

# Topographic Analysis of Esophageal Double-Peaked Waves

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**Background & Aims:** Esophageal double-peaked waves occur with increased frequency in patients with functional esophageal symptoms. This study was undertaken to further understand the mechanisms responsible for their production. **Methods:** Topographic methods that consider temporal and spatial relationships of pressure data were used to examine 74 double-peaked waves detected in 18 subjects referred for manometric evaluation of unexplained symptoms. The studies were performed with a computerized data acquisition and analysis system designed for topographic plotting. **Results:** The second peak appeared to represent muscle contraction that merged with an unusually strong pressure site in the third topographic segment and covered  $6.3 \pm 1.6$  cm ( $33.5\% \pm 8.5\%$  esophageal length) proximal to this site. In 50 swallows (67.6%), the peak itself progressed in a retrograde direction at  $13.2 \pm 10.8$  cm/s, suggesting cephalad extension of a strong distal motor event. Analysis of wave onsets and movement of the peristaltic trailing edge detected retrograde propagation in up to 33.8% of waves, antegrade propagation in 2.7%, and simultaneous contraction in the remainder. **Conclusions:** In symptomatic patients, the second peak in a double-peaked wave is typically a short, simultaneous, or retrograde pressure event in the region of and merging with the third topographic segment in the distal esophageal body. Topographic methods help explain the common association of these waveforms with other features of exaggerated contraction in the distal esophagus and suggest their relationship to inadequate inhibitory nerve function.

Double-peaked waves are common findings by esophageal manometry. The configurations are detected occasionally with swallows in asymptomatic subjects and occur with abnormally increased frequency in up to 28% of patients undergoing evaluations for unexplained esophageal symptoms.<sup>1-3</sup> Double-peaked waves tend to associate with other features of exaggerated contraction, including increased distal wave amplitudes and duration, but the mechanisms underlying the production of these manometric findings are unknown.<sup>3</sup> Further understanding of their pathogenesis might help clarify the vague associa-

tion of this and related motor abnormalities to symptoms.<sup>4,5</sup>

Topographic methods consider both temporal and spatial relationships of pressure data.<sup>6,7</sup> An increased number of recording sites provides more accurate representation of pressure events in the axial orientation; 3-dimensional plotting methods interpolate between sites and conveniently display the large data set.<sup>8</sup> Topographic methods have shown that normal peristalsis is comprised of a chain of 3 pressure segments in the esophageal body that merge with a fourth segment during lower esophageal sphincter after-contraction.<sup>7,9</sup> In the esophageal body, the first segment extends from the upper esophageal sphincter, ends in a prominent pressure trough that separates it from the remaining segments in the esophageal body, and presumably represents skeletal muscle contraction.<sup>7</sup> Peristalsis through the remainder of the smooth muscle esophageal body appears as 2 sequential segments that show more variability in their relative strength and separation from swallow to swallow.<sup>10</sup> A pressure trough further separates these segments from lower sphincter after-contraction as peristalsis is completed. Because topographic methods interpolate pressure data across recording sites, the findings can be visualized using 3-dimensional plots or as a cine of the propagating pressure wave as it travels in the axial direction.<sup>8</sup>

Formative studies employing topographic methods in the esophagus used averaged results from many swallows to overcome limitations in the number of available recording sites.<sup>7,9</sup> Using these methods, double-peaked waves appeared clustered near the junction of the 2 segments in the distal esophageal body.<sup>7</sup> The hypothesis was offered that the waveforms may result from poor coordination in contraction of these segments.<sup>7</sup> The mechanism could not be further clarified, however, because double-peaked waves are sporadic events that are poorly represented when other swallows are intermixed in an averaged model. A system has since been developed for creating topographic plots from individual swallows that is not restricted by these methodological limitations.<sup>8</sup> These methods were applied in the present investigation

to see if the mechanisms underlying development of double-peaked waves could be further determined in a group of patients without diabetes or other disorders associated with neuropathy.

## Patients and Methods

### Subjects

The manometric studies used in this report were selected from those of subjects referred to the Digestive Disease Clinical Center of Barnes-Jewish Hospital, St. Louis, Missouri, for clinical esophageal manometry. Included subjects were identified post hoc if the study showed one or more double-peaked waves as defined below. Patients with diabetes mellitus or other disorder associated with neuropathy were excluded. Using these criteria, swallows with double-peaked waves were identified in 18 subjects of 78 consecutive referrals for clinical manometry. Of the 18 subjects, 13 were female and 5 male; the mean age of the group was  $46 \pm 15$  years. All subjects had been referred for further investigation of unexplained symptoms, primarily chest pain (15 subjects [83%]).

