Inspiratory muscle training improves antireflux barrier in GERD patients

Miguel Ângelo Nobre e Souza,1 Maria Josire Vitorino Lima,1 Giovanni Bezerra Martins,2 Rivianny Arrais Nobre,1 Marcellus Henrique Loiola Ponte Souza,4 Ricardo Brandt de Oliveira,3 and Armênio Aguiar dos Santos4

1Department of Clinical Medicine, Federal University of Ceará, Ceará, Brazil; 2Department of Surgery, Federal University of Ceará, Ceará, Brazil; 3Department of Clinical Medicine, Ribeirão Preto School of Medicine, University of São Paulo, São Paulo, Brazil; and 4Department of Physiology and Pharmacology, Federal University of Ceará, Ceará, Brazil

Submitted 21 February 2013; accepted in final form 7 October 2013

Nobre e Souza MÁ, Lima MJ, Martins GB, Nobre RA, Souza MH, de Oliveira RB, dos Santos AA. Inspiratory muscle training improves antireflux barrier in GERD patients. Am J Physiol Gastrointest Liver Physiol 305: G862–G867, 2013. First published October 10, 2013; doi:10.1152/ajpgi.00054.2013.—The crural diaphragm (CD) is an essential component of the esophagogastric junction (EGJ), and inspiratory exercises may modify its function. This study’s goal is to verify if inspiratory muscle training (IMT) improves EGEJ motility and gastroesophageal reflux (GER). Twelve GER disease (GERD; 7 males, 20–47 yr, 9 esophagitis, and 3 nonerosive reflex disease (NERD)) and 7 healthy volunteers (3 males, 20–41 yr) performed esophageal pH monitoring, manometry, and heart rate variability (HRV) studies. A 6-cm sleeve catheter measured average EGEJ pressure during resting, peak inspiratory EGEJ pressures during sinus arrhythmia maneuver (SAM) and inhalations under 17–35-, and 70-cmH2O loads (TH maneuvers), and along 1 h after a meal. GERD patients entered a 5-days-a-week IMT program. One author scored heartburn and regurgitation before and after IMT. IMT increased average EGEJ pressure (19.7 ± 2.4 vs. 29.5 ± 2.1 mmHg, P < 0.001) and inspiratory EGEJ pressure during SAM (89.6 ± 7.6 vs. 125.6 ± 13.3 mmHg, P = 0.001) and during TH maneuvers. The EGEJ-pressure gain across 35- and 70-cmH2O loads was lower for GERD volunteers. The number and cumulative duration of the transient lower esophageal sphincter relaxations decreased after IMT. Proximal progression of GER decreased after IMT but not the distal acid exposure. Low-frequency relaxation decreased after IMT. Proximal progression of GER de-

METHODS

Twelve subjects (7 males, 20–47 yr old) with the diagnosis of GERD [8 grade A, 1 grade B, Los Angeles Classification; 3 nonerosive reflex disease (NERD) defined by ambulatory esophageal pH monitoring] were selected to participate in this study. Three GERD volunteers had a 2-cm hiatal hernia. All GERD volunteers presented heartburn and attended the Gastroenterology Outpatient Facility at Walter Cantidio University Hospital (Federal University of Ceará). The study protocol had been publicly announced at the hospital. Also, seven healthy volunteers (3 males, 20–41 yr old) without any typical or atypical GERD symptom were studied. A gastroenterologist interpreted GERD volunteers and scored the frequencies of both heartburn and regurgitation with a standardized questionnaire (0: no symptom; 1: less than once a week; 2: once a week; 3: 2–4 times a week; and 4: more than 5 times a week). All volunteers had a normal physical examination and no antecedents of abdominal surgery. Written informed consent was obtained from each participant. The Research Ethics Committee of the Walter Cantidio University Hospital approved the study protocol before the experiments (no. 044.06.09).

