Antireflux Action of Nissen Fundoplication and Stretch-Sensitive Mechanism of Lower Esophageal Sphincter Relaxation

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BACKGROUND & AIMS: Surgical fundoplication is an effective treatment for gastroesophageal reflux disease. One of the proposed mechanisms for its antireflux action is that it reduces lower esophageal sphincter (LES) relaxation. We investigated whether fundoplication works through a stretch-sensitive mechanism of LES relaxation. **METHODS:** Studies were performed in rats. Intravenous and arterial lines were placed and tracheal intubation was performed. A midline laprotomy was performed to place sutures through the esophagus to exert axial stretch on the LES, and the vagus nerve was isolated in the neck for electrical stimulation. The LES pressure was monitored with a 2F solid-state pressure transducer placed through a gastrostomy. Cranial displacement of the LES was recorded using piezoelectric crystals. Data were recorded before and after 360-degree Nissen fundoplication. **RESULTS:** Axial stretch and vagus nerve stimulation induced cranial displacement of the LES as well as LES relaxation in a dose-dependent manner. LES relaxation and axial stretch were each significantly reduced after fundoplication ($P < .01$). Nitric-oxide–induced LES relaxation was not affected by fundoplication. Removal of fundoplication restored axial stretch- and vagus nerve-stimulated LES relaxation as well as LES cranial displacement. **CONCLUSIONS: Fundoplication reduces LES relaxation by interfering with axial stretch on the LES. Based on this mechanism of the antireflux actions of fundoplication, it might be possible to design new surgical strategies to treat reflux disease and reduce complications of fundoplication surgery.**

Keywords: Transient LES Relaxation; Mechanosensitive Neurons; Esophageal Longitudinal Muscle.

Lower esophageal sphincter (LES) guards the entrance of the esophagus into stomach. It works like a two-way valve, allowing passage of esophageal contents into the stomach with swallow and passage of gastric contents into the esophagus with belching and vomiting. LES incompetence (too much relaxation and low LES pressure) leads to gastroesophageal reflux (GER), one of the most prevalent medical conditions worldwide.[1–3] Complications of reflux disease, ie, esophagitis, esophageal strictures, angina-like pain, and extraesophageal symptoms related to ear, nose and throat; larynx; and respiratory tract are the leading cause of medical morbidity and consume significant health care resources. Even though current medical treatment of GER diseases is quite effective in suppressing acid, it does not prevent GER.[4,5] In patients taking adequate acid-inhibition therapy, reflux of weakly acid/neutral contents may play a significant role in the pathogenesis of pulmonary aspiration and other extraesophageal manifestations of GER disease.[6]

Surgical fundoplication is an effective treatment to prevent GER. By restoring the competency of LES, fundoplication prevents both acid and nonacid reflux. There are several mechanisms by which fundoplication may improve LES function: (1) reduction of hiatus hernia, (2) restoration of intra-abdominal length of the esophagus, (3) re-creation of the flap valve of esophagus, (4) mechanical compression of the esophagus, and (5) reduction in the triggering and completeness of transient LES relaxation. Several studies suggest that both swallow-mediated LES relaxation and transient LES relaxation after fundoplication are incomplete.[7–9] Fundoplication also reduces the triggering of transient LES relaxations.

Recent studies from our laboratory prove that axial stretch on the LES induces neurogenic relaxation of the LES.[10,11] During peristalsis and transient LES relaxation, axial stretch on the LES is caused by contraction of longitudinal muscles of the esophagus.[12] We propose that fundoplication reduces axial stretch on the LES, which in turn reduces stretch-activated LES relaxation. Our goal was to determine the effects of surgical fundoplication on the axial stretch and relaxation of LES. We tested our hypothesis in rats using the state-of-art measurement techniques. Our data provide, for the first time, evidence for the role of axial stretch in the physiology of LES relaxation.

Materials and Methods

Studies were performed in rats weighing 250 to 400 g (Charles River, Wilmington, MA). The animal safety committee of the San Diego Veterans Affairs Health Care System approved the study protocol. Ani-

Abbreviations used in this paper: GER, gastroesophageal reflux; LES, lower esophageal sphincter.

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mals were anesthetized with an intraperitoneal injection of 0.4 mL/kg stock solution that contained 3.75 mL ketamine solution (concentration: 100 mg/mL), 0.4 mL xylazine solution (concentration: 100 mg/mL), and 0.75 mL acepromazine (concentration: 10 mg/mL) diluted in 20 mL sterile water. Twenty percent of the initial induction dose was injected as needed during the experiment for maintenance of anesthesia. A venous cannula was placed in the internal jugular vein (for injection of pharmacological agents), an arterial line was placed in the carotid artery (to measure blood pressure), and tracheotomy was performed for intubation and ventilation. Vagus nerve was isolated on both sides in the cervical region; transected and peripheral end of one of the vagus nerve was placed on a pair of platinum electrodes for electrical stimulation. Rats were ventilated at 85 strokes/minute at a tidal volume of 2 mL using a ventilator (Harvard Pump, model 683, Holliston, MA).

