Genesis of multipeaked waves of the esophagus: repetitive contractions or motion artifact?

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Sampath NJ, Bhargava V, Mittal RK. Genesis of multipeaked waves of the esophagus: repetitive contractions or motion artifact?. Am J Physiol Gastrointest Liver Physiol 298: G927–G933, 2010. First published April 1, 2010; doi:10.1152/ajpgi.0044.2010.—Multipeaked waves (MPW) in the distal esophagus occur frequently in patients with esophageal spastic motor disorders and diabetes mellitus and are thought to represent repetitive esophageal contractions. We aimed to investigate whether the relative movement between a stationary pressure sensor and contracted peristaltic esophageal segment that moves with respiration leads to the formation of MPW. We mathematically modeled the effect of relative movement between a moving pressure segment and a fixed pressure sensor on the pressure waveform morphology. We conducted retrospective analysis of 100 swallow-induced esophageal contractions in 10 patients, who demonstrated ≥30% MPW on high-resolution manometry (HRM) during standardized swallows. Finally, using HRM, we determined the effects of suspended breathing and hyperventilation on the waveform morphology in 10 patients prospectively. Modeling revealed that relative movement between a stationary pressure sensor and a moving contracted segment, contraction duration, contraction amplitude, respiratory frequency, and depth of respiration affects the waveform morphology. Retrospective analysis demonstrated a close temporal association with the onset of second and subsequent contractions in MPW with respiratory phase reversals. Numbers of peaks in MPW and respiratory phase reversals were closely related to the duration of contraction. In the prospective study, suspended breathing and hyperventilation resulted in a significant decrease and increase in the MPW frequency as well as the number of peaks within MPW respectively. We conclude that MPW observed during clinical motility studies are not indicative of repetitive esophageal contraction; rather they represent respiration-related movement of the contracted esophageal segment in relation to the stationary pressure sensor.

manometry; esophageal motor disorders; diabetic neuropathy; diaphragmatic movement; peristalsis

NORMAL ESOPHAGEAL CONTRACTIONS recorded by manometry usually have a single peak. Double, triple, and multipeaked contraction waves (MPW), presently thought to be attributable to repetitive contractions of the esophagus, are not uncommonly observed during routine clinical manometry studies in patients with esophageal symptoms. Loo et al. (12) observed that MPW contractions occur more frequently in those patients with diabetes mellitus who have autonomic neuropathy. On the other hand, Richter et al. (14, 15) found that bipeaked contractions are not uncommon in normal healthy subjects, albeit their frequency is much lower than those observed by Loo et al. in diabetic patients. Clouse et al. (5) suggested that MPW are seen most frequently in the distal esophagus and reflect an imbalance between excitatory and inhibitory innervation of the distal esophagus. The imbalance in innervation occurs commonly in patients with spastic motor disorders, i.e., diffuses esophageal spasm and nonspecific motor disorders of the esophagus. Impaired inhibitory innervation is felt to be the cause of simultaneous contractions of the esophagus (1). On the basis of our review of the literature, the present thinking is that MPW occurring with a frequency of >30% during clinical motility studies reflect dysmotility of the esophagus.

Dodds et al. (6, 7) observed that the lower esophageal sphincter (LES) moves in oral and aboral directions with expiration and inspiration, respectively, but the pressure sensor of the manometry catheter does not move with it. The relative movement between the pressure sensor and LES introduces a motion artifact in the LES pressure recording. At any given time during peristalsis (primary or secondary), a segment of the esophagus is contracted, and this segment moves sequentially along the length of the esophagus. The pressure is usually highest in the center of contracted segment (bell-shaped pressure distribution). We propose that the relative movement between a pressure sensor (that does not move with inspiration and expiration) and a moving/peristaltic-contracted segment (that moves up with expiration and down with inspiration) may affect the pressure waveform morphology. To test the above hypothesis, we conducted a three-part study: 1) mathematical modeling in which we tested the effects of relative movement between a peristaltic-contracted segment and a stationary pressure sensor on the waveform morphology, 2) retrospective analysis of manometric recordings of patients with esophageal symptoms who demonstrated >30% MPW during standardized swallows to determine the relation between respiratory phase reversal and the onset of second and subsequent peaks in the MPW, and 3) a prospective study in which we tested the effect of suspended breathing and hyperventilation on the pressure waveform morphology in patients with >30% MPW during the baseline recording period.