### Manometric Methods

Each subject had undergone manometry using a recently developed system that permits both conventional and topographic analysis of pressure data.<sup>8</sup> Subjects were studied after an overnight fast. A 21-lumen silicone extruded catheter (4.0-mm OD) was passed transnasally into the stomach (Dentsleeve Pty., Parkside, South Australia). Each lumen of this catheter was perfused by a pneumohydraulic capillary perfusion device (Mui Scientific, Mississauga, Ontario, Canada) such that a flow rate of 0.28 mL/min per lumen allowed measurement of pressure upstrokes  $>300$  mm Hg/s with a total-catheter perfusion rate of 5.9 mL/min. The transducers were, in turn, attached to a data-acquisition and analysis system designed for conventional and topographic analysis (Millar-MMS, Enschede, Holland).<sup>8</sup> Pressure data were acquired at a rate of 10 Hz.

A station pull-through of the proximal 10 recording sites was performed during quiet respiration, sampling the circumference of the lower sphincter in helical fashion. The catheter was then positioned so that the most distal 2–3 recording sites were intragastric and more proximal sites sampled the lower sphincter and  $\sim 80\%$  of the esophageal body.<sup>8</sup> Ten swallows of 4-mL ambient-temperature water were taken by the subject, each spaced by at least 20 seconds from the previous swallow. The catheter was repositioned such that the most proximal recording site rested in the upper sphincter. Ten additional water-bolus swallows were taken before the catheter was removed. Total intubation time for these methods averages 22 minutes.<sup>11</sup>

### Analytical Methods

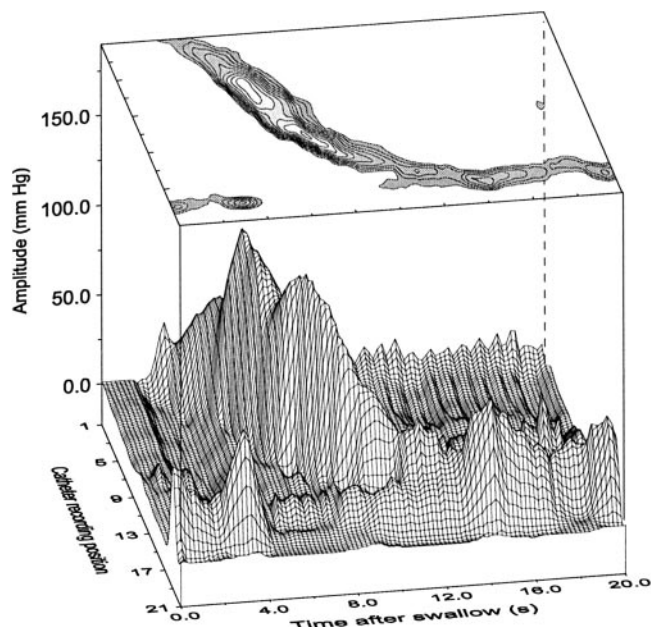
Studies were first analyzed using conventional methods, categorical characterization of abnormal manometric parameters (peristaltic performance, distal contraction wave parameters, lower sphincter basal pressure, lower sphincter

relaxation), and a classification scheme of the resultant patterns.<sup>12,13</sup> Abnormalities were defined by normal values reported previously.<sup>12</sup> Only the 10 swallows recorded when the catheter was in the distal position were used for determining peristaltic performance and distal contraction wave parameters. Swallows with double-peaked waves were identified during conventional analysis when a second peak met the following criteria: (1) the trough between peaks did not reach esophageal baseline; (2) the peak of least amplitude was  $\geq 10$  mm Hg above the interpeak trough; and (3) the peak of least amplitude was separated from the neighboring pressure slope by  $\geq 1$  second.<sup>14</sup>

The manometric system employed has the capability of internally generating topographic plots or exporting pressure data for use in other gridding and plotting programs.<sup>8,10</sup> Three-dimensional surface and contour plots were created for this report using exported  $x,y,z$  data sets, where  $x$  represents the location on the recording catheter (in centimeters),  $y$  the time after swallow (in seconds), and  $z$  the pressure amplitude at that location and time (in mm Hg), and a plotting program designed primarily for geographical mapping (Golden Software, Golden, CO).<sup>15</sup> Interpolated grid intersections are derived from nearby data on the 3-dimensional grids using a search radius of available neighboring pressure points. Exported pressure data for the selected swallows with double-peaked waves included a 20-second time window following the onset of the swallow.

Surface and contour plots were created using methods described previously.<sup>7,8</sup> Surface plots were drawn with grid lines at 0.2-second and 0.2-cm intervals. Plots were viewed using the 3-dimensional perspective required for identifying the first and second peaks and for designating the precise location of the peaks on each grid line. Contour plots display the 3-dimensional data as an overhead representation of surface plots, concentric rings of higher amplitude indicating regional peaks in the contraction profile (Figure 1).<sup>7,8,10</sup> Contour plots were used to detect contraction regions in the peristaltic wave and locate the origins of the second peaks. Propagation velocities (including measurement of peak progression) in this report were calculated using the inverse of the slope of regression lines drawn using locations of the leading edge of propagation (10 mm Hg over esophageal baseline) or locations of peak values.<sup>16</sup> Each value extracted from the surface grids (at 0.2-cm intervals) was used to draw the regression line when calculating velocity over the segment length of interest.