A midline laprotomy was performed and a 20-cm length of polyethylene tubing (size: 0.04 × 0.07 inch, from Fisher Scientific, Pittsburgh, PA) was passed through the mouth into the esophagus. A curved RB-1 needle with a 45-cm long, 3-0 silk suture was passed through the esophageal wall (1 cm above the LES), polyethylene tube (placed in the lumen of the esophagus), and the opposite esophageal wall. The needle was removed and a 20-cm length of silk sutures was left on each side of the esophageal wall. Knots were placed at both ends of sutures and polyethylene tubing along with sutures were pulled out from the mouth for exerting axial stretch on the LES in the oral direction, as shown in the schematic (Figure 1*A*). A 2.5F solid-state pressure transducer catheter equipped with 4 sensors (custom designed, from Millar Instruments, Houston, TX) was passed through a small incision, 2 cm below the LES, on the stomach wall. Tissue adhesive (NEXABAND S/C manufactured by Closure Medical and distributed by Abbott, North Chicago, IL) was used to glue the pressure transducer catheter to the stomach wall so as to prevent relative movement between the LES and pressure trans-

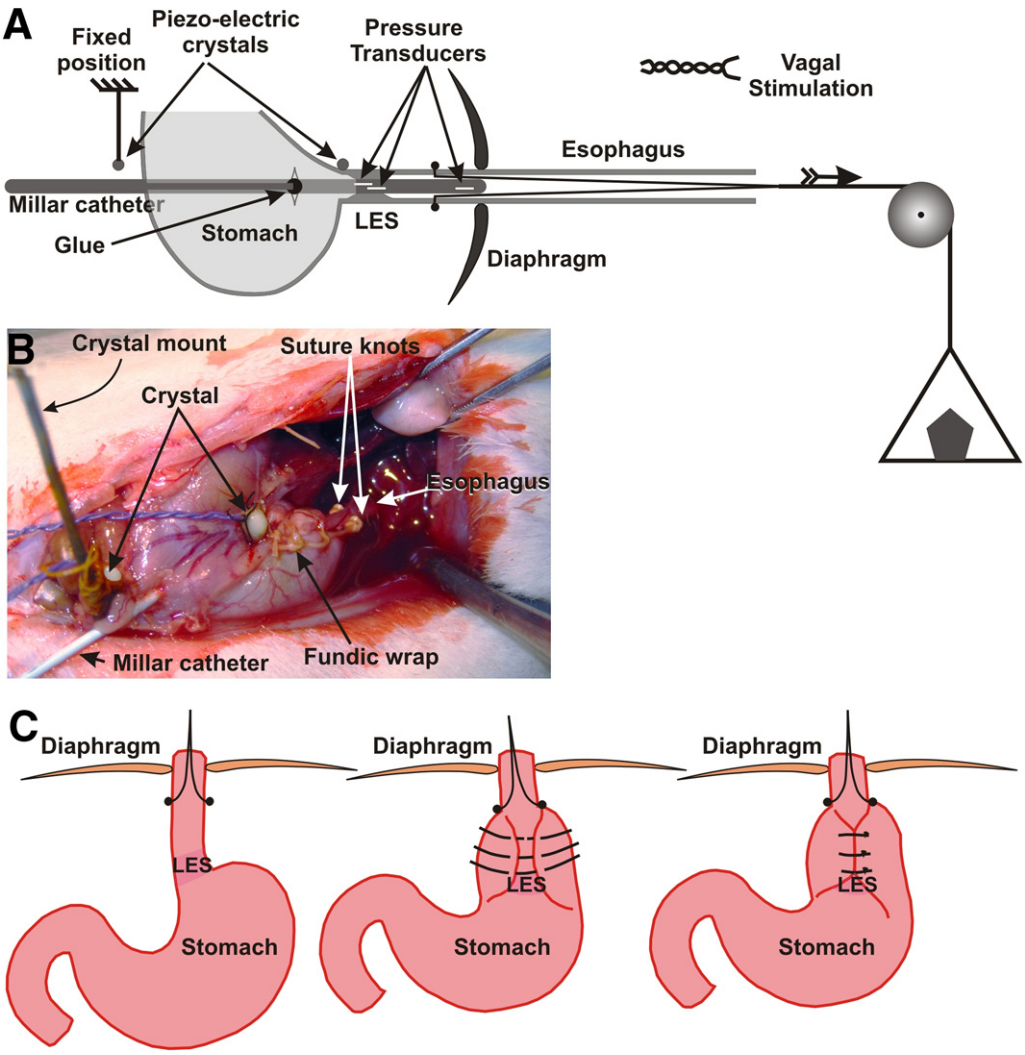

Figure 1. (*A*) Schematic of experimental design, (*B*) photograph of fundoplication, and (*C*) schematic of the fundoplication.

ducer. Sutures exiting through the esophagus and mouth were passed over a pulley (attached to the end of the table) and weights were applied to exert graded stretch on the esophageal wall in the oral direction. Oro-axial (longitudinal) stretch was applied to the esophageal wall with weights of 8, 12, 16, 20, and 24 g. The 24-g weight usually produced maximal relaxation of the LES.