MATERIALS AND METHODS

MPW are esophageal contraction waves that have two or more peaks instead of having a bell shaped sinusoidal morphology and single peak. Our criteria for determining a MPW were as follows: 1) the trough between the peaks did not reach esophageal baseline; 2) the peak of least amplitude was greater than or equal to 10 mmHg above the interpeak trough; and 3) the peak of least amplitude was separated from the neighboring pressure peak by greater than or equal to 1 s (3). In the first part of the study, we generated a mathematical model to test the effects of relative movement between a contracted segment with peristaltic propagation and a stationary pressure sensor on the pressure waveform morphology (see the appendix in the supplemental material; supplemental material for this article is available online at the American Journal of Physiology Gastrointestinal and Liver Physiology website). The model simulated esophageal physiology and respiration-related movement on the basis of the following input

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parameters, contraction duration, propagation velocity, diaphragm excursion during respiration, respiratory frequency, and phase of respiration relative to the onset of esophageal contraction. The following assumptions were made in our model: 1) at a given time, a 8–13-cm length of the esophagus is contracted, and the pressure in this contracted segment is distributed semisinusoidally (bell-shaped curve) (4). 2) A contraction wave traverses the length of the esophagus at a velocity of 1.5–6.0 cm/s. 3) With inspiration, the diaphragm moves down 1–3 cm, along with the lower end of the esophagus, and the contracted segment moves with it because the lower end of the esophagus and the diaphragm are attached by the phrenoesophageal ligament. On the other hand, with expiration, the esophagus and the contracted segment move in the oral direction. 4) The distal end of the esophagus, which is anchored to the diaphragm, will move the most with inspiration and expiration, and the degree of movement decreases in direct proportion to the distance proximal to the diaphragm. 5) The pressure transducer does not move with inspiration and expiration because the manometry catheter is anchored to the tip of the nose (7). 6) The frequency of respiration varies between 10–20 breaths/min. 7) The movement of the esophageal segment attributable to respiration is sinusoidal. All of the above assumptions are based on generally well-accepted and published physiological data. The mathematical model helped us to identify the effect of various parameters such as respiratory phase reversal, respiratory frequency, depth of respiration, duration of contraction, and amplitude of contraction on the waveform morphology. In the second part of the study, we conducted retrospective review of high-resolution manometry (HRM) recordings of 10 patients, who demonstrated equal to or >30% MPW during standardized wet swallows on routine clinical manometry. One hundred wet swallow-induced esophageal contractions were analyzed (8–12/subject). These motility studies were performed at the UCSD GI function laboratory using the HRM system (Sierra Scientific Instruments, Los Angeles, CA.) Patients included in the study were referred to the UCSD Motility Laboratory for evaluation of dysphagia, chest pain, and/or heartburn. We arbitrarily chose three pressure sensors, located 3, 7, and 11 cm above the LES in the distal esophagus, and these were kept constant across subjects. A MPW was identified when it met the criteria listed above at one or more of these three esophageal sites. A gastric pressure sensor was used as a surrogate marker for the pressure changes in the abdominal cavity with inspiration and expiration. Inspiration causes the diaphragm to move down, resulting in increase in gastric pressure, and conversely with expiration the diaphragm moved up, causing the gastric pressure to decrease. A change in the polarity of gastric pressure was used to denote respiratory phase reversal during a swallow. Each respiratory cycle consists of two phases, i.e., inspiration and expiration, and therefore has two phase reversals. For each MPW, the relationship between respiratory phase reversal and the onset of each peak in the MPW was determined. We conducted an intra- as well as intersubject comparison to identify differences in the respiratory waveform and pressure waveform characteristics between swallows that resulted in single-peaked vs. MPW. In the third part of the study, we recruited patients whose clinical motility studies demonstrated >30% MPW during standardized swallows in the baseline recording period. All clinical esophageal motility studies were performed using the Sierra Scientific HRM system.

