. Esophageal biomechanical changes in patients with EoE are more closely related to distensibility than with contractile response to distension. The fact that we did not find a lower EGJ DI in patients with EoE, a finding described only in patients with primary esophageal motor disorders, such as achalasia and EGJ outflow obstruction, deserves highlighting. In this regard, while our study could not compare its findings with manometry results, these are distinct techniques used under different conditions that provide supplementary information on esophageal clearance. They assess different characteristics (contractility and distensibility-diameter), with manometry focusing on the assessment of deglutition-induced primary peristaltism, whereas EndoFLIP™ evaluates repetitive contractions in response to balloon-induced esophageal distension.

In our study, improvement with treatment was neither consistent nor concordant with clinical manifestations, endoscopic findings or biomechanical parameters, which might be related to the variability in disease presentation and the "short" six-week duration of treatment for a review with impedance planimetry. Further studies are needed to establish follow-up criteria and the technique's usefulness for both the diagnosis and follow-up of patients with EoE.

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