

## Pressure dynamics of the esophagogastric junction at rest and during inspiratory maneuvers after Nissen fundoplication

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**SUMMARY.** Low sphincter pressure and inability of the crural diaphragm to elevate it at the esophagogastric junction are important pathophysiological mechanisms of gastroesophageal reflux disease (GERD). The object of this study was to depict how Nissen fundoplication changed the resting and inspiratory pressures of the anti-reflux barrier. We selected 14 patients (eight males; mean age 42.7 years; mean body mass index 27.8) for surgery. They answered symptoms questionnaires and underwent high-resolution manometry (HRM) before and 6 months after Nissen fundoplication. We used a standard manometric protocol (resting and liquid swallows) and assessment of esophagogastric junction (EGJ) pressure metrics during standardized forced inspiratory maneuvers against increasing loads (Threshold Maneuvers). We used the Wilcoxon test for comparison of pre and postoperative data. After fundoplication, heartburn and regurgitation scores diminished remarkably (from 4.5 and 2, respectively, to zero;  $P = 0.002$  and  $P = 0.0005$ , respective medians). Also, the median expiratory EGJ pressure had a significant increase from 8.1 to 18.1 mmHg ( $P = 0.002$ ), while mean respiratory pressure and EGJ contractility integral (EGJ-CI) increased without statistical significance ( $P = 0.064$  and  $P = 0.06$ , respectively). Axial EGJ displacement was lower after fundoplication. The EGJ relaxation pressure ( $P = 0.001$ ), the mean distal esophageal intrabulbus pressure ( $P = 0.01$ ) and the distal latency ( $P = 0.017$ ) increased after fundoplication. There was a reduction in the contraction front velocity ( $P = 0.043$ ). During evaluation with standardized inspiratory maneuvers, the inspiratory EGJ pressures (under loads of 12, 24, 36 and 48 cmH<sub>2</sub>O) were lower after surgery for all loads (median for load 12 cmH<sub>2</sub>O: 145.6 vs. 102.7 mmHg;  $P = 0.004$ ). Fundoplication and hiatal closure increased the expiratory EGJ pressure and promoted a great GERD symptom relief. The surgery seemed to overcompensate a reduced EGJ mobility and inspiratory pressure.

**KEY WORDS:** diaphragm, esophagogastric junction, gastroesophageal reflux disease (GERD), high-resolution manometry, Nissen fundoplication.