The Human Research and Safety Committee of the University of California San Diego approved the study protocol, and each subject signed an informed consent before their participation in the study. Patients were trained to hold their breath at end-expiration for at least 15 s (suspended breathing) after each standardized (5 ml) swallow. Adequate suspension of breathing was confirmed by observing cessation of phasic variations of gastric pressure recording. Subjects were also trained to increase the frequency of respiration to at least 1.5 times their baseline frequency (hyperventilation). During hyperventilation, subjects increased the depth of diaphragm movement by performing “diaphragmatic breathing.” For the latter, the trainer placed his/her hand over the anterior abdominal wall and asked the subject to push the hand out (anteriorly) with inspiration. Adequate rate and depth of respiration during hyperventilation were confirmed by observing the gastric pressure recording. Following 10 standardized swallows in the baseline condition, 10 swallows were performed during suspended breathing and another 10 swallows while subjects hyperventilated with abdominal breathing. In addition, one subject with no MPW in the baseline period during standardized swallows performed 10 swallows with the hyperventilation protocol.

**Data analysis.** The frequency of MPW and the average number of peaks in the MPW during swallow-induced contractions at baseline (spontaneous) breathing, suspended breathing, and hyperventilation protocols were determined. The criteria for MPW in this protocol were identical to those used in the retrospective analysis of MPW. In the final analysis of differences in frequency of MPW and number of peaks in MPW, only those subjects who were able to complete both suspended breathing and hyperventilation protocols were included (n = 8). For the nine prospective subjects who were able to complete at least the spontaneous (baseline) breathing and hyperventilation part of the protocols, we determined the frequencies of MPW in the distal (at sensors located 3, 7, and 11 cm above the LES) and proximal (at sensors located 15, 18, 21, and 24 cm above the LES) esophagus during baseline and hyperventilation breathing.

We analyzed pressure tracings from the mathematical model, retrospective data during baseline recording, and prospective data during baseline and hyperventilation to evaluate whether the onset of second peak traversed the esophagus in a retrograde or antegrade fashion. For this analysis, pressure tracings from the pressure transducers spaced 1 cm apart in the distal esophagus were reviewed with regard to the progression of onset of second and subsequent pressure peaks in the MPW. All patients recruited in the prospective study were compensated with a nominal amount of money.

**Statistical analysis.** All data are shown as median values, unless otherwise indicated. For the prospective study, all statistical comparisons were performed using Wilcoxon Signed-Rank test with post ad hoc comparison.

**RESULTS**

The mathematical model demonstrated that the timing of respiratory phase reversal relative to the pressure waveform, depth of respiration, frequency of respiration, contraction duration, and contraction amplitude has significant effects on the waveform morphology. Figure 1 shows the effects of some of these parameters on the waveform morphology. In addition, when we took into account the relative movement of peristaltic wave with respect to the respiratory phase reversal and considered that the respiration-related movement of the esophagus is largest close to the esophagogastric junction, we observed a retrograde conduction of the onset of second and subsequent wave in the MPW (Fig. 2).

The records of patients with spontaneous MPW (retrospective analysis) demonstrated a close temporal correlation between the onset of second and subsequent contractions in the MPW with respiratory phase reversals (inspiration or expiration) (Fig. 3). The onset of the second contraction in the MPW coincided with the onset of expiration (peak of gastric pressure wave) in 90% of MPW and with the onset of inspiration in 10% of MPW studied. The onset of each peak in the MPW was associated with respiratory phase reversal. Therefore, the numbers of peaks in the esophageal contraction are closely related to the duration of contraction as well as the number of respiratory phase reversals, i.e., inspiration and expirations (Fig. 4). The contraction amplitude also demonstrated a correlation with the incidence of MPW, but this association was not as strong as...
the one with the contraction duration. Analysis of the onset of second and subsequent contractions in the MPW, in the pressure sensors, spaced 1 cm apart, revealed a retrograde propagation of the onset of second and subsequent waves (Fig. 2).