Mechanisms responsible for the development of the second peak were also determined by examining movement of the axial pressure wave. This wave is created from splined curves connecting pressures across the recording sites at any one time after the swallow.<sup>17</sup> Individual frames drawn at the acquisition rate (10 Hz) were viewed in cine fashion for each swallow and evaluated qualitatively.<sup>8</sup> For this report, retrograde propagation was defined as cephalad movement at the base of the trailing edge by  $>1$  cm of esophageal length.



**Figure 1.** Normal appearance of esophageal peristalsis on 3-dimensional topographic plots. The peaks in the surface plot (*bottom*) are represented as concentric lines on the contour plot (*top*). Pressure data below 10 mm Hg are censored on the contour plot. For these plots, the catheter is positioned so that the distal recording site (position 21) is situated just distal to the lower sphincter, shown in the foreground. Decay of the first topographic segment in the proximal esophagus soon after initiation of the swallow can be seen at the back of the plot. The first trough resumes with contraction in the distal esophagus that is divided into 2 pressure segments before merging with the lower sphincter after-contraction in the foreground.<sup>8</sup>

### Statistical Methods

Grouped values are reported as mean  $\pm$  SD unless stated otherwise. Peak values and locations were compared using 2-tailed Student *t* tests; distributions were compared using  $\chi^2$  analyses. Velocity correlations are reported as Pearson's *r*. In all cases,  $P < 0.05$  was required for statistical significance.

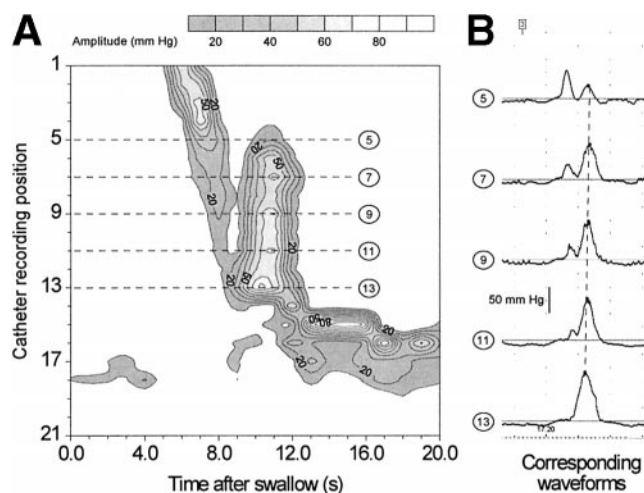
### Results

A total of 74 swallows with double-peaked waves were identified and analyzed in the 18 subjects. Median percentage of swallows with double-peaked waves was 30% (range, 10%–90%). The tracings were classified as showing evidence of a spastic disorder (nonspecific spastic disorder or diffuse esophageal spasm) in 15 subjects (83.3%), a normal pattern in 2 subjects (11.1%), and a hypomotility disorder in 1 (5.6%). When double-peaked waves were excluded from contributing to the manometric diagnosis, spastic disorders were still overrepresented compared with the distribution of diagnoses in 60 other consecutive patients evaluated over the same time period (11 of 18 [61.1%] vs. 17 of 60 [28.3%];  $P = 0.02$ ).

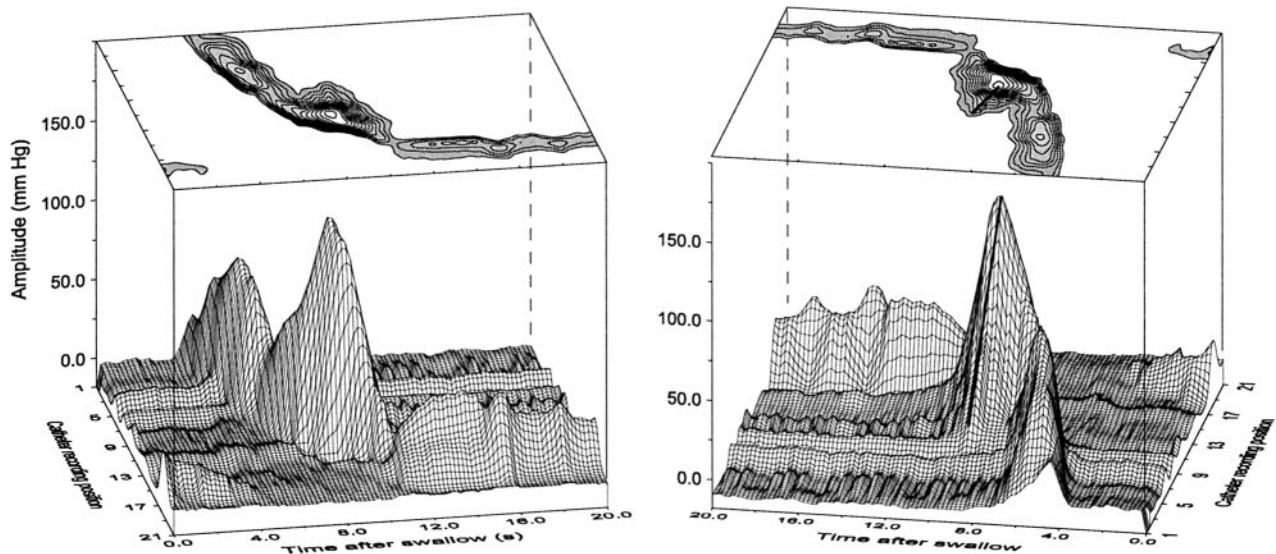
The topographic appearance of a double-peaked wave