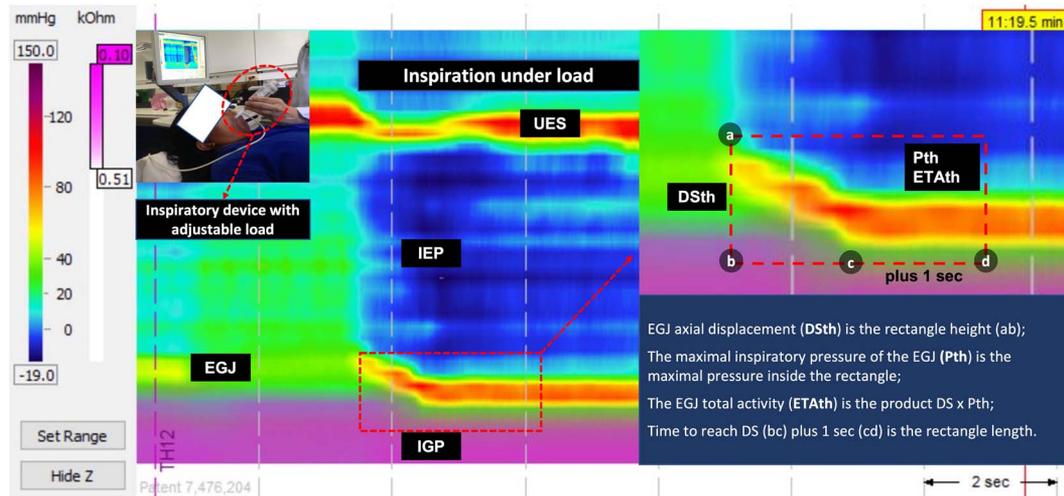
### INTRODUCTION

The pathophysiological mechanisms involved in gastroesophageal reflux disease (GERD) may be explained by a dysfunction of the anti-reflux barrier at the esophagogastric junction (EGJ),<sup>1</sup> with the consequent appearance of symptoms and mucosal injury. Lower esophageal sphincter (LES) incompetence, functional deterioration of the LES and anatomical alterations at the EGJ were associated with long standing GERD.<sup>2</sup> The EGJ provides an efficient barrier in healthy people. The crural diaphragm (CD) and the tonic pressure of the LES are essential components of the anti-reflux barrier.<sup>3</sup> Some studies have shown that a dysfunctional CD,

which fails to increase the inspiratory EGJ pressure, was an independent predictor of GERD.<sup>4,5</sup> Some patients with GERD have a lower inspiratory EGJ pressure that does not increase after inspiratory loads, suggesting a crural deficit.<sup>6</sup> Laparoscopic Nissen fundoplication is the gold-standard surgical procedure for the treatment of GERD, with a success rate of 90% in 5 years.<sup>7–10</sup> The surgical technique involves a gastric wrap over the distal esophagus and a hiatal closure due to approximation of the crura branches. Therefore, fundoplication may alter the EGJ manometric dynamics. High-resolution manometry (HRM) can evaluate the EGJ for its functional (inspiratory/expiratory pressures, swallow relaxation) and morphological (LES—CD separation, EGJ

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**Fig. 1** A typical inspiratory maneuver during esophageal HRM, under 12 cmH<sub>2</sub>O load (TH12): A patient performing the maneuver (upper-left corner); a detail of the EGJ descent and pressure response and the definitions of the EGJ metrics during the maneuver (right); the pressure profile from the pharynx to the proximal stomach during the maneuver (central). The transdiaphragmatic pressure is IGP minus IEP. EGJ, esophago-gastric junction; IEP, minimal intraesophageal pressure; IGP, maximal intragastric pressure; UES, upper esophageal sphincter.

**Table 1** Demographics, esophageal acid exposure, esophagitis grade of the volunteers, hiatal hernia and manometric CD-LES separation before fundoplication.

Gender	Age (year)	Weight (kg)	Height (cm)	BMI (kg/cm <sup>2</sup> )	AET (%)	Esophagitis (LA)	HH (cm)	CD-LES (cm)
F	57	61	144	29.5	10.7	B	0	0
F	26	63	156	25.9	5.4	B	2	0
F	32	69	153	29.5	15.3	A	3	1
F	62	62	148	28.3	12.7	A	4	3
F	38	67	155	27.9	8.1	C	3.5	3.8
F	55	80	155	33.3	6.2	B	5	3.9
M	43	88	172	29.8	10.3	A	0	0
M	44	73	172	24.0	8.9	B	3	0
M	45	72	170	24.9	18.6	C	3	0
M	47	80	160	31.3	8.6	Barrett	2.5	0
M	27	57	158	22.6	5.6	B	4	3
M	30	89	167	31.9	10.3	C	2	1.7
M	57	57	158	22.6	4.4	A	3.5	2.1
M	36	79	169	27.7	18.1	A	4.5	4.3
Mean	42.8	71.1	159.8	27.8	10.9	—	—	—
SD	11.8	10.8	8.9	3.4	4.5	—	—	—

BMI, body mass index; CD-LES, crural diaphragm-lower esophageal sphincter separation on manometry; HH, hiatal hernia (endoscopy); LA, Los Angeles classification; SD, standard deviation.

