

# Metoclopramide Does Not Attenuate Cricoid Pressure-induced Relaxation of the Lower Esophageal Sphincter in Awake Volunteers

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**Background:** The authors examined the influence of metoclopramide on cricoid pressure-induced relaxation of the lower esophageal sphincter (LES) in awake human volunteers.

**Methods:** With local institutional review board approval, measurements of LES and intragastric pressures were made in 10 consenting volunteers before cricoid pressure application, during 15 s of cricoid pressure application, and after release of cricoid pressure. The measurements were repeated after 0.15 mg/kg intravenous metoclopramide. Cricoid pressure was applied by one investigator trained to consistently apply a force of 44 N.

**Results:** Cricoid pressure resulted in immediate decrease in LES and barrier pressures from  $14.1 \pm 2.9$  mmHg to  $3.2 \pm 3.7$  mmHg and from  $9.6 \pm 3.4$  mmHg to  $-1.8 \pm 2.9$  mmHg, respectively. These pressures promptly returned to baseline values after release of cricoid pressure. LES and barrier pressures increased after metoclopramide from  $14.5 \pm 3.1$  to  $19.6 \pm 4.7$  mmHg and from  $10.2 \pm 3.6$  to  $14.1 \pm 5.5$  mmHg, respectively. Cricoid pressure applied after metoclopramide resulted in immediate decreases in LES and barrier pressures to levels comparable to cricoid pressure before metoclopramide, but immediately returned to precricoid values after release of pressure.

**Conclusions:** The current investigation demonstrates that cricoid pressure reflexly decreases LES tone and barrier pressure in awake subjects. Although metoclopramide increased LES and barrier pressures, it did not attenuate cricoid pressure-induced relaxation of the LES and barrier pressures and thus seems to have no value in preventing gastroesophageal reflux during cricoid pressure. Metoclopramide may be useful in preventing reflux when there is need to release or discontinue cricoid pressure.

SINCE its description by Sellick<sup>1</sup> in 1961, cricoid pressure has become an integral component of the rapid sequence induction-intubation technique in patients at risk of aspiration of gastric contents.<sup>1-5</sup> It has also been shown to prevent gastric insufflation in pediatric<sup>6</sup> and adult patients.<sup>7</sup> More recently, it has been demonstrated that cricoid pressure induces relaxation of the lower esophageal sphincter (LES) in human volunteers.<sup>8</sup> This

decrease in LES tone<sup>8</sup> has been proposed to explain the occasional occurrence of pulmonary aspiration before tracheal intubation despite the application of cricoid pressure.<sup>9,10</sup>

For more than three decades, metoclopramide has been used for the treatment of gastrointestinal disorders.<sup>11-15</sup> In addition to acting centrally as a neuroleptic dopamine D2 receptor antagonist, it also acts peripherally to facilitate acetylcholine transmission at selective muscarinic receptors, resulting in an increased gastric and intestinal motility, enhanced gastric emptying, an antiemetic effect, and increased tone of the LES.<sup>11-15</sup>

To our knowledge, there have been no studies examining the influence of metoclopramide on cricoid pressure-induced relaxation of the LES. This investigation was designed to determine whether metoclopramide can prevent or modify the decrease in LES pressure induced by cricoid pressure. Such findings could have clinical relevance and may yield information regarding the mechanism of LES relaxation accompanying cricoid pressure.

## Materials and Methods

After the study protocol was approved by the institutional review board at Illinois Masonic Medical Center, Chicago, Illinois, signed informed consents were obtained from 11 male volunteers (medical students and resident physicians). Each volunteer received financial compensation for participating in the study. The volunteers were fully informed about the study details beforehand. The mean age was  $32 \pm 6.7$  yr, and the mean body mass index was  $24.7 \pm 1.6$  kg/m<sup>2</sup>. The volunteers had no history of cardiac, respiratory, neurologic, or gastrointestinal disorders. No subject was receiving any long-term medications, and none had any known contraindications to metoclopramide. Each volunteer had a light breakfast on the day of the studies and then fasted until mid afternoon, when the studies were performed in the Gastrointestinal Laboratory. The volunteers were told that cricoid pressure required rather firm compression and were instructed to signal (raise their hand) when the pressure became too painful to sustain or when airway obstruction was felt. They were also informed that the duration of cricoid pressure would last 15 s at each application and were asked not to swallow during the maneuver.