on a contour plot is shown in Figure 2. Individual tracings from 5 recording sites are provided next to the contour plot for comparison. The second peak is seen to follow a normally progressive pressure front in the distal esophagus. The slope of the pressure front on the left aspect of the plot indicates antegrade pressure propagation. The reversed slope of pressure measurements responsible for the second peak, however, indicates retrograde progression of this peak. The same findings are seen on the surface plots from a swallow in another subject (Figure 3). The pressure front of peristalsis in the distal esophagus resembles normal (Figures 1 and 2A). The contour plot reveals the second peak extending behind the prominent contraction in the third topographic segment of the esophageal body (Figure 3, left). Changing the 3-dimensional perspective on the surface plot exposes the second peak as merging with this distal segment (Figure 3, right).

Additional examples of double-peaked waves are shown in Figure 4. The lines drawn on the figures are regression lines established from the locations of peak pressures or near wave onset. In 50 (67.6%) of the swallows, progression of the second peak was identified as retrograde ( $-13.2 \pm 10.8$  cm/s; Figure 5). In only 9.4% of swallows was peak progression in the antegrade direction ( $18.9 \pm 14.7$  cm/s). In the remaining 23.0%, velocity exceeded 50 cm/s, and a direction could not be assigned confidently (simultaneous occurrence; Figure 5). For the large



**Figure 2.** A representative contour plot from a swallow with a double-peaked wave. The plot shows peristalsis entering the distal esophagus (regions of the second and third topographic segments) and reaching the lower sphincter (*bottom*). The second peak appears as an extension arising from the region of the third segment near its maximal pressure site. Tracings from 5 of the 21 recording sites (5,7,9,11,13) used to create the plot are shown. Numbers on the contour rings indicate amplitude in mm Hg. The retrograde progression of the peak pressures in the second peak is shown with the *dashed line* extracted from a regression of peak pressures on the topographic plot.



**Figure 3.** Surface and contour plots from a swallow with a double-peaked wave. (Left) The propagation front appears normal from a distal perspective. (Right) When the plot is rotated 180° with the lower sphincter in the distance, the second peak is seen to extend from the back of the third topographic segment, decaying in pressure as it reaches more proximal sites. The regression line drawn from peak amplitudes at 0.2-cm levels on the surface plot establishes the retrograde progression and velocity of this peak.

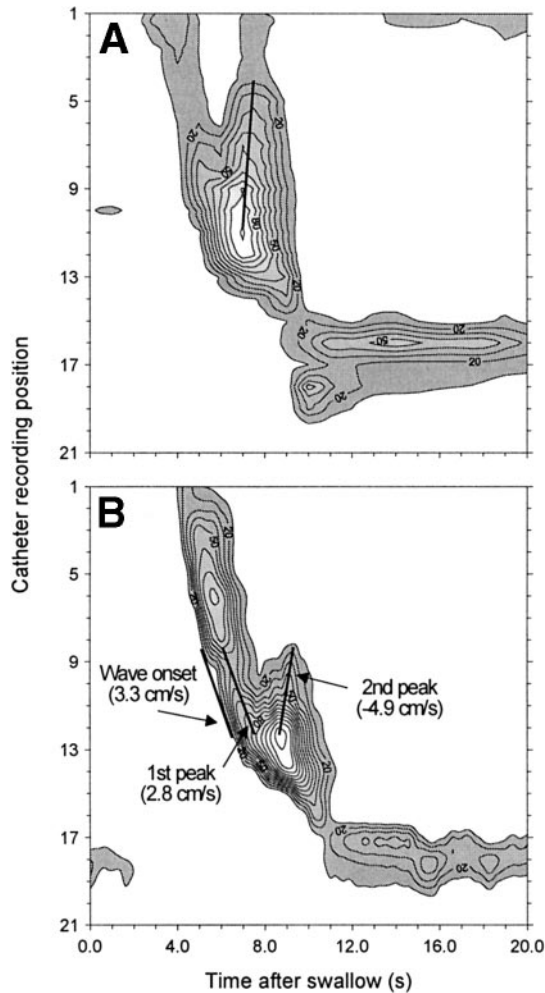
group with retrograde progression of second-peak pressures, the retrograde velocity was similar to antegrade propagation velocity of primary wave onset ( $12.9 \pm 8.6$  cm/s;  $P = 0.9$ ), but faster than progression of the primary wave peak in the same region ( $7.5 \pm 7.2$  cm/s;  $P < 0.01$ ).