Inspiratory EGJ metrics were further obtained during the standardized inspiratory maneuvers. During each inspiratory load, the maximal inspiratory EGJ pressure and the maximal axial EGJ displacement were measured. Since the respiratory maneuvers consisted of a single inspiration, we also defined a composite metric, like the EGJ-CI, given in mmHg × cm (EGJ Total Activity), as the product of the maximal inspiratory EGJ pressure by the maximal axial EGJ displacement during each maneuver. Each inspiratory load generated its own set of variables. Figure 1 shows a typical 12-cmH<sub>2</sub>O Threshold Maneuver and details how the EGJ variables were figured out.

## Statistical analysis

The data were expressed as medians and minimum/maximum. The continuous variables of HRM were compared using the Wilcoxon Test for paired samples. For this statistical test,  $P < 0.05$  was considered significant. Demographic variables were described as mean and standard deviation.

## RESULTS

### Demographics

The volunteers consisted of eight male and six female patients. The mean age was  $42.7 \pm 11.8$  years, ranging

**Table 2** Scores of each individual item of the RDQ before and after Nissen fundoplication, according to frequency or intensity of symptoms.

Questions	Before Nissen Median (min; max)	After Nissen Median (min; max)	<i>P</i> value
<i>Frequency based score</i>			
A burning feeling behind your breastbone	4.5 (0; 5)	0 (0; 2)	0.002
Pain behind your breastbone	0 (0; 5)	0 (0; 2)	0.513
A burning feeling in the center of the upper stomach	1 (0; 5)	0 (0; 2)	0.0103
A pain feeling in the center of the upper stomach	0 (0; 5)	0 (0; 5)	0.3720
An acid taste in your mouth	4 (0; 5)	0 (0; 1)	0.0008
Unpleasant movement of material upwards from the stomach	2 (0; 5)	0 (0; 0)	0.0005
<i>Intensity based score</i>			
A burning feeling behind your breastbone	3 (0; 5)	0 (0; 2)	0.0003
Pain behind your breastbone	0 (0; 5)	0 (0; 3)	0.5130
A burning feeling in the center of the upper stomach	1 (0; 5)	0 (0; 3)	0.5400
A pain feeling in the center of the upper stomach	0 (0; 5)	0 (0; 4)	0.2815
An acid taste in your mouth	3 (0; 5)	0 (0; 3)	0.0030
Unpleasant movement of material upwards from the stomach	3 (0; 5)	0 (0; 0)	0.0002

**Table 3** Baseline variables of the esophagogastric junction assessed before and after Nissen fundoplication.

Variables	Before Nissen Median (min; max)	After Nissen Median (min; max)	<i>P</i> value
Axial displacement (cm)	4.85 (2.5; 6.4)	3.9 (2.7; 5.7)	0.238
Inspiratory pressure (mmHg)	39.5 (18.8; 67.9)	49.4 (19.9; 53.3)	0.272
Expiratory pressure (mmHg)	8.1 (3.8; 18.1)	13.0 (7.6; 24)	0.002
Mean pressure (mmHg)	17.5 (6.5; 27)	20.7 (15.4; 30.6)	0.060
EGJ-CI (mmHg x cm)	27.1 (8.5; 41)	36.7 (14.9; 75.5)	0.064

Mean pressure: inspiratory and expiratory EGJ pressure; EGJ-CI, EGJ contractility integral.

from 23 to 62 years. The mean body mass index (BMI) was  $27.8 \pm 3.3$  kg/m<sup>2</sup>, ranging from 22.6 to 33.3 kg/m<sup>2</sup>. All volunteers had typical GERD and were on long-term PPI to control their symptoms. According to Los Angeles classification, five patients had grade A, five had grade B, three had grade C and one patient had Barrett esophagus, without dysplasia. Preoperatively, all patients had AET > 4% on the 24-hour pHmetry examination (mean  $10.2\% \pm 4.5\%$ , with a range of 4.4–18.6%). Eight volunteers had a manometric separation of the LES and crura before surgery. After fundoplication, one patient had a 1-cm LES-crura separation (before surgery: 3.8 cm) and all the others had a complete LES-crura superposition (Table 1).