Before the study commenced, an intravenous access was obtained and pulse rate was monitored continuously. A multilumen manometric catheter (Synectics

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Medical, Irving, TX) was introduced *via* the nose after topical anesthesia (2% lidocaine jelly) was applied to the nares. The catheter was advanced while the volunteer sipped small amounts of water until the distal end of the catheter was in the stomach. The high-pressure zone, defined as the LES, was identified using a pull-through technique as has been previously described.<sup>16,17</sup> The catheter was thereafter fixed for the duration of the study. Transducers were zeroed to the mid chest position and calibrated before each measurement. Pressure tracings were recorded using a multichannel recording system.

Measurements of LES and intragastric pressures were obtained in each subject before cricoid pressure application, during cricoid pressure application, and after release of cricoid pressure, and all measurements were repeated after administration of metoclopramide. Therefore, each subject acted as his own control. The pressures were continuously recorded, with the volunteers in the supine position. After a 15-min stabilization period following catheter placement, baseline values were recorded with the head in an extended position. A standardized single-handed cricoid pressure was then applied, always by one investigator (M.R.S.) experienced in performing the maneuver and trained to consistently apply a force of 44 N.<sup>1,18</sup> The pressure was applied to the extent tolerated by the volunteer for a period of 15 s. The procedure was performed in triplicate at 45-s intervals. Lower esophageal pressure and intragastric pressures were again recorded after cricoid pressure was released.

After a 15-min recovery period, 0.15 mg/kg metoclopramide was slowly given intravenously over a period of 1 min. After 5 min, baseline recordings were again obtained, followed by cricoid pressure for 15 s in triplicate at 45-s intervals. The pressures were again recorded after release of cricoid pressure. The volunteers were ques-

tioned about their experience and their comments were sought.

The pressure tracings were interpreted by an experienced gastroenterologist who had no previous knowledge of the study protocol or its objectives. The mean values of intragastric and LES pressures were obtained in triplicate at each measurement period and averaged. The barrier pressure was calculated as LES pressure minus the intragastric pressure.

#### Statistical Analysis

All statistical analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL). One-way analysis of variance for repeated measures and the Student-Newman-Keuls tests were used to determine statistically significant differences between mean measured or calculated pressures obtained at each measurement period. The Levene test of equality of error variances was used to confirm equal error variance is equal across time periods. Statistical significance was accepted at  $P < 0.05$ . Data are displayed as mean  $\pm$  SD.

#### Results

One volunteer was unable to tolerate the insertion of the nasogastric catheter and was excluded from the study. All other volunteers tolerated the procedure and were able to sustain 15-s periods of cricoid pressure at each application. Data were available for 10 subjects. There were no complications associated with this study. Three volunteers commented that there was a transient feeling of airway obstruction during cricoid pressure, but they were able to tolerate the pressure for periods of 15 s.

Figure 1 displays a typical tracing of LES and intragastric pressure recordings before application of cricoid

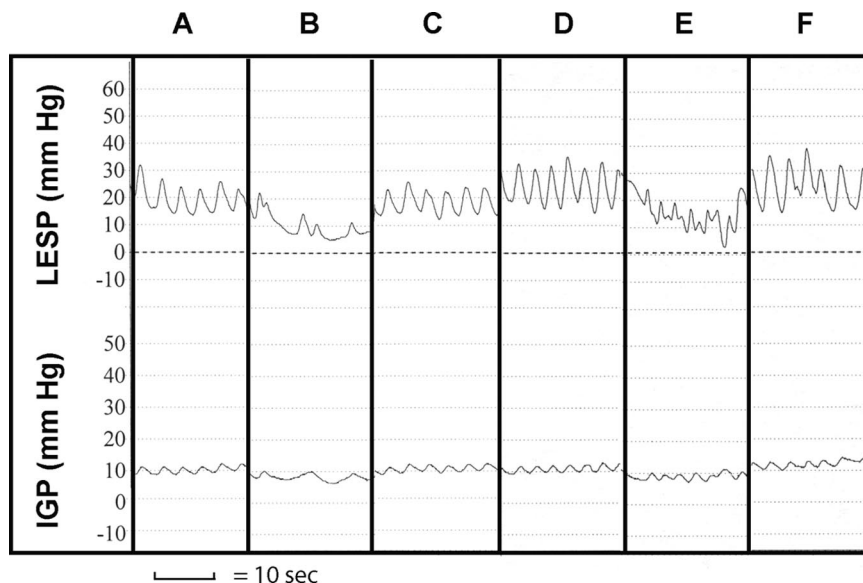


Fig. 1. A typical tracing showing lower esophageal sphincter pressure (LESP) and intragastric pressure (IGP) recordings before application of cricoid pressure (A), during application of cricoid pressure (B), after release of cricoid pressure (new baseline) (C), after administration of 0.15 mg/kg metoclopramide (D), during application of cricoid pressure (E), and after release of cricoid pressure (F). Paper speed = 1 mm/s.