Peripheral end of one of the vagus nerves was stimulated electrically with various frequencies using a pulse generator (model S48 Astro-Med; Grass Instruments, West Warwick, RI). Cranial displacement of the LES during vagal stimulation and stretch were recorded using two, 2-mm piezoelectric crystals (Sonometrics, London, ON, Canada). One crystal was anchored on the upper edge of LES with a suture (moving crystal) and the other crystal was mounted on a wooden stick and placed in the abdomen close to the LES (fixed crystal).[11]

After obtaining control data, fundus of the stomach was wrapped around the esophagus (360-degree wrap) using 3 sutures (Figure 1*B* and *C*). The first stitch included a small bite of the esophageal wall with the catheter still located in the esophageal lumen. The following protocols were used for the experiments: (1) control period: graded axial stretch, vagal stimulation at various frequencies and intravenous infusion of sodium nitroprusside (2 μg/kg; Sigma-Aldrich, Milwaukee, WI); (2) after fundoplication, steps listed in control period were repeated; and (3) sutures were removed to undo fundoplication followed by repeat of iterations listed in the control period. In some experiments, tetrodotoxin (30 μg/kg; Sigma-Aldrich, Milwaukee, WI) was used to determine if the stretch-mediated LES response was neurologically mediated. At the end of each experiment, euthanasia was administered with an intravenous injection of potassium chloride solution (2 mM/kg). The latter procedure is in accordance with the euthanasia guidelines of the San Diego Veterans Affairs Animal Committee.

Data Analysis

LES pressure was measured as an end-expiratory pressure above the gastric pressure and percent LES relaxation was calculated. Changes in distance between the 2 piezoelectric crystals were recorded as a measure of cranial displacement of the LES. Effects of vagal stimulation and axial stretch on the esophageal contraction pressure, LES cranial movement, and LES relaxation were determined before and after fundoplication.

Statistical Analysis

LES pressure differences between control and fundoplication period was determined by paired *t* test. Data are presented as mean ± standard error. $P < .05$ was considered statistically significant.

Results

Effect of Axial Stretch on LES Pressure and LES Axial Displacement

Axial stretch of the esophagus induced a dose-dependent cranial displacement of the LES and relaxation of the LES (Figures 2 and 3). A 24-g axial stretch caused >80% relaxation of the LES in the majority of animals and cranial LES displacement of 2.8 ± 0.4 mm. Axial stretch did not cause any esophageal contractions. Tetrodotoxin completely blocked the effects of vagal stimulation and axial stretch on the LES relaxation in all animals but had no effect on the LES cranial displacement (Figure 4). The latter proves that the axial stretch induced LES relaxation is neurologically mediated.

Effect of Electrical Vagal Stimulation on LES Pressure, LES Cranial Displacement, and Esophageal Contractions

Electrical stimulation of the peripheral end of cervical vagus nerve induced a frequency-dependent increase in the amplitude of esophageal contraction, cranial displacement of the LES, and relaxation of the LES. Durations of esophageal contraction, LES displacement, and LES relaxation were similar to the duration of electrical stimulus (duration response). A 20-Hz stimulus produced >80% LES relaxation in the majority of animals and a cranial displacement of 1.4 ± 0.3 mm. Figure 5 shows mean LES cranial displacement and LES relaxation induced by vagus nerve stimulation. There is a direct correlation between LES relaxation and LES cranial displacement, with an *r* value of 0.87.

Effect of Fundoplication on the Stretch and Vagal Stimulus Induced LES Relaxation and Cranial Displacement

Vagal stimulation-induced esophageal contractions were unaltered by fundoplication. On the other hand, fundoplication resulted in a decrease in the vagal stimulus-induced cranial displacement of LES and relaxation of LES (Figures 2 and 5). However, the effects of fundoplication on LES relaxation revealed some heterogeneity. In response to vagal stimulation, 4 of 18 animals showed complete block of LES relaxation after fundoplication, 4 demonstrated LES contraction, and in the remainder LES relaxation was partially blocked. Similarly, in response to axial stretch, LES contraction was observed in 40% of the animals and in the remainder LES relaxation was either partially or completely blocked (Figure 3). For the purpose of mean data calculation, LES relaxation was considered to be 0% when LES contraction response was observed with the vagus nerve stimulation and axial stretch. There was a statistically significant correlation between the reduction in the cranial displacement and reduction in LES relaxation; $r = 0.71$ and 0.92, respectively (Figures 3 and 5). This correlation was ob-