### Symptom improvement

Heartburn and regurgitation scores were significantly lower after Nissen fundoplication. Dyspepsia scores were low before fundoplication and did not change significantly after the surgery (Table 2).

### Comparison of the baseline esophagogastric junction pressure profile before and after Nissen fundoplication

The baseline pressures were recorded during quiet breathing and no swallowing (resting). The recordings were compared before and after the surgical procedure (Table 3). There was a statistically significant

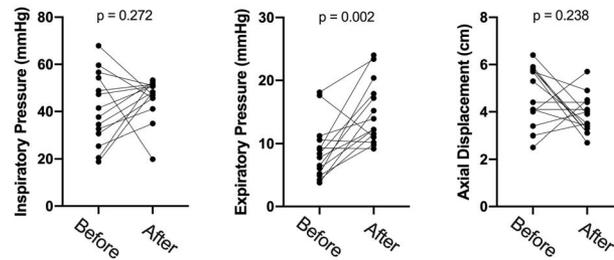
increase in the expiratory EGJ pressure after fundoplication ( $P = 0.002$ ), but there was no significant difference in inspiratory EGJ pressure (Figure 2). The mean (inspiratory and expiratory) EGJ pressure and the EGJ contractility integral (EGJ-CI) had a non-significant postoperative increase ( $P = 0.064$  and  $P = 0.060$ , respectively). The aboral axial displacement of the EGJ was similar before and after Nissen fundoplication ( $P = 0.238$ ).

### Comparison of the esophageal motility profile during wet swallowing, before and after Nissen fundoplication

The IRP was significantly higher in patients after Nissen ( $P = 0.001$ ). The median intrabolus pressure (IBP) also increased after fundoplication ( $P = 0.01$ ). No difference in the median DCI pre and postoperatively was observed in the present study ( $P = 0.77$ ). The distal latency (DL) was higher in patients after fundoplication ( $P = 0.01$ ). A reduction in CFV was also observed after Nissen fundoplication ( $P = 0.043$ ). All values were within the normal range after fundoplication (Table 4).

### Comparison of the esophagogastric junction pressure profile during forced inspiration under respiratory load (Threshold Maneuver), before and after Nissen fundoplication

The median of the axial displacements of the EGJ were lower after Nissen fundoplication, for all



**Fig. 2** The expiratory EGJ pressure improved significantly after Nissen fundoplication. On the other hand, the axial, aboral inspiratory displacement of the EGJ high-pressure zone and the inspiratory EGJ pressure did not change after Nissen fundoplication. Here, inspiration occurred without load.

**Table 4** HRM variables assessed after 10 liquid swallows, before and after Nissen fundoplication

Variables	Before Nissen Median (min; max)	After Nissen Median (min; max)	<i>P</i> value
DCI mean (mmHg.s.cm)	759.2 (231.6; 3039.9)	774.1 (276.7; 2699.6)	0.778
IRP (mmHg)	6.55 (1.8; 11.8)	12.8 (7.0; 17.9)	0.001
CFV (cm/s)	3.85 (1.7; 5.1)	2.9 (1.9; 4.7)	0.043
DL (s)	5.7 (4.7; 10.6)	6.8 (5.2; 8.8)	0.017
IBP mean (mmHg)	0.7 (−3.7; 5)	4.0 (−0.1; 9.9)	0.012
IBP max (mmHg)	10.1 (2.4; 21.1)	11.2 (3.5; 52.2)	0.638

HRM, high-resolution manometry; CFV, contraction front velocity; DCI, distal contractility integral; DL, distal latency; IBPmean, IBPmax, intrabolus pressure mean and maximum; IRP, relaxation pressure integral.