The pressure event responsible for the second peak appeared anchored to primary peristalsis near the maximum pressure in the third peristaltic segment (Figures 2–4). This was examined analytically by connecting peak pressures along the main peristaltic front in a dot-to-dot fashion. The point at which the regression line drawn for peak pressures of the second event crossed this connected line was recorded and compared with the location of the actual maximum pressure in the third topographic segment (Figure 4A). The regression line crossed the peak of the primary wave  $3.6 \pm 2.1$  cm above the lower sphincter at  $10.1 \pm 1.5$  seconds after swallow onset, and maximal pressures in the third segment were found  $3.8 \pm 3.5$  cm above the lower sphincter  $9.8 \pm 1.5$  seconds after swallow onset. The differences between these locations and times were not significant ( $P > 0.5$  for each). Using the intersection of the 2 lines as the distal anchor point for the second peak, these peaks extended  $6.3 \pm 1.6$  cm proximally into the esophageal body (covering  $33.5\% \pm 8.5\%$  of esophageal length).

The second pressure event also appeared typically associated with a site of maximal pressure in the third topographic segment that was higher than usual or exaggerated for the subject (Figures 3 and 4). To study this further, we compared maximum pressure in the third segment of the distal esophagus in swallows having

double-peaked waves to the same measurement in the remaining swallows without this finding. Subjects having  $<3$  swallows with double-peaked waves were excluded from this analysis. For each remaining subject, maximal pressures in the third segment were greater for the swallows having double-peaked waves than for the remaining swallows (combining mean values for the subjects:  $157 \pm 27$  vs.  $124 \pm 22$  mm Hg;  $P < 0.01$ ). The values in the swallows with double-peaked waves represented a  $24.1\% \pm 3.8\%$  increment over the remaining swallows,  $<15\%$  of the latter having maximum amplitudes reaching mean values in the swallows with double-peaked waves.

Retrograde progression of peak pressures from a site of unusually high pressure in the third topographic segment therefore explains the typical topographic appearance of these waveforms. Two additional analyses were performed to see if retrograde propagation of a second contraction was actually responsible for this appearance. First, an attempt was made to calculate propagation velocity using the onset of contraction of the second peak. Because interpeak pressures approached baseline for very short distances along the esophagus, regression lines for onset velocity of the second peak could not be drawn accurately. Conventional methods were used: velocity was determined over the region of the second peak using the most proximal and distal recording sites that clearly demonstrated a second upstroke (Figure 6). Using the same thresholds for determining propagation direction as described for the regression lines, 25 (33.8%) of the second events propagated in a retrograde direction, 2



**Figure 4.** Contour plots from 2 swallows with double-peaked waves. The catheter is in the distal position, showing distal esophageal peristalsis and the lower sphincter (*bottom*). In both swallows, the pressure event responsible for the second peak appears to originate near the maximal pressure in the topographic segment proximal to the lower sphincter (the third topographic segment) and extend cephalad into the esophageal body. Contour rings begin at 10 mm Hg in both panels. (A) The second peak extends >7 cm proximally over the region normally represented by the second topographic segment, a region that was poorly developed on this swallow. (B) The second peak extends for a short distance with retrograde peak progression. The regression lines used to calculate velocities for the onset and peak pressure of the first (primary) wave and the peak pressure of the second peak are shown.

(2.7%) propagated in an antegrade direction, and, in the remainder (47 [63.5%]), propagation velocity was too rapid to confidently determine direction (simultaneous).