A total of nine patients met inclusion criteria for the prospective study. The main indication(s) for the motility study referral were heartburn, chest pain, and dysphagia. On the basis of the clinical manometry data during spontaneous breathing, three patients met criteria for nutcracker esophagus, and six were diagnosed with a nonspecific motor disorder. We saw distinct changes in the waveform morphology in all subjects during different breathing patterns, and an example of this is illustrated in Fig. 5. Eight of nine patients completed swallows

Fig. 1. Mathematical modeling of factors affecting pressure waveform morphology. In each row, the top trace represents the esophageal pressure waveform, whereas the bottom one represents respiration. i: Effect of change in temporal relationship between the onset of respiratory phase (inspiration and expiration) relative to the onset of contraction wave on the waveform morphology. The spikes in the respiratory waves in A, B, and C show the subtle variation in the temporal occurrence of peak inspiration. The model demonstrates that both the number of peaks in the multipeaked waves (MPW) increases as the temporal relationship between respiration and waveform morphology change. ii: Increase in the difference between adjacent peaks is related to the amplitude of diaphragmatic excursion. D: total diaphragmatic excursion = 0.5 cm. E: total diaphragmatic excursion = 1.5 cm. F: total diaphragmatic excursion = 3 cm. iii: Increase in the number of peaks related to the total duration of the contraction. G: contraction duration = 4 s. H: contraction duration = 6 s. I: contraction duration = 9 s. In each panel, except for the parameter being manipulated, all other parameters were kept constant.

Fig. 2. Retrograde propagation of the onset of second and subsequent peaks in the MPW. i: Mathematical model simulates changes in the amplitude and timing of esophageal movement in the proximal and distal esophagus. Because the diaphragm is anchored to the lower end of esophagus, diaphragm-related movement of the esophagus will occur earlier and will be of greater amplitude in the distal compared with the proximal esophagus. A, B, and C: pressure tracings from proximal esophagus, middle, and distal esophagus, respectively. ii: Waves D, E, and F are from 3 consecutive pressure transducers, spaced 1 cm apart, in the distal esophagus. This pressure record was obtained from a patient with spontaneous MPW during baseline breathing. iii: Similarly, waves G, H, and I are pressure records from 3 transducers located 1 cm apart from a prospective study subject during the baseline breathing period.

Fig. 3. Temporal correlation between the onset of second and subsequent contractions of the MPW and respiratory phase reversal. The pressure recording from a single transducer (solid white line) located 7 cm above the lower esophageal sphincter (LES) that recorded a MPW was superimposed on the high-resolution manometry contour plot. The lower pressure tracing (solid red line) shows measurement from a pressure transducer located in the stomach and represents respiratory cycle. The dashed black lines indicate a single point in time. Note that the onset of each peak in a MPW correlates temporally with the respiratory phase reversal (from peak inspiration to expiration).

Fig. 4. Relationship between the contraction duration and the number of respiratory phase reversals during the contraction with the number of peaks in the MPW. Left: each data point represents the mean pressure duration for all swallows that resulted in MPW and the corresponding number of peaks. Right: each data point represents the mean number of respiratory phase reversals during all swallows that resulted in MPW and number of peaks. The error bars in each graph represent the standard error of the mean. Note a strong relationship between the contraction duration and number of phase reversals with the number of peaks in the MPW.
During all three study periods, i.e., spontaneous (baseline) breathing, suspended breathing, and hyperventilation. One subject could not adequately suspend her breath following swallows but was able to perform the hyperventilation breathing protocol. In the eight subjects who completed all three parts of the study, the frequency of MPW in the distal esophagus was significantly higher during hyperventilation (Fig. 6C), compared with the baseline period (median value 95 vs. 60%, P = 0.024). On the other hand, the frequency of MPW during suspended breathing (Fig. 6C) was significantly lower compared with the spontaneous breathing (median value of 20 vs. 60%, P = 0.024). The average number of peaks within the MPW (Fig. 6D) increased from a median value of 1.6 at the baseline to 2.3 with hyperventilation (P = 0.024) and decreased to 1.2 with suspended breathing (P = 0.022).