respiratory loads, significant with the highest load (12 cmH<sub>2</sub>O,  $P = 0.11$ ; 24 cmH<sub>2</sub>O,  $P = 0.069$ ; 36 cmH<sub>2</sub>O,  $P = 0.075$ ; 48 cmH<sub>2</sub>O,  $P = 0.017$ ). Another finding was that the median maximal inspiratory pressure was lower after fundoplication. This reduction was statistically significant for all loads (12 cmH<sub>2</sub>O,  $P = 0.004$ ; 24 cmH<sub>2</sub>O,  $P = 0.004$ ; 36 cmH<sub>2</sub>O,  $P = 0.01$ ; 48 cmH<sub>2</sub>O,  $P = 0.01$ ). We also measured the product (maximal inspiratory pressure) × (axial displacement), given in mmHg × cm, called EGJ Total Activity, as a composite metric related to the EGJ-CI but figured out over a single inspiration. This was significantly lower after surgery for all loads (Table 5).

## DISCUSSION

Laparoscopic Nissen fundoplication<sup>13</sup> has become the gold-standard procedure for the surgical treatment of GERD. Careful patient selection and well-established technical concepts of mechanical sphincter augmentation can provide satisfying results in most patients with severe GERD.<sup>14</sup> Nissen fundoplication has three important principles in its execution: abdominalization of the LES, confection of a valve mechanism using the gastric fundus and closure of the diaphragmatic pillars with consequent narrowing of the diaphragmatic hiatus. All may have a direct impact on the baseline pressure pattern of the EGJ. This work brings news information regarding the inspiratory EGJ pressure. At first glance, one would imagine that fundoplication and hiatal closure would increase the EGJ pressure during inspiration

under resistance. Below, we discuss why this may not be true.

After the fundoplication, the gastric fundus wrap around the LES, in theory, maintains a tonic pressure component over the LES. The abdominalization of the esophagus brings the EGJ into a higher-pressure zone, compared to the thorax. Considering the principle of the pressure gradient between the abdominal and thoracic cavities,<sup>15</sup> keeping the EGJ in the abdomen contributes to the anti-reflux barrier by increasing its basal pressure tonus, which is higher in the abdomen. The contraction of the diaphragmatic pillars contributes to the cyclic increase of the intraluminal EGJ pressure during the inspiratory phase of respiration. It is one of the main elements contributing to the overall basal EGJ pressure. Also, when it fails to raise the inspiratory EGJ pressure, it can be an important independent predictor of GERD.<sup>4,5</sup> The effectiveness of the surgical procedure was evident in this study. The symptom improvement was remarkable, similarly to other authors<sup>10,16</sup> and the expiratory EGJ pressure significantly increased to normal values.<sup>11</sup> It is well known that esophageal acid exposure significantly decreases even after many years of an effective fundoplication.<sup>10</sup> Therefore, we did not include reflux monitoring after the surgery as a study goal.

During swallowing, the IRP and mean IBP values had a significant increase, corroborating previous studies.<sup>7,17</sup> These measurements denoted a relative difficulty in the passage of the bolus through the EGJ. If there was an increase in the basal pressure profile of the EGJ, there would be a greater difficulty for the bolus to pass through it and an increase in the IRP

**Table 5** Esophagogastric junction inspiratory variables assessed during the Threshold Maneuver protocol (inspiration under increasing inspiratory loads), before and after Nissen fundoplication