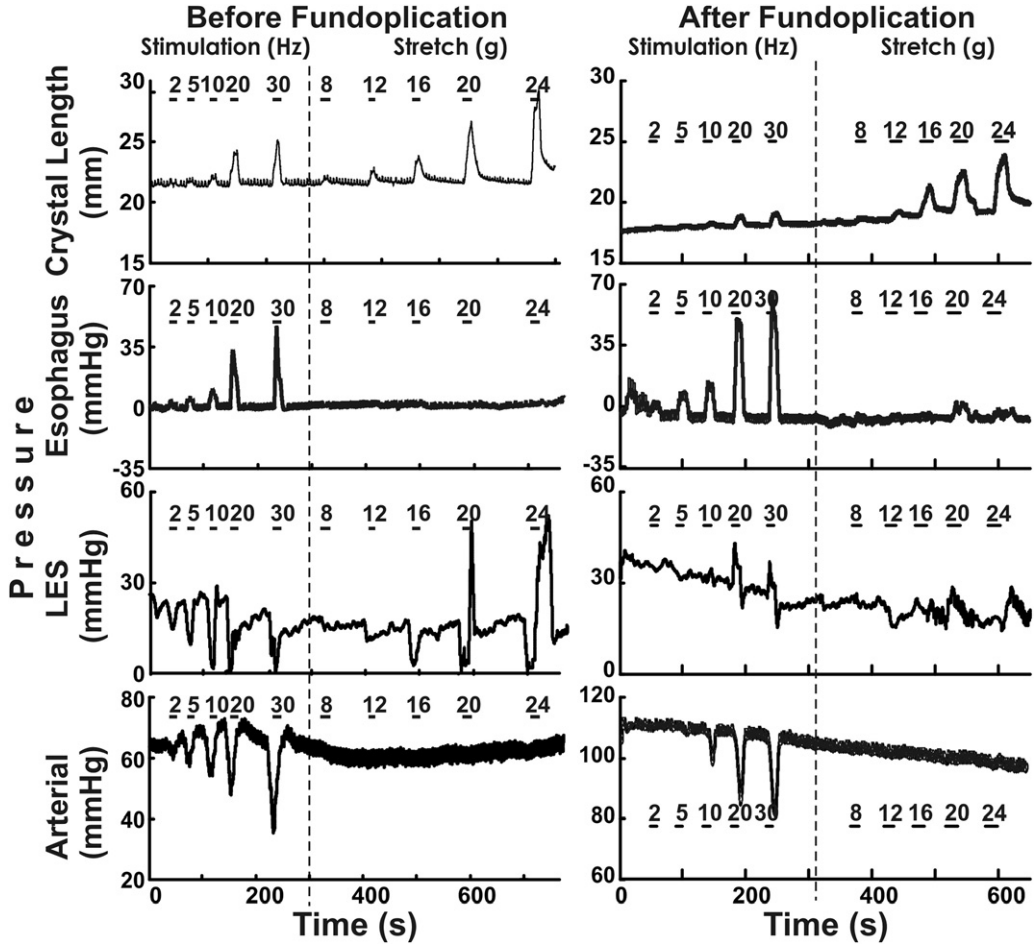

Figure 2. Tracings of cranial lower esophageal sphincter (LES) displacement (distance between 2 crystals), esophageal, LES and arterial pressures during vagal stimulation (at 1, 2, 5, 10, 20, and 30 Hz; pulse amplitude 10 V, pulse width 10 ms, and 5 s train duration) and axial stretch (8, 12, 16, 20, and 24 g weights) before (*left panel*) and after fundoplication (*right panel*). Fundoplication inhibited both the vagus nerve- and axial stretch-induced LES relaxation.

served with both stretch- and vagal stimulation-induced LES relaxation and cranial displacement.

Effect of Sodium Nitroprusside on LES Pressure Before and After Fundoplication

Sodium nitroprusside caused near-complete relaxation of the LES, both before and after fundoplication, 90% ± 3% and 82% ± 5%, respectively (n = 12, $P = .19$). The latter suggests that the effects of fundoplication on LES were not related to the mechanical or compressive effects of fundoplication on the LES (Figure 6).

Effect of Removing Fundoplication on Axial Stretch and Vagus Nerve Induced LES Relaxation

Removal of fundoplication restored axial stretch activated (Figure 7*A*) and vagus nerve stimulus induced LES relaxation (Figure 7*B*). LES relaxation with fundoplication was significantly reduced but the LES relaxation before fundoplication and after removal of fundoplication was similar (Figure 7*C*).

Discussion

In summary, our data show several new findings: (1) fundoplication reduces vagus nerve stimulated and axial stretch induced LES relaxation and LES cranial displacement, (2) removal of fundoplication restores vagus nerve and axial stretch induced LES relaxation, (3) effect of fundoplication is not mediated by the compressive effects of fundoplication on the LES because after fundoplication, sodium nitroprusside induced complete LES relaxation. Taken together our data provide strong support for our hypothesis that fundoplication affects LES relaxation by restricting cranial axial stretch on the LES. Furthermore, axial stretch is an important element in the physiology of LES relaxation.