EGJ manometry. Esophageal manometry was performed after a 4-h fast using an eight-lumen catheter with a 6-cm sleeve at the distal end. There were seven side-hole recording orifices, one 1 cm distal to the sleeve, and six at 3-cm intervals, starting 3 cm proximal to the sleeve (Andorfer Specialties, Greendale, WI). A low-compliance pneumohydraulic pump (JS Biomedical, Ventura, CA) perfused the sleeve and the side holes with distilled water at 0.5 ml/min. The catheter was connected to external pressure transducers, which were coupled to a manometry system (Synectics Medical/Polygram, Stockholm, Sweden). The sleeve straddled the EGI 1 cm deeper to the pressure inversion point so that deep inspiration yielded a positive pressure wave. All volunteers and patients were studied in the supine position.

EGJ pressure measurements. The sleeve measured the average EGI pressure during normal respiration and no swallowing and the peak
gastric sphincter relaxations (tLESR). Indeed, CD also relaxes during tLESR (18). The autonomic nervous system (ANS) controls the EGI relaxation and may be impaired in GERD (6).

Since the CD is an inspiratory striated muscle, its function may be modified by training (11). In fact, inspiratory muscle training (IMT) may increase diaphragm strength and tone in different clinical settings (2, 16). There is some evidence that prolonged inspiratory effort can improve gastroesophageal reflux. In children with adenotonsillar hypertrophy and obstructive sleep apnea syndrome, there are both GERD and prolonged inspiratory effort due to airway obstruction. Despite most of such children having pathological reflux, those with the worst apnea indexes tended to have less esophageal acid exposure (20). Had such children naturally trained their diaphragms, therefore, compensating a bit for their antireflux barrier weaknesses?

The goal of this studied is to verify if IMT improves EGI motor function, autonomic function, and GERD.

GASTROESOPHAGEAL REFUX DISEASE (GERD) is a “condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications” (28). GERD symptoms affect ~5% of the population in Asia and 15% in the Western world, comprising a significant medical condition (8).

The primary line of defense against GERD is the unity of the antireflux barrier. The crural diaphragm (CD) exerts an extrinsic sphincteric action at the esophagogastric junction (EGJ) and is a key component of the antireflux barrier (18). In GERD, the increase of EGI inspiratory pressure is reduced, further setting up the importance of the CD (21). Most episodes of gastroesophageal reflux (GER) occur during transient lower esoph-

Address for reprint requests and other correspondence: M. Â. Nobre e Souza, Dept. of Clinical Medicine, Federal Univ. of Ceará, Rua Prof. Costa Mendes 1608-4 andar CEP, 60430-040, Fortaleza, Ceará, Brazil (e-mail: mans@ufc.br).
EGJ pressures during two respiratory maneuvers. The average EGJ pressure comprises both inspiratory and expiratory pressures. All the points along a 15-s swallow-free window on the EGJ pressure tracing were averaged to yield it, referenced to intragastric pressure. The first respiratory maneuver consisted of six cycles of 5-s deep inhalation and 5-s exhalation without airflow resistance [sinus arrhythmia maneuver (SAM); Ref. 9]. SAM produced six inspiratory peak pressures of the EGJ that were averaged to yield the SAM pressure. The second maneuver consisted of a quick and forced inhalation through a device that incorporated a flow-independent one-way spring-loaded valve that provided an adjustable airflow resistance (in cmH$_2$O; Ref. 2; Threshold IMT; Philips Respironics). Each subject carried on inhalations under 17-, 35-, and 70-cmH$_2$O resistance loads and the inspiratory peak pressures under each load were registered: threshold (TH) maneuvers. All maneuvers were carried out twice and the inspiratory peak pressures of each maneuver were presented as averages of the respective individual pressures. Inspiratory pressures of the respiratory maneuvers were referenced to the mean EGJ pressure during a stable 30-s period before the maneuvers.