For nine subjects who completed the hyperventilation protocol, the frequency of MPW increased in the distal esophagus (Fig. 6B) from a median value of 55% at baseline breathing to 100% with hyperventilation (P < 0.01). In the proximal esophagus (Fig. 6A), where MPW are not known to occur commonly, the frequency of MPW increased from median value of 0% at baseline breathing to 40% with hyperventilation (P < 0.01). Similar to the observations made in the mathematical model and retrospective analysis, the onset of second and subsequent contractions in the hyperventilation-induced MPW revealed retrograde propagation (Fig. 2iii).

In a single subject with no MPW during baseline breathing, hyperventilation induced MPW in eight out of ten swallows. Of these, seven were double peaked and one was a triple-peaked wave.

**DISCUSSION**

In summary, our data show the following: 1) the mathematical model demonstrates the effect of relative movement between the contracted esophageal segment and pressure sensor on the waveform morphology. It revealed that the waveform morphology changes with the relative movement, from a single peak wave to bipeaked or triple-peaked wave; 2) analysis of spontaneous MPW in patients revealed that the onset of second and subsequent peaks in the MPW correspond to the respiratory phase reversals. Contraction duration and number of respiratory phase reversals are the major determinants of the number of peaks in the MPW; and 3) in patients with MPW, suspended breathing decreases and hyperventilation increases the incidence of MPW and the number of peaks in the MPW.

The major abnormalities detected during routine clinical manometry studies are disorders of peristalsis (aperistalsis or simultaneous contractions), abnormality of contraction amplitude (low or high), and contraction duration (16). Increased duration of contraction may occur along with some of the above described abnormalities, or it may occur by itself (8, 11). Similarly, increased incidence of MPW occurs with other esophageal contraction abnormalities but at times may occur even when the other esophageal contraction parameters are normal. MPW have been associated with the presence of autonomic neuropathy in diabetics (12) and spastic motor disorders such as diffused esophageal spasm and nutcracker esophagus (5). Clouse et al. (5) suggested that MPW are markers of defective inhibitory innervation of the esophagus. However, Richter et al. (15) found that bipeaked waves are not uncommon in normal subjects and reported a prevalence of 11% after wet swallows in
a study of 95 normal subjects. According to Clouse et al. (3), three or more peaks in the esophageal contractions are never seen in normal subjects and are strongly suggestive of abnormal esophageal motility. Our study shows that the respiration-induced relative motion between the pressure sensor and a moving contracted segment of the esophagus may cause the MPW. We observed that the onset of second and subsequent peaks in the MPW occur with the onset of expiration, at a time when the contracted segment moves in the oral direction (because diaphragm moves in the oral direction and the esophagus moves with it) while the pressure sensor remains stationary. Furthermore, the onset of second peak occurs during the descending limb of the contraction wave in almost 90% of MPW. To visualize how the MPW are recorded, imagine that the peak of the contracted segment has already passed over the pressure sensor, and the latter is recording the descending phase of contraction. At such a time, with the movement of contracted segment in the oral direction, the stationary pressure sensor comes in contact with a different location of the contracted segment that has different pressures. The contracted segment with higher pressure then passes over the pressure sensor one more time, resulting in one more peak or a bipeaked contraction. One can visually see the oral movement of the contracted segment with expiration in HRM (Figs. 3 and 5). A schematic of the sequence of events that we believe produces a MPW is shown in Fig. 7. The same phenomenon may repeat itself if the esophageal contraction duration is prolonged and velocity of peristalsis is low, and more respiratory phase reversals occur during the contraction, thus producing several peaks, i.e., a MPW.