First described in 1957,[13] Nissen fundoplication is the most commonly performed surgical procedure to treat reflux disease.[14] Laproscopic Nissen fundoplication has become the surgical procedure of choice to treat reflux disease[15,16] during the last 20 years. More recently, a transoral endoscopic approach to perform fundoplica-

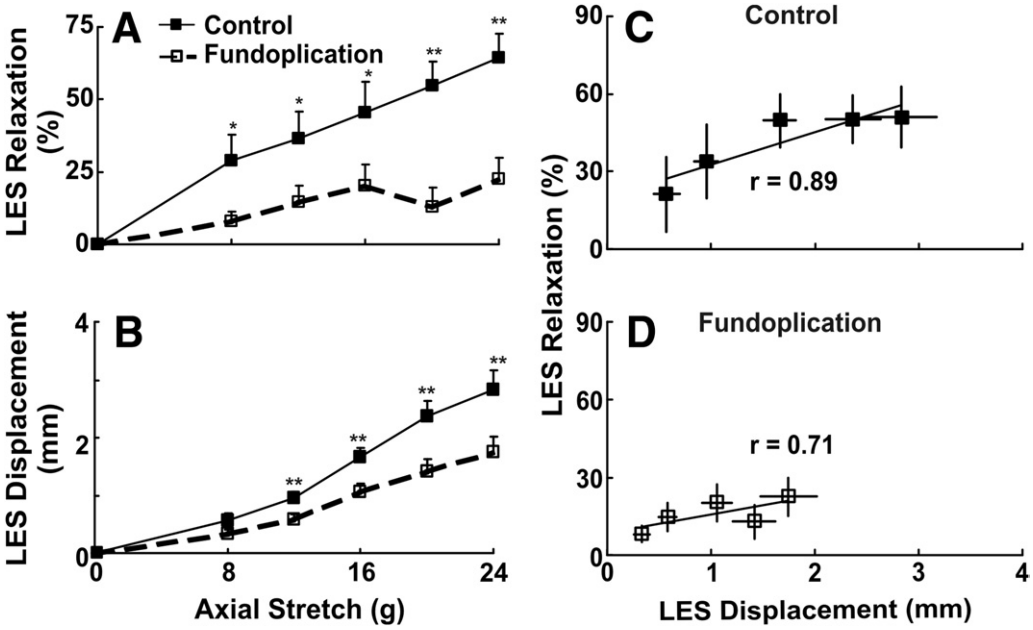

Figure 3. Effect of fundoplication on the axial stretch-induced lower esophageal sphincter (LES) relaxation (*A*, n = 14), and LES displacement (*B*, n = 12). A significant decrease in the LES displacement or axial shortening of the esophagus and LES relaxation after fundoplication (*$P < .05$; **$P < .01$). Correlation between the reduction in degree of cranial displacement and degree of LES relaxation is shown in (*C*), $r = 0.89$ (control), and (*D*), $r = 0.71$ (fundoplication).

tion has been tested and early reports are encouraging.[17,18] A large number of studies show the effectiveness of fundoplication in reducing reflux as documented by pH monitoring and, more recently, by combined impedance and pH-monitoring technique.[19] Since its first description, various modifications of fundoplication have been described,[20] but 3 basic steps of the surgery remain unchanged. These steps include: (1) reduction of sliding hiatal hernia and restoration of LES into the abdomen; (2) plication of diaphragmatic crura to reduce the size of esophageal hiatus and; (3) wrapping of the fundus of stomach around the distal 2 cm of the esophagus.[20] The entire LES (and maybe distal esophagus) is usually located inside the surgical wrap after fundoplication. There are several proposed mechanisms by which fundoplication may prevent reflux: (1) reduction of hiatus hernia, (2) restoration of a length of intra-abdominal esophagus that may restore the angle of His and LES flap valve, (3) improvement of the sphincter function of crural diaphragm, and (4) effects on the basal LES pressure and transient LES relaxation.[21] With regard to the effect of fundoplication on LES pressure, there are conflicting data about whether it increases basal LES pressure by exerting a mechanical compressive effect on the LES.[22] Surgeons usually place a 40F−60F bougie in the lumen of the esophagus at the time of fundoplication to prevent mechanical compression on the LES. In our experiment, the pressure-sensing catheter was in place in the lumen of the esophagus at the time of fundoplication and we intentionally performed a loose wrap to avoid mechanical compression on the LES. We did not find any significant change in basal LES pressure after fundoplication. Furthermore, sodium nitroprusside (donor of nitric oxide)−induced LES relaxation was not affected by fundoplication. Because nitric oxide acts on the muscle directly to induce LES relaxation,[23] our findings prove that the effects of fundoplica-