Assessment of tLESR. After the respiratory maneuvers, the volunteers drank a 200-ml chocolate-soya liquid meal (117 kcal, 16 g carbohydrates, 5.6 g protein, and 3.3 g fat; ADES, Unilever, Brazil) and lay down in the right lateral position. The sleeve position was fine tuned so that it could measure the highest postprandial LES pressure, which was registered for 1 h. tLESRs were analyzed blindly by one of the authors (M. A. Nobre e Souza) according to Holloway’s criteria. All relaxations >10 s irrespective of swallowing were considered tLESR if they fulfilled the following criteria: relaxation rate of ≥1 mmHg/s, time from onset to complete relaxation of ≥10 s, nadir pressure of ≤2 mmHg (14). All relaxations were longer than 13 s.

Esophageal pH monitoring. Ambulatory 24-h esophageal pH was monitored using a probe with two antimony sensors 15 cm apart, with an external skin reference, in 11 GERD volunteers, before and after IMT (Alacer Biomédica). Data was stored on a single portable digital recorder (AL-3; Alacer Biomédica). Before each study, the pH probes were calibrated in buffer solutions of pH 7 and pH 1. The distal pH sensor were placed 5 cm above the proximal LES border. Volunteers reported meals, supine position, and symptoms on a diary card. Patients stopped antisecretory or prokinetic drugs at least 1 wk before the first pH study. Distal reflux was defined as a pH drop below 4. Proximal reflux was evaluated manually and was defined as drops of at least one pH unit, associated with distal reflux (29). The numbers of proximal and distal refluxes were counted for the upright, supine, and symptoms on a diary card. All GERD volunteers presented heartburn at least once a week, and 10 also had regurgitation. The scores of heartburn and regurgitation decreased significantly after IMT [3 (3–4) vs. 0 (0–0.7), $P = 0.003$; and 2.5 (1–3.7) vs. 0 (0–0), $P = 0.008$, respectively].

Average EGJ pressure in GERD volunteers (19.7 ± 2.4 mmHg) was similar to healthy ones (25.5 ± 5.6 mmHg, $P = 0.256$) and increased after IMT (29.5 ± 2.1 mmHg, $P < 0.001$; Fig. 1). Inspiratory EGJ pressure during SAM was nonsignificantly lower in GERD volunteers (89.6 ± 7.6 mmHg) than in IMT program. After the initial manometric, pH, and autonomic functional studies, GERD volunteers enrolled in a progressive 5-days-a-week IMT program under progressive inspiratory resistance. A physical therapist (M. J. V. Lima) managed the exercise program held in the Walter Cantidio University Hospital outpatient facility. Initial resistance was set at 30% of maximal inspiratory pressure (maxIP) and was increased, as long as tolerated, by 5% every 5 days for 2 mo. Each IMT session consisted of 10 series of 15 inspirations and lasted ~30 min (10). maxIP was measured with an analog vacuummeter, and the inspiratory resistance was accomplished with the Threshold IMT device described previously in the text. At some point during the IMT, two Threshold IMT devices connected in series were generally needed to accomplish the required inspiratory resistance. All initial functional studies were repeated within 1 wk of the IMT end. One volunteer did not perform the pH and autonomic studies at the end of the protocol.

Statistical analysis. The number of proximal reflux progression was presented as the difference between the number of nonprogressing distal reflux and proximal reflux. The increment of acid exposure (%pH <4) and LF power after IMT were tested for correlation (Spearman’s rank correlation). Scores, number of tLESR, and number of GER that progressed proximally were presented in median and range. Continuous data are presented as means ± SE. Student’s paired $t$-test was employed to compare quantitative and continuous variables before and after IMT and unpaired $t$-test to compare healthy and GERD volunteer variables. Wilcoxon’s matched pair test was used to compare the distribution of quantitative and discrete variables before and after IMT. The EGJ pressure difference between 70 and 35 cmH$_2$O inspiratory loads was compared between healthy and GERD volunteers. The level of statistical significance was set at 0.05 for differences in mean values and distributions (JMP Statistical Discovery Software, version 7.0.1, SAS Institute (Cary, NC); GraphPad Prism, GraphPad Software (La Jolla, CA)).