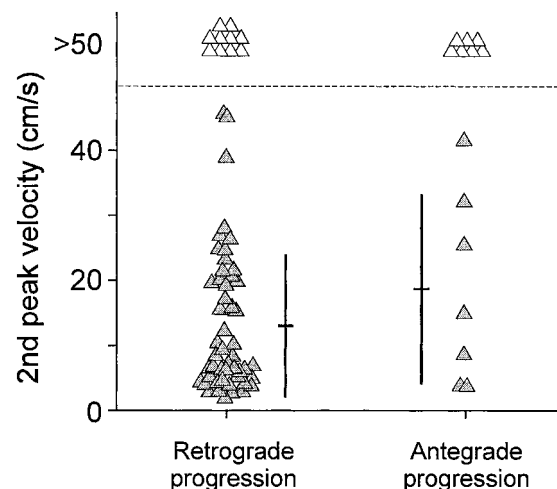
Second, the axial waveforms from each swallow were examined to see if retrograde propagation could be demonstrated from movement of the trailing edge. Sample frames from the 2 double-peaked waves represented in Figure 4 are shown in Figure 7. The curves represent data from all 21 recording sites at the designated times after the swallow. The most proximal esophageal site (recording position 1) is represented on

the left on these curves. For each double-peaked wave examined, the second peak was formed by a transient pressure elevation at the trailing edge of the propagating wave form that displaced the trailing edge in a cephalad direction (Figure 7). This pressure elevation was occasionally associated with isobaric increase in intraesophageal pressure proximal to the propagating complex (Figure 7A). In 7 waves (9.5%), the pressure elevation was associated with retrograde movement of >1 cm at the base of the axial waveform. Each of these showed retrograde propagation of the second upstroke in the previous analysis. In the remainder, the base of the trailing edge was stationary.

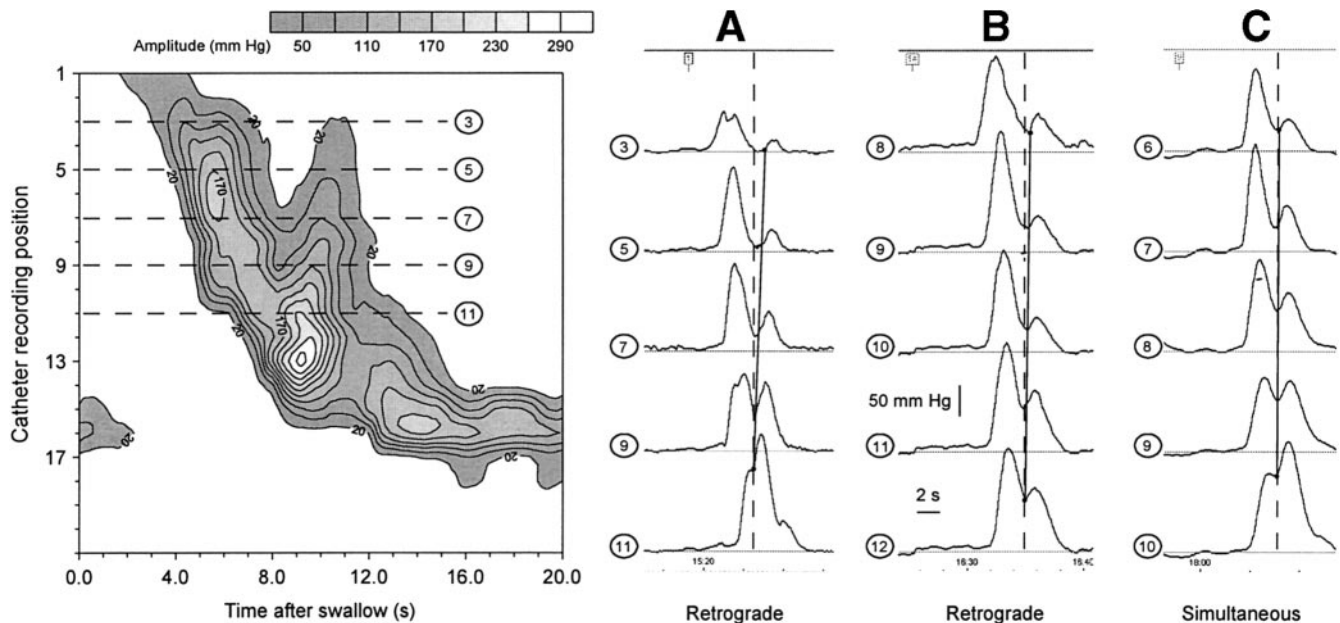
**Discussion**

This investigation of esophageal double-peaked waves used topographic manometric methods. The waves appeared to merge typically with or originate occasionally near the site of maximum contraction in the third topographic segment, the distal half of the smooth-muscle esophagus, and covered an average of 6.3 cm proximal to this site within the esophageal body.<sup>7,9</sup> Second peaks were more likely to occur in swallows with unusually strong contraction in the third segment. Although the maximal pressures in the second event typically progressed in a retrograde fashion, a brief second contraction of simultaneous onset along its length was responsible for more than half of the waves. A retrograde contraction was found in a third, making the second peaks frequently appear as if they were bursts of pressure moving backward from exaggerated distal contractile events.

Pursuing the pathogenesis of these waveforms would



**Figure 5.** Progression velocities of maximal pressures in the double-peaked waves. Velocities were determined from the slopes of regression lines. The direction was considered uncertain ( $\Delta$ ) when the calculated velocity exceeded 50 cm/s in either direction.