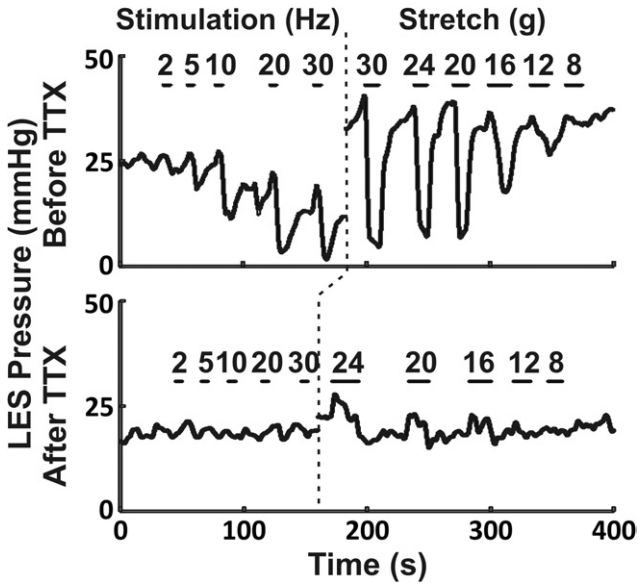

Figure 4. Effect of tetrodotoxin (TTX) on the vagal stimulus and stretch-induced lower esophageal sphincter (LES) relaxation. Note the vagal stimulus frequency-dependent and stretch weight-dependent relaxation of the LES. After administration of TTX, both electrical stimulus and stretch-activated LES relaxations are completely blocked.

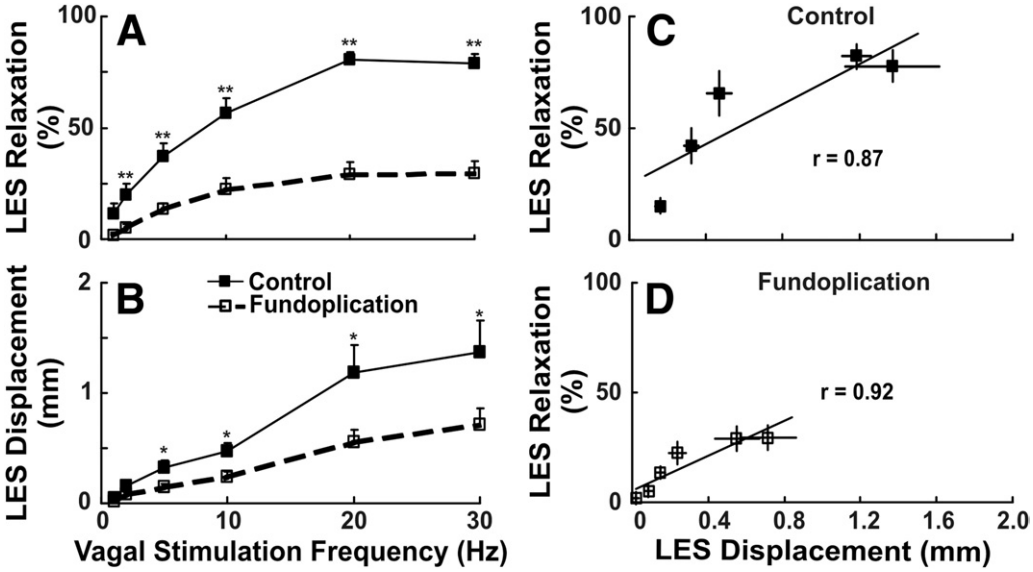

Figure 5. (*A*) Percent lower esophageal sphincter (LES) relaxation (n = 19) and (*B*) plot of mean values of LES displacement (n = 12) before and after fundoplication with vagal stimulation (1, 2, 5, 10, 20, and 30 Hz; at 10 V, pulse width 10 ms and 5 s train duration, $^{*}P < .05$; $^{**}P < .01$). Correlation between degree of LES relaxation before and after fundoplication is shown in (*C*), $r = 0.87$ (control) and reduction in degree of cranial displacement in (*D*), $r = 0.92$ (fundoplication).

tion in our experiment were not related to the compressive effects of surgical wrap on the LES.

We tested the effects of fundoplication on the neurologically mediated LES relaxation because transient LES relaxation is the major mechanism of GER and fundoplication is known to reduce the triggering as well as completeness of transient LES relaxation. The major finding of our study is that fundoplication reduces cra-