RESULTS

All GERD volunteers presented heartburn at least once a week, and 10 also had regurgitation. The scores of heartburn and regurgitation decreased significantly after IMT [3 (3–4) vs. 0 (0–0.7), $P = 0.003$; and 2.5 (1–3.7) vs. 0 (0–0), $P = 0.008$, respectively].

Average EGJ pressure in GERD volunteers (19.7 ± 2.4 mmHg) was similar to healthy ones (25.5 ± 5.6 mmHg, $P = 0.256$) and increased after IMT (29.5 ± 2.1 mmHg, $P < 0.001$; Fig. 1). Inspiratory EGJ pressure during SAM was nonsignificantly lower in GERD volunteers (89.6 ± 7.6 mmHg) than in healthy ones (117.9 ± 5.3 mmHg, $P = 0.008$).

**Fig. 1.** Average resting esophagogastric junction (EGJ) pressure in gastroesophageal reflux disease (GERD) volunteers increased significantly after inspiratory muscle training (IMT). EGJ pressure was the average of inspiratory and expiratory pressures during a 15-s swallow-free period (paired $t$-test).
healthy ones (119.4 ± 14.4 mmHg, \( P = 0.06 \)) and increased significantly after IMT (125.6 ± 13.3 mmHg, \( P = 0.001 \); Fig. 2). Inspiratory EGJ pressures during inspiratory loads of 17, 35, and 70 cmH\(_2\)O increased significantly after IMT (Table 1). Increasing inspiratory load from 35 to 70 cmH\(_2\)O yielded a greater inspiratory EGJ pressure in the healthy group (120.2 ± 6.5 vs. 154 ± 16.4 mmHg, \( P = 0.065 \)) but not in the GERD one (123.3 ± 12.2 vs. 119.9 ± 12.6 mmHg, \( P = 0.494 \); Fig. 3). The increment in EGJ inspiratory pressure between the 70- and the 35-cmH\(_2\)O loads was significantly higher for the healthy group (33.8 ± 14.6 vs. −3.4 ± 4.8 mmHg, \( P = 0.009 \); Fig. 3).

The inspiratory load of 17 cmH\(_2\)O yielded an inspiratory EGJ pressure similar to the 35-cmH\(_2\)O load in healthy volunteers (137.3 ± 16.2 mmHg, \( P = 0.193 \), vs. 35 cmH\(_2\)O) and lower in GERD ones (110.9 ± 11.5 mmHg, \( P = 0.009 \), vs. 35 cmH\(_2\)O).

The number of tLESR in GERD volunteers decreased after IMT [8.5 events/h (4–17) vs. 7 events/h (2–13), \( P = 0.032 \)]. The sum of tLESR durations was shorter after IMT (199.1 ± 23.5 vs. 156.8 ± 25.9 min, \( P = 0.034 \)). The mean durations of the tLESR events were similar before and after IMT (22 ± 1.3 vs. 21.7 ± 1.3 min, \( P = 0.91 \)).

Total acid exposure before and after IMT was similar, both for the proximal (10.4 ± 4.4 vs. 12.5 ± 4.1 min, respectively, \( P = 0.751 \)) and distal (50.9 ± 15.1 vs. 56.9 ± 13.1 min, respectively, \( P = 0.765 \)) esophagus. Proximal progression of reflux was lower after IMT [−8 (−16; 5) vs. −10 (−28; −3), \( P = 0.04 \)] (Fig. 4). Such a phenomenon was mostly due to a reduced proximal progression of upright reflux [−8 (−19; 5) vs. −14 (−30; −3), \( P = 0.041 \)]. Supine reflux did not progress significantly less after IMT [−21 (−30; −12) vs. −19 (−42; −11), \( P = 0.26 \)].

The LF band power of HRV increased after IMT (Table 2). The difference of the LF power after and before IMT correlated negatively with the difference of supine acid exposure after and before the workout. The higher the increment in LF power, the lower the increment of supine acid exposure (%time pH <4) after IMT, both in the proximal (\( r = −0.615 \), \( P = 0.044 \)) and distal esophagus (\( r = −0.755 \), \( P = 0.007 \); Table 3).