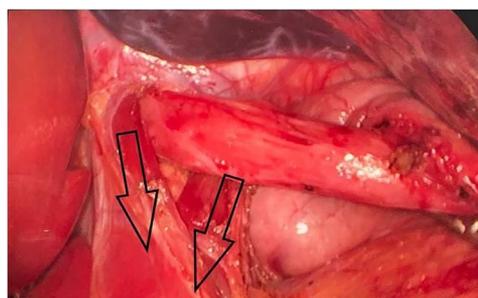
Load (cmH <sub>2</sub> O)	Variables	Before Nissen Median (min; max)	After Nissen Median (min; max)	P value
12	Inspiratory pressure	145.6 (86.2; 268.1)	102.7 (58.7; 132.0)	0.004
	Axial displacement	5.8 (2.8; 8.9)	5.3 (3.0; 6.8)	0.116
	EGJ total activity	784.2 (470.8; 1957.1)	530.6 (275.9; 749.3)	0.009
24	Inspiratory pressure	134.8 (59.7; 273.3)	98.7 (23.1; 130.8)	0.004
	Axial displacement	5.7 (3.4; 9.9)	5.0 (2.8; 7.3)	0.069
	EGJ total activity	794.8 (203.0; 1694.5)	485.0 (120.1; 661.5)	0.004
36	Inspiratory pressure	130.6 (52.0; 255.5)	91.6 (47.9; 132.0)	0.011
	Axial displacement	6.0 (2.7; 10.4)	4.9 (2.7; 6.1)	0.075
	EGJ total activity	736.3 (140.4; 1839.6)	466.8 (131.5; 739.2)	0.004
48	Inspiratory pressure	129.7 (52.4; 249.0)	97.9 (44.3; 137.1)	0.011
	Axial displacement	5.7 (2.8; 9.5)	4.5 (1.8; 6.5)	0.017
	EGJ total activity	842.1 (214.8; 1817.7)	393.2 (99.5; 788.4)	0.006

The parameters measured during the respiratory maneuvers were all inspiratory, under increasing resistances of 12, 24, 36 and 48 cmH<sub>2</sub>O (inspiratory pressure in mmHg, axial displacement in cm and EGJ total activity in mmHg × cm).

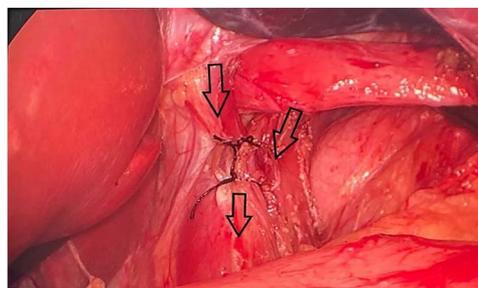
and IBP values. However, these values varied within the normal range. CVF diminished and DL increased significantly after fundoplication. This implied that the surgery had a direct effect on the motility pattern of the distal esophagus, mainly by changing the velocity of the contraction wave propagation. Unlike other publications,<sup>4,13</sup> we did not observe a significant increase in the contraction vigor of the esophageal body (DCI). These publications suggested that the creation of a high-pressure zone at the level of the EGJ would favor an increase in the distal esophageal contractility for the swallowed contents to overcome the created barrier. However, in our study this effect did not occur.

This study shed light on the inspiratory EGJ pressure after Nissen fundoplication, both at rest breathing and during inspirations under increasing loads. The inspiratory pressure during breathing at rest slightly increased after fundoplication, but it was not statistically significant. When forced inspirations under increasing loads (Threshold Maneuvers) were carried out, requiring a greater diaphragmatic work, the inspiratory EGJ pressure was lower after fundoplication. Possibly, the contraction of the sutured diaphragm had a lower capacity to elevate the dynamic extrinsic pressure of the EGJ in forced inspiration. However, the procedure could maintain the static pinchcock pressure effect after surgery.

The exact mechanisms of the lower inspiratory pressure after fundoplication are not known. One possible reason lies in the contraction vector of the CD. The diaphragmatic pillars are inserted in the spine caudal to the EGJ, causing their contraction and consequent action on the distal esophagus to occur in the antero-posterior-caudal direction. The sutures applied to the pillars are perpendicular to its contraction movement, which could lead to a reduction in the contractile effectiveness of the CD, unveiled by the inspiratory maneuvers with increasing loads (Figures 3, 4). In this situation, the effective



**Fig. 3** This picture shows the CD before hiataloplasty. The arrows indicate the contraction vectors of the crural branches of the right diaphragmatic pillar. During forced inspiration (Threshold Maneuver), the entire contractile muscle mass contributes to inspiratory EGJ pressure.