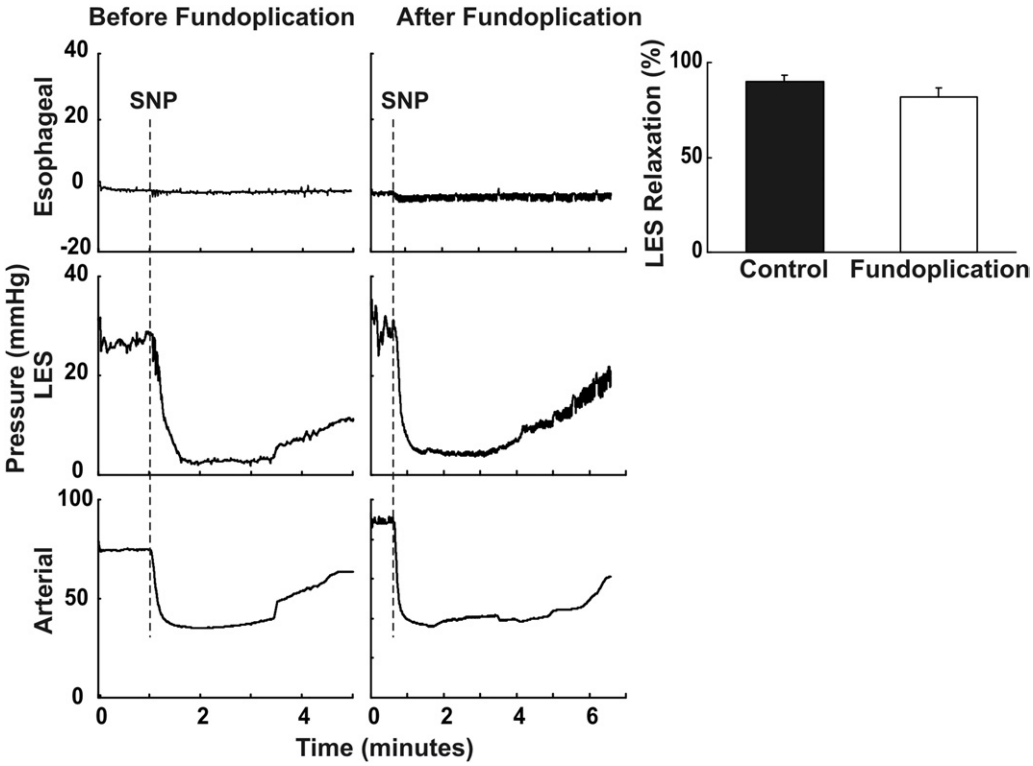

Figure 6. Effect of sodium nitroprusside (SNP, 2 μg/kg) on esophageal, lower esophageal sphincter (LES), and arterial pressures before and after fundoplication. Fundoplication had no effect on the LES relaxation induced by SNP. *Bar graph* shows the mean percent LES relaxation induced by SNP before and after fundoplication. (n = 12, $P = .19$ by *t* test: 2-sample assuming unequal variances).