**DISCUSSION**

The main results of our study show that both average and inspiratory EGJ pressures are increased, and tLESR rate, the proximal esophagus acid exposure, as well as the GER symptoms are reduced in GERD patients by IMT. Also, there is a graded increment in inspiratory pressure during TH maneuvers in healthy controls but not in GERD patients. Since CD phasic activity contributes to EGJ pressure (18), the increase in inspiratory EGJ pressure is probably a direct consequence of an IMT-induced enhancement of CD strength. Similarly, inspiratory muscle strengthening by IMT has been well described in respiratory diseases (5). Since the average EGJ pressure consisted of both inspiratory and expiratory pressures, its increase after IMT was probably due to the increase in inspiratory EGJ pressure (No IMT) vs. IMT (increase at the bars (paired \( t \)-test)).

**DISCUSSION**

The main results of our study show that both average and inspiratory EGJ pressures are increased, and tLESR rate, the proximal esophagus acid exposure, as well as the GER symptoms are reduced in GERD patients by IMT. Also, there is a graded increment in inspiratory pressure during TH maneuvers in healthy controls but not in GERD patients. Since CD phasic activity contributes to EGJ pressure (18), the increase in inspiratory EGJ pressure is probably a direct consequence of an IMT-induced enhancement of CD strength. Similarly, inspiratory muscle strengthening by IMT has been well described in respiratory diseases (5). Since the average EGJ pressure consisted of both inspiratory and expiratory pressures, its increase after IMT was probably due to the increase in inspiratory EGJ pressure (No IMT) vs. IMT (increase at the bars (paired \( t \)-test)).

**DISCUSSION**

The main results of our study show that both average and inspiratory EGJ pressures are increased, and tLESR rate, the proximal esophagus acid exposure, as well as the GER symptoms are reduced in GERD patients by IMT. Also, there is a graded increment in inspiratory pressure during TH maneuvers in healthy controls but not in GERD patients. Since CD phasic activity contributes to EGJ pressure (18), the increase in inspiratory EGJ pressure is probably a direct consequence of an IMT-induced enhancement of CD strength. Similarly, inspiratory muscle strengthening by IMT has been well described in respiratory diseases (5). Since the average EGJ pressure consisted of both inspiratory and expiratory pressures, its increase after IMT was probably due to the increase in inspiratory EGJ pressure (No IMT) vs. IMT (increase at the bars (paired \( t \)-test)).
pressure. Moreover, CD tone may also have changed after IMT. Striated muscle tone depends physiologically on two factors: the basic viscoelastic properties of the soft tissues associated with the muscle and the degree of activation of the contractile apparatus of the muscle (26). IMT would change the contractile apparatus of the CD so as to shift its length-tension relationship and increase CD tone and the average EGJ pressure.

An interesting finding in our study was the reduction of acid exposure of the proximal esophagus after IMT. GERD patients particularly with hiatal hernia have a wide, highly compliant EGJ at low-pressure distension as well as a less asymmetrical EGJ relative to healthy controls. This asymmetry probably is related to the anatomical disposition of the CD around the EGJ that seems to compress its lateral aspects. IMT may partly restore this normal asymmetry and reduce the EGJ opening by improving CD tone. If this is the case, transpneumonic flow would be reduced as well as the refluxate volume (22). Consequently, migration of reflux from distal to proximal esophagus and associated symptoms would be reduced. This notion is supported by the finding that reducing the EGJ compliance by the endoscopic insertion of a hydrogel expandable prostheses diminishes the proximal progression of GER and reduces symptoms but does not modify the distal esophageal acid exposure (4). CD strengthening may improve the EGJ gatekeeper role and would decrease the number of proximal refluxes.