**Table 1. Lower Esophageal Sphincter, Intra-gastric, and Barrier Pressures Obtained in 10 Volunteers before and after Administration of 0.15 mg/kg Intravenous Metoclopramide**

	Before Metoclopramide			After Metoclopramide		
	Baseline	Cricoid Pressure Applied	Cricoid Pressure Released	Baseline	Cricoid Pressure Applied	Cricoid Pressure Released
Lower esophageal pressure	14.1 ± 2.9	3.2 ± 3.7*	14.5 ± 3.1	19.6 ± 4.7†	5.0 ± 4.3*	20.2 ± 5.2†
Intra-gastric pressure	4.6 ± 1.4	5.4 ± 1.3	4.1 ± 2.3	5.7 ± 1.9	5.8 ± 2.3	6.5 ± 2.8
Barrier pressure	9.6 ± 3.4	-1.8 ± 2.9*	10.2 ± 3.6	14.1 ± 5.5†	-0.2 ± 5.1*	13.8 ± 6.1†

Data are in mmHg ± SD.

\*  $P < 0.05$  vs. respective baseline value. †  $P < 0.05$  vs. respective pre-metoclopramide value.

pressure, during application of cricoid pressure, after release of cricoid pressure (new baseline), after administration of 0.15 mg/kg metoclopramide, during application of cricoid pressure, and after release of cricoid pressure.

Mean values for LES, intra-gastric, and barrier pressures with and without cricoid pressure and before and after metoclopramide administration are shown in table 1. The initial application of cricoid pressure resulted in significant decreases in LES pressure from  $14.1 \pm 2.9$  mmHg to  $3.2 \pm 3.7$  mmHg and barrier pressure from  $9.6 \pm 3.4$  mmHg to  $-1.8 \pm 2.9$  mmHg, but the intra-gastric pressure remained unchanged. Upon release of cricoid pressure, there was an immediate return of LES and barrier pressure to baseline values (table 1). After administration of metoclopramide, LES and barrier pressures increased significantly from  $14.5 \pm 3.1$  to  $19.6 \pm 4.7$  mmHg and  $10.2 \pm 3.6$  to  $14.1 \pm 5.5$  mmHg, respectively. Intra-gastric pressure did not change. Application of cricoid pressure after metoclopramide administration resulted in significant decreases in LES pressure from  $19.6 \pm 4.7$  mmHg to  $5.0 \pm 4.3$  mmHg and barrier pressure from  $14.1 \pm 5.5$  mmHg to  $-0.2 \pm 5.1$  mmHg, but immediately returned to the precricoid pressure values when cricoid pressure was released (table 1). The mean values for LES and barrier pressures obtained during cricoid pressure, before or after metoclopramide administration, were not different. Intra-gastric pressure did not change with application of cricoid pressure before or after administration of metoclopramide.

## Discussion

A dose-response study of the effect of metoclopramide on the LES and barrier pressure would have been desirable in the current study. Because of its known side effects, only one dose of metoclopramide, which is the commonest dose used clinically, was investigated. A previous study, however, demonstrated a dose-related increase in LES pressure with oral and intravenous administration of metoclopramide in normal subjects and in patients with symptomatic gastroesophageal reflux.<sup>19</sup> The drug was injected slowly as recommended by the

manufacturer to minimize side effects. Because the onset of action after intravenous injection is 1–3 min, 5 min was allowed before measurements were made.

To minimize the variability in the application of cricoid pressure and to produce accurate and consistent pressure, a single experienced investigator, trained to apply a force of 44 N, applied cricoid pressure in all volunteers. Herman *et al.*<sup>18</sup> showed that with proper training, the use of correct force applied to the cricoid cartilage is reproducible within a range of 2 N. We used a greater force (44 N) than that used in a previous investigation, where 20, 30, and 40 N were used, which is sufficient to occlude the esophagus in most patients.<sup>20,21</sup> Cricoid pressure was limited to 15 s because some awake volunteers may not tolerate cricoid force for more than 20 s and may also experience airway obstruction. In the current study, swallowing, which can cause a transient decrease in LES pressure,<sup>22,23</sup> was eliminated during the measurements.