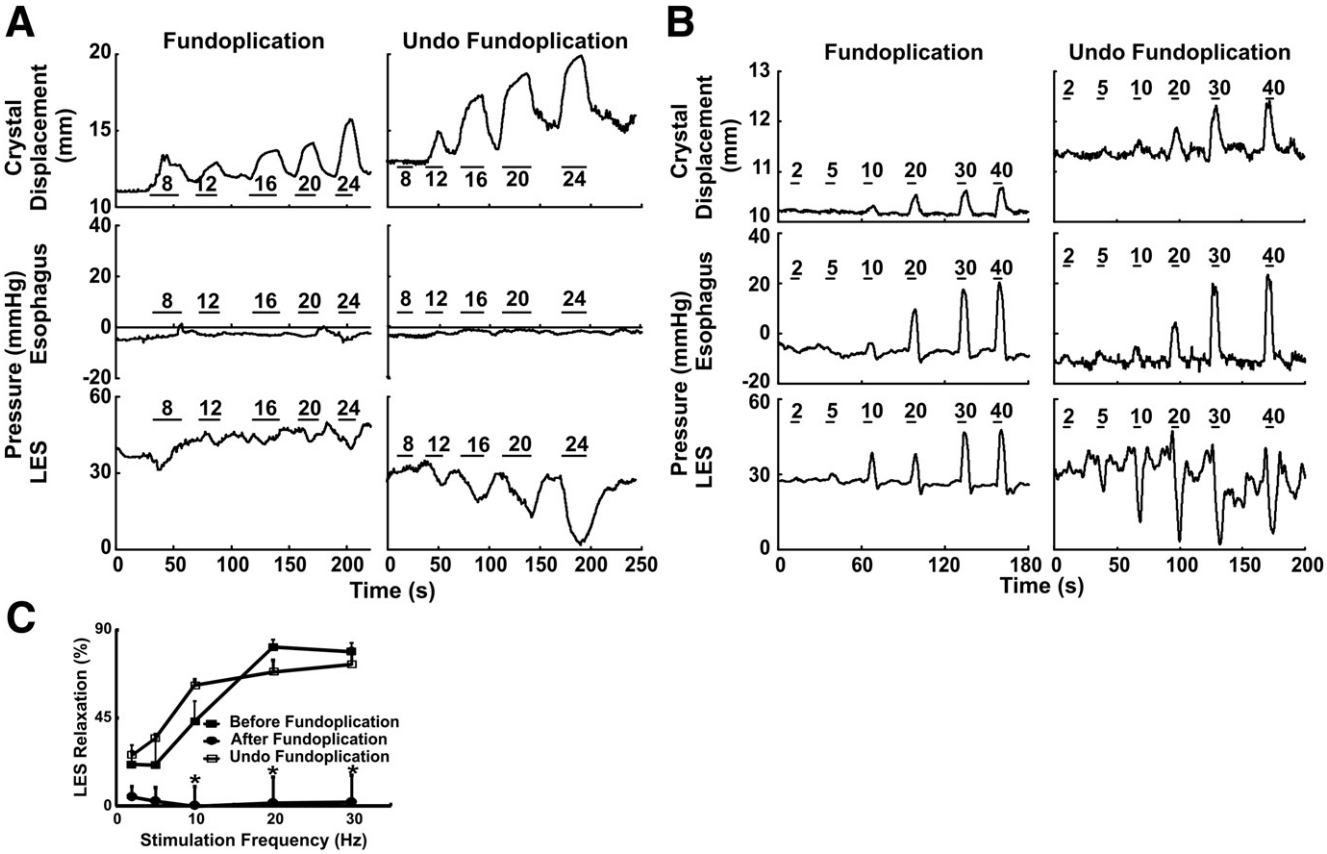

Figure 7. (*A*, *B*) Effect of fundoplication and removal of fundoplication on lower esophageal sphincter (LES) displacement, esophageal contraction, and LES relaxation induced by axial stretch (*A*; numbers represent weight in g) and vagal stimulation-induced LES relaxation (*B*; numbers represent frequency in Hz). Removal of fundoplication restored vagal stimulus and axial stretch-activated LES relaxation. (*C*) Mean percent LES relaxation induced by vagal stimulation before, during, and after removal of fundoplication relaxation (n = 7, $^*P < .01$, comparing before with after fundoplication).

nial displacement and relaxation of the LES in response to axial stretch and vagal nerve stimulation. Diminution of cranial displacement of LES after fundoplication surgery was also reported by Kahrilas et al.[24] They and others have also observed that after fundoplication, swallow-induced LES relaxation is reduced and transient LES relaxations are incomplete.[7–9] Our study makes an important connection between axial shortening and LES relaxation and proves that these 2 things are causally related. Recent studies from our laboratory show that axial stretch on the LES induces LES relaxation through direct activation of inhibitory neurons of the LES.[10,11] In mice that have skeletal muscle esophagus and smooth muscle LES, vagal stimulation-induced LES relaxation is blocked by pancuronium.[11] The latter blocks longitudinal muscle contraction of the esophagus and cranial displacement of the LES. In the current study, we found that the effects of fundoplication are similar to pancuronium in that the cranial displacement of LES and relaxation of LES are both reduced after fundoplication.

Vagus nerve stimulation causes cranial displacement as well as relaxation of the LES and both of the previously mentioned parameters are inhibited by fundoplication. Our findings have implications as to the mechanism by which LES relaxes under physiological conditions. Current thinking is that vagus nerve contains inhibitory and excitatory efferent nerve fibers that innervate the inhibitory and excitatory neurons of the myenteric plexus of the LES, respectively.[25] According to the theory mentioned, inhibitory nerve fibers synapse with the inhibitory neuron,[23,26] which in turn releases nitric oxide to cause LES relaxation. We suggest an alternate mechanism; vagus nerve may only contain excitatory efferent nerve fibers to the esophagus and LES muscles. Those excitatory nerve fibers that mediate contraction of longitudinal muscles of the esophagus may actually be responsible for LES relaxation through activation of stretch-sensitive inhibitory motor neurons of the LES.

Fundoplication is a time-tested efficacious surgical therapy to treat reflux disease. Our study, for the first time, suggests that the mechanism by which fundoplication may prevent reflux is by reducing axial stretch on LES. However, there are a few limitations of our study: (1) it is performed in rats, in which the entire esophagus is comprised of skeletal muscle as opposed to humans, in which distal esophagus is mostly smooth muscle and (2)

we did not study the effects of hiatus hernia on the antireflux mechanism. We described stretch-sensitive mechanism of LES relaxation in opossum in which distal esophagus is entirely smooth muscle and therefore do not believe that mechanism of LES relaxation is different in the rats from the humans. Our findings have relevance for the better design of fundoplication surgery and reducing its complication. Surgeons are extremely careful about preventing mechanical compression of the esophagus by performing either a loose fundoplication or a partial 270-degree wrap, and placing a large bougie in the distal esophagus and LES. However, to the best of our knowledge, no attention is generally paid to the degree of axial restriction placed by fundoplication on the LES. Dysphagia is a common complication of fundoplication for which there may be several reasons, one of which is reduced swallow-induced LES relaxation. Our findings suggest that some sort of calibration with regard to excessive restriction of cranial stretch on LES imposed by fundoplication may prevent its untoward effects. Furthermore, it may be possible to develop novel endoscopic or minimally invasive surgical therapies with a focus toward the axial stretch-sensitive mechanism of LES relaxation.

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Conflicts of interest

The authors disclose no conflicts.

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