Smooth muscle tone and tLESR are under ANS control (13). The relationship between HRV and autonomic function is a complex phenomenon, and it is generally accepted that the greater the HRV, the healthier the individual (1). Ultimately, IMT is a physical exercise that would improve autonomic function, particularly vagal tone. IMT improves ANS function (27), similarly to regular physical training (17). IMT would drive a new and healthier balance in ANS activity that could be a detrimental role and would decrease the number of proximal refluxes.

### Table 2. Heart rate variability (LF power) increased after IMT

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLF</td>
<td>1.942 ± 357.6</td>
<td>3806 ± 1157</td>
<td>0.068</td>
</tr>
<tr>
<td>LF</td>
<td>363 ± 69.3</td>
<td>511.4 ± 112.1</td>
<td>0.038</td>
</tr>
<tr>
<td>HF</td>
<td>268.6 ± 44.2</td>
<td>216.5 ± 34.4</td>
<td>0.248</td>
</tr>
<tr>
<td>Total</td>
<td>2573 ± 435.4</td>
<td>4534 ± 1266</td>
<td>0.070</td>
</tr>
<tr>
<td>LF/HF</td>
<td>1332 ± 391.8</td>
<td>2273 ± 516.6</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Values are means ± SE (paired t-test); n = 11. VLF, very low frequency; LF, low frequency; HF, high frequency.

Table 3. Higher the increment in LF power the lower the increment of supine acid exposure after IMT

<table>
<thead>
<tr>
<th></th>
<th>VLF</th>
<th>LF</th>
<th>HF</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GER (n)</td>
<td>−0.543; 0.085</td>
<td>−0.667; 0.025</td>
<td>−0.051; 0.883</td>
<td>−0.570; 0.067</td>
</tr>
<tr>
<td>%Time &lt;4</td>
<td>−0.450; 0.165</td>
<td>−0.615; 0.044</td>
<td>−0.193; 0.570</td>
<td>−0.495; 0.121</td>
</tr>
<tr>
<td>Distal reflux</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GER (n)</td>
<td>−0.519; 0.102</td>
<td>−0.733; 0.010</td>
<td>−0.132; 0.699</td>
<td>−0.601; 0.050</td>
</tr>
<tr>
<td>%Time &lt;4</td>
<td>−0.655; 0.029</td>
<td>−0.755; 0.007</td>
<td>0.018; 0.958</td>
<td>−0.718; 0.013</td>
</tr>
</tbody>
</table>

Data are Spearman’s $r$ and $P$ values; $n = 11$. This was mainly shown by the negative correlation between the difference of heart rate variability (LF power) after and before IMT and the difference of supine acid exposure after and before the workout.

AJP-Gastrointest Liver Physiol • doi:10.1152/ajpgi.00054.2013 • www.ajpgi.org
show a signal drift after several minutes of study (23). In the case of acid exposure, impedance/pH esophageal monitoring would have improved GERD detection. However, a double sensor pH study was sufficient to detect proximal GER progression and to study the correlation with autonomic function variables in our conditions.

There may also be significant concerns about the practicality of the IMT program since it was intense and held in a clinical setting. A general physical exercise program for GERD patients could include IMT. Together with other GERD treatment regimens, this would be a reasonable and affordable way to treat GERD. In fact, most volunteers felt it could be done at home and inspiratory muscle trainers are not much expensive. The ones used in this work cost around $50 plus tax and were reused by the same volunteer all along the training program.

Recently, Eherer and coworkers (7) showed that vocal training reduced GERD symptoms and esophageal acid exposure. However, there was not any improvement in either the antireflux barrier or tLESR rate. This fact could be due to the lack of inspiratory load during their vocal training program. Vocal training involves changing from thoracic to abdominal breathing and would not strengthen the CD. The acid pocket position is important in the pathogenesis of GERD and can be changed pharmacologically (24). Would vocal training displace the acid pocket distally? If so, it would change GER pattern without impacting on antireflux barrier or autonomic function.

The new information presented here shows a CD failure in GERD patients and may stimulate GERD treatment trials concerning which patients would mostly benefit from IMT and which training regimen would be the most effective.

GRANTS

This study was funded in full by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) Grant 481098/2009-7.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