Baseline measurements of the LES, intra-gastric, and barrier pressures in the current study were all within normal values. Our findings confirm previous findings<sup>8</sup> that cricoid pressure is associated with substantial reduction of the LES tone, while there was no change in intra-gastric pressure. The LES to intra-gastric pressure gradient (the barrier pressure) disappeared completely during application of cricoid pressure. Tournadre *et al.*<sup>8</sup> showed that a decrease in LES pressure occurs even with cricoid pressure less than that required to occlude the esophagus. In that study, LES pressure decreased by 38% with the application of cricoid pressure using a force of 20 N. Increasing the force to 40 N resulted in an additional 12% decrease in LES pressure. The greater decrease in LES pressure accompanying cricoid pressure found in our study (70%) may be related to the greater force applied.

It has been postulated that the mechanism of cricoid pressure-induced relaxation of the LES tone is reflex in nature.<sup>8</sup> A similar decrease in LES tone occurs during swallowing,<sup>22,23</sup> pharyngeal stimulation,<sup>24</sup> and laryngeal mask airway insertion.<sup>25</sup> This seems to be initiated by stimulation of mechanoreceptors in the pharynx.<sup>8,24,25</sup> The finding that metoclopramide did not prevent or

even attenuate cricoid pressure-induced relaxation of the LES lends support to a reflex mechanism. A recent study of 10 awake volunteers suggested that cricoid pressure-induced relaxation of the LES can be abolished by remifentanyl infusion and a bolus of propofol, suggesting that by blocking the pain or discomfort due to cricoid pressure, opioids and drugs used to induced anesthesia can prevent stimulation of the mechanoreceptors in the pharynx, which causes relaxation of the LES.<sup>26</sup> More studies are needed to confirm the beneficial effects of opioids and other drugs in preventing or attenuating cricoid pressure-induced relaxation of the LES.

Based on the belief that a decrease in barrier pressure increases the risk of regurgitation, particularly if intragastric pressure is increased or LES pressure is decreased,<sup>27</sup> it has been suggested that the occurrence of pulmonary aspiration despite cricoid pressure may be related to the associated relaxation of the LES.<sup>8</sup> This seems unlikely for several reasons. First, the purpose of cricoid pressure is to occlude the esophageal lumen, so that gastric or esophageal contents do not reach the pharynx and tracheobronchial tree, and not to prevent gastroesophageal reflux. Second, the occurrence of pulmonary aspiration despite cricoid pressure may be related to inadequate or improper application.<sup>28</sup> Third, the incidence of pulmonary aspiration, with the use of a laryngeal mask airway, which is known to decrease LES tone by a mechanism similar to that of cricoid pressure, is not higher than that associated with tracheal intubation.<sup>29</sup> Fourth, although there is a known relation between the decrease in LES pressure and gastroesophageal reflux, it is not possible to establish or define the barrier or LES pressure values below which reflux will occur.<sup>30</sup>

The current investigation confirms previous findings demonstrating the efficacy of metoclopramide in increasing the tone of the LES.<sup>11-15</sup> In all volunteers, there was consistent increase in LES and barrier pressures after metoclopramide administration. Nevertheless, the LES-intragastric pressure gradient still disappeared when cricoid pressure was applied. Upon release of cricoid pressure, the gradient was immediately reestablished to its post-metoclopramide values. Although metoclopramide does not seem to offer any benefit in increasing the barrier pressure during cricoid pressure, it may have clinical significance in preventing gastroesophageal reflux when there is a need to release or discontinue cricoid pressure. Although not all investigators are in agreement,<sup>31-33</sup> studies have shown that cricoid pressure may displace the esophagus,<sup>34</sup> compromise airway patency,<sup>35,36</sup> make ventilation with a facemask or with a laryngeal mask airway more difficult,<sup>37</sup> cause difficulty placing a endotracheal tube<sup>38,39</sup> or threading a tube over an introducer,<sup>37</sup> and alter visualization of the larynx by a fiberoptic scope.<sup>36</sup> Also, repositioning of the hand dur-

ing cricoid pressure and inadvertent release of cricoid pressure are common occurrences during anesthetic induction.<sup>28</sup> If cricoid pressure is released under these circumstances, to enhance ventilation, glottic visualization, or tracheal intubation or to improve the application of cricoid pressure, previously administered metoclopramide could maintain a higher baseline LES tone and thus possibly prevent gastroesophageal reflux.

In conclusion, the current study concurs with previous investigations demonstrating that in awake subjects, cricoid pressure induces reflex relaxation of the LES, resulting in a decrease in barrier pressure. Upon release of cricoid pressure, there is an immediate return of the LES tone and barrier pressure to baseline values. Although metoclopramide increases the tone of the LES, it does not attenuate cricoid pressure-induced relaxation of the LES. However, metoclopramide may be beneficial in maintaining higher barrier pressure, thus preventing gastroesophageal reflux in situations where cricoid pressure is released.

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