MPW occur with greater frequency in the distal esophagus and are seen rarely in the proximal esophagus. We proposed that the reason for the increased incidence of MPW in the distal esophagus is twofold: 1) contraction duration is greater in the distal esophagus compared with the proximal esophagus; 2) respiratory-related movement of the esophagus is largest in the distal esophagus and smallest in the proximal esophagus. The fundamental reason for the respiratory related movement of the esophagus is the movement of the diaphragm that is anchored to the esophagus by the phrenoesophageal ligament. In accordance with the above explanation, we observed that the majority of MPW occurred between 3- and 11-cm sites above the LES in our retrospective and prospective studies. Also, the increase in incidence of MPW with hyperventilation occurred mostly in the distal esophagus. In the prospective study, there was a slight increase in the incidence of MPW during hyperventilation even in proximal esophagus, which is likely attributable to the fact that the voluntary increase in the diaphragmatic excursion may increase esophageal movement even in the proximal esophagus. In addition, the increased respiratory frequency following each swallow offers increased opportunity for the relative timing of esophageal contraction and respiratory phase reversal to result in a MPW.

Our study suggests a strong temporal correlation between the respiratory phase reversal and the onset of second and subsequent waves of the MPW. Theoretically, it is possible that, with inspiration as the esophagus gets longer, the contracted segment gets stretched, thereby resulting in the pressure distribution over a longer length and therefore a fall in pressure. However, in practical terms, we believe it is unlikely because both the circular and longitudinal muscles are contracted in the contracted segment (2) and a contracted longitudinal muscle would make the elongation of the contracted segment difficult and unlikely. Clouse et al. (5) observed that the onset of second and third pressure peaks in the MPW progresses in an oral direction, or in other words, show a retrograde peristalsis (5). We observed the same in spontaneous MPW analyzed in the retrospective study and induced MPW during hyperventilation in the prospective study. In fact, our mathematical model also predicted the same. We believe the retrograde spread of the onset of second and subsequent pressure waves in the MPW is related to the fact that a point located distally in the esophagus moves greater than the one located proximal to it, and the respiratory phase reversal occurs
at different times of the esophageal pressure wave form at the distal and proximal points.

There are a few limitations of our study. The mathematical model used sinusoidal waves to represent the respiratory cycle, which is only an approximation of actual morphology of respiratory cycle in a real subject. In the prospective part of the study, it was difficult to achieve complete cessation of diaphragmatic movement in some subjects, which was true even in subjects in whom breathing appears to be suspended, on the basis of the gastric pressure waveform morphology. MRI studies of diaphragmatic movement show that some subjects cannot suspend movements of diaphragm completely on a voluntary basis (9, 13). Despite above limitations, our data are quite convincing in that the fundamental abnormality in the MPW is not that the esophageal contractions are repetitive; rather it is that the contraction duration is prolonged (or velocity of peristalsis is slow) and that there is respiration-related movement between the contracted segment and the pressure transducer. A MPW in normal subject is a chance phenomenon of respiratory phase reversal during the descending phase of contraction in the distal esophagus. Because the duration of contraction in normal subject is only 3–6 s, more than two respiratory phase reversals during one esophageal contraction period are highly unlikely, thereby explaining the observation that three or more peaks in the MPW do not occur in the normal subjects. On the other hand, in the presence of prolonged contraction duration, as may be the case in patients with spastic motor disorder and diabetic patients with autonomic neuropathy, several respiratory phase reversals may occur, thus causing many peaks in the MPW. Accordingly, in our study subjects, we found a strong correlation between the number of peaks and the duration of esophageal contraction. We propose that, even though MPW are artifacts of the recording system, they do reflect an abnormality of esophageal contraction, i.e., prolonged duration of esophageal contraction.

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GRANTS

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DISCLOSURES

No conflicts of interest are declared by the authors.

Fig. 7. Schematic of genesis of MPW in the esophagus. A series of images of the esophagus are shown in this schematic in the top and bottom panels. Top: images at different time intervals from t1 through t5. During the entire period of contraction, there is no respiration and no movement of the diaphragm or esophagogastric junction, and hence the pressure sensor does not move in relationship to the contracted segment, thus causing a single-peaked pressure wave. Bottom: on the other hand, at time t3 diaphragm starts to move in the cranial direction with the onset of expiration, thus causing the contracted segment to move in the cranial direction. The latter results in the pressure sensor to come in contact with the part of contracted segment that has higher pressure (p4). As the contracted segment passes over the pressure sensor, a second peak is recorded, resulting in a biphasic wave (p5).
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