**Fig. 4** This picture shows the CD after hiataloplasty. The arrows indicate the contraction vectors interrupted and segmented by the suture of the crura. The effective contractile muscle mass around the EGJ is smaller, which would partly justify the lower pressure during forced inspiration (threshold maneuvers).

contractile muscle mass of the CD would be smaller. Moreover, fibrosis caused by healing of the pillar sutures is also an element that could hamper muscle activity, limiting the contractile activity of the CD on the EGJ. However, even with the achievement of lower-pressure elevations during forced inspiratory maneuvers after Nissen fundoplication, the plicated pillars and the overall procedure maintained the basal pressure over the EGJ within the normal range after the surgery.

The hiatal closure stitches involved only part of the thicknesses of the CD branches. Consequently, other factors may also contribute to the diminished inspiratory EGJ pressure after fundoplication. Indeed, the axial displacement of the EGJ, significant at a maximal diaphragmatic work, was lower after fundoplication, both during normal breathing and forced inspiration under load (Threshold Maneuvers). This showed that the procedure tended to make the EGJ more fixed, reducing its movement below the diaphragmatic hiatus. This was desired, since a more fixed EGJ in the abdomen would prevent it from sliding into the thorax. Another explanation for the lower movement of the EGJ would be that the valve served as a bulkhead, contained by the reduced hiatus diameter. The fundoplication bulk could also impede the aboral EGJ displacement. This movement restriction could partly explain the decrease in the inspiratory EGJ pressures after fundoplication. These phenomena and its relation to the EGJ pressure profile have not been described previously.

The evaluation of the CD after Nissen fundoplication was highlighted in this study. The Nissen procedure is highly effective even after partially blocking the aboral displacement of the EGJ. The pinchcock effect of the fixed wrap and the hiatal closure overcompensated any deficit of the crura contraction. Indeed, the inspiratory EGJ displacement has not been sufficiently studied neither in physiological nor in disease conditions. Respiratory maneuvers, HRM and advanced imaging analysis, like segmentation, may add to the understanding of the phenomenon depicted in this study.

## CONCLUSION

Laparoscopic Nissen fundoplication was successful in controlling GERD symptoms and increasing the resting expiratory and the mean pressures of the EGJ. The distal latency increased, and the front contraction velocity diminished, indicating a possible improvement of the esophageal peristalsis after fundoplication. After fundoplication, there was a limitation of the craniocaudal displacement of the EGJ during inspiration. During inspiration under increasing loads (Threshold Maneuvers), there was a lower capacity of the inspiratory EGJ pressure to rise, possibly due to the sutured crura and the fundoplication bulk around the EGJ. However, the surgery improved the overall pressure of the EGJ. This was mainly due to its static action on the anti-reflux barrier.

## AUTHOR CONTRIBUTIONS

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Participated in drafting the article or revising it critically for important intellectual content: Leonardo Adolpho Sá Sales, Miguel Angelo Nobre Souza, Fernando Antônio Siqueira Pinheiro, João Odilo Gonçalves Pinto, Armênio Aguiar Santos.

Gave final approval of the version to be submitted and any revised version to be published: Leonardo Adolpho Sá Sales, Miguel Angelo Nobre Souza, Fernando Antônio Siqueira Pinheiro, João Odilo Gonçalves Pinto, Armênio Aguiar Santos.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

## DATA AVAILABILITY

The raw data is available to the editors in datasheet format upon request.

## CREDIT AUTHOR STATEMENT

Leonardo Adolpho Sales (Conceptualization, Methodology, Writing—original draft), Fernando Antônio Pinheiro (Conceptualization, Methodology, Supervision, Writing—review & editing), João Odilo Pinto (Methodology, Writing—review & editing), Armênio Santos (Funding acquisition, Resources, Writing—review & editing), Miguel Angelo Souza (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Writing—original draft, Writing—review & editing)

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