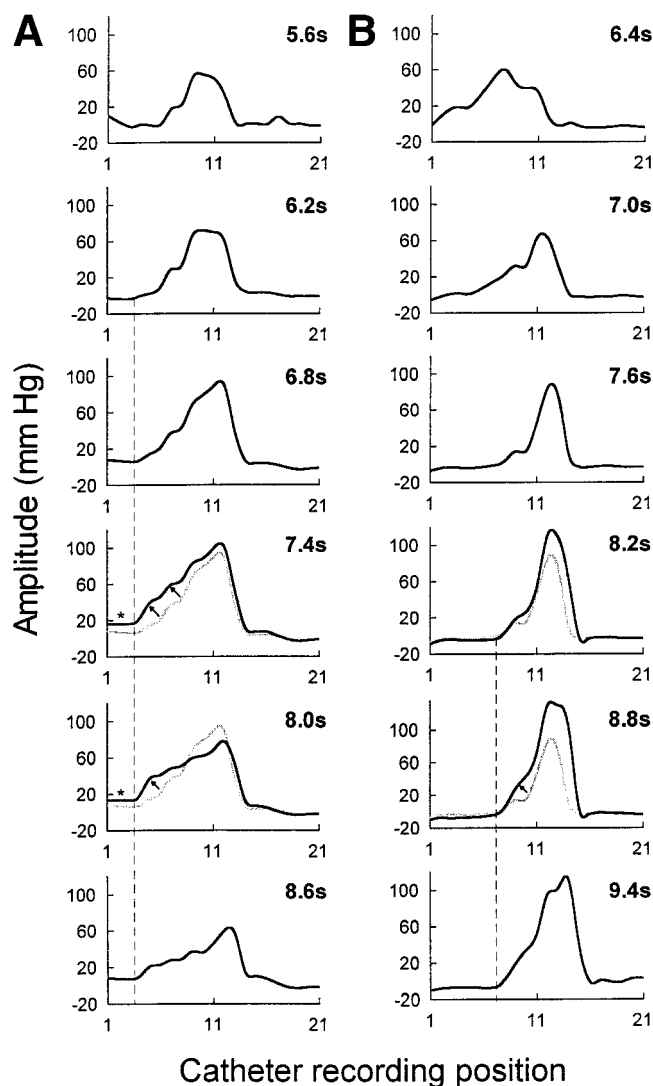
**Figure 6.** Conventional analysis of propagation direction of the second peak using onsets of the second upstroke. (A) Topographic and conventional appearance of a double-peaked wave. Circled numbers represent corresponding catheter recording positions. Onset of contraction producing the second peak propagates in a retrograde direction. (B and C) Two additional swallows from other subjects showing either retrograde or simultaneous onset of the second event.

be less consequential if a mechanism for unexplained or functional esophageal symptoms was more readily apparent. The mechanism has remained elusive, however, and the contribution of motor events is unclear in most cases, even when evidence of abnormally exaggerated contraction is present in the distal esophagus.<sup>4,5</sup> Cross-sectional studies of patients seeking care for unexplained chest pain or dysphagia readily demonstrate the high prevalence of increased distal wave amplitudes, prolonged wave durations, and abnormally high frequency of multi-peaked waveforms—"nonspecific spastic" findings.<sup>5,18,19</sup> The abnormalities co-occur at high rates and vary in prevalence with the referral rate for unexplained symptoms.<sup>13</sup> Consequently, their statistical association with symptoms is undisputed. The direct relationship of dysmotility of this type to symptoms has been difficult to establish in the individual patient, and the manometric abnormalities change independently of symptoms when monitored in longitudinal fashion.<sup>5</sup> Because functional esophageal symptoms remain poorly managed in general, further investigation of clues to their etiology is desirable.<sup>4,5</sup>

Double-peaked waves are one manifestation of dysmotility that has not been fully studied despite the common increase in these waveforms in patients with functional esophageal complaints. The finding can occur in a small percentage of swallows in normal subjects, indicating that the mechanism is potentially a minor deviation from normal physiology.<sup>1,2</sup> Loo et al.<sup>20</sup> suggested that double-peaked waves may also be a manifestation of autonomic

neuropathy in diabetic patients. This is not fully established, however, because similar waveforms are seen in patients without neuropathy, they are not universally present in diabetics with neuropathy, and dysmotility of this type cannot be correlated with neuropathic status when other confounding variables are taken into consideration.<sup>21,22</sup> The waveforms also have been found with increased frequency in alcoholic subjects.<sup>23</sup> These and other findings of exaggerated contraction abate rapidly with abstinence, arguing against a neuropathic basis in these patients.<sup>24</sup> An observation common to all subject groups is that the waves are primarily located in the distal esophagus and that the double-peaked configuration normalizes at some point with progression of peristalsis, several centimeters above the lower sphincter.

Topographic methods have demonstrated aspects of peristalsis that were unknown at the time of the prior investigations of double-peaked waves.<sup>7,9</sup> In particular, the 78% of the esophageal body distal to the major manometric trough (presumably dividing skeletal and smooth muscle regions) is separated into 2 segments of roughly equal length (the second and third topographic segments).<sup>7</sup> Identical segmental divisions are found in the opossum.<sup>25</sup> The second segment is sensitive to the cholinergic effects of cisapride, whereas the third segment is minimally affected by such stimulation in normal subjects.<sup>26</sup> The segments have considerable independence in their pressure responses from swallow to swallow<sup>10</sup> and likely represent the conversion from cholinergic- to



**Figure 7.** Frames from the series of propagating axial waveforms taken from the 2 swallows shown in Figure 4. More proximal esophageal locations are represented on the left of each frame. (A) By 5.6 seconds, the peristaltic wave had entered the third topographic region. As pressure climbed at the leading edge, the trailing edge arrested in forward motion (6.8 seconds). Cephalad movement of this trailing edge is well appreciated by 7.4 seconds. (The 6.8-second image is reproduced faintly on the 7.4- and 8.0-second frames for comparison.) With this cephalad movement, isobaric increase in intraesophageal pressure is noted in the proximal esophagus (\*), reversing the usual gradient across the propagating waveform produced by the intrabolus pressure at the leading edge (right side of waveform). The trailing edge and cephalad extension responsible for the second peak decay as the leading edge proceeds. (B) The second segment dissipates with appearance of the third segment at 7.0 seconds. Forward progression of the trailing edge is arrested at 7.6 seconds with increasing pressures at the leading edge. Cephalad movement of the trailing edge is appreciated at 8.2 seconds and is maximal at 8.8 seconds. (The 7.6-second image is reproduced on these frames.) The trailing edge decays as antegrade propagation proceeds at 9.4 seconds. The *dashed lines* show the cephalad margins of the peristaltic front over the time represented by the double-peaked wave. Actual retrograde propagation is not present in either of these swallows.

noncholinergic-dominant control mechanisms as peristalsis traverses the esophageal body.<sup>27</sup> Topographic methods are ideal for clarifying waveform abnormalities because they consider pressure data in both their temporal and spatial orientations. Knowledge of the segmental nature to the peristaltic wave further helps in determining the relationship of findings to underlying neuromuscular control.

One prior investigation examined the topographic characteristics of exaggerated distal contraction in the nutcracker esophagus, a subset of patients with nonspecific spastic findings.<sup>9</sup> The increased wave amplitude primarily involved the third topographic segment, suggesting that factors responsible may have greatest influence on noncholinergic mechanisms.<sup>27</sup> The present report indicates that double-peaked waves also are generated primarily from this region, again favoring an abnormality in regulation of pressure events in the smooth muscle segment dominated by noncholinergic control. Our findings help explain the common coexistence of vigorous contraction wave abnormalities in the distal esophagus, because the same topographic region appears involved.<sup>3</sup> Although intraluminal pressures represent more than just local muscle contraction, the lack of any isobaric component within the second peak and its gradual decay in the most cephalad component strongly favors the notion that the findings represent contractile events.<sup>28</sup>

The course of maximal pressures in the second peak was easily identified on topographic plots and typically had a retrograde progression. It explains the peculiar appearance of these forked waves: a second peak seemingly originating in a region of high pressure in the third segment and extending cephalad over a short distance. Extracting the mechanism underlying contraction from analysis of maximal pressures, however, is faulted. Maximal contraction pressure is representative of local muscle characteristics, and axial relationships of these pressures do not necessarily reflect the direction of excitation. Unfortunately, because the second contractile event occurs before the primary wave is completed, calculating its propagation direction is difficult. We used 2 different approaches to show that retrograde sequencing in this event does occur in up to one third of instances, an observation that was convincing for some waves by each analysis method. Simultaneous onset of contraction, as described in a previous analysis of double-peaked waves,<sup>20</sup> is more common, however. Because these second events merged with unusually high pressures in the third topographic segment, several explanations are tenable: (1) exaggerated or uninhibited stimulus to distal contraction also produced a second, simultaneous contraction in more proximal sites of the same region; or (2) the second peak

represented a burst of retrograde contraction from the overstimulated distal site.

Regulation of contraction in the region under dominant noncholinergic control should be a focus of further investigation aimed at understanding the relevance of nonspecific spastic findings to functional esophageal syndromes. Errors in the balance of inhibitory and excitatory nerve function have been demonstrated in patients with spastic disorders, abnormalities that influence contractile strength, as well as sequencing of contraction along the smooth muscle region.<sup>29,30</sup> Could such errors produce more pronounced effects in the distal segment where their influence is greatest or promote retrograde contraction by, for example, influencing normal refractoriness?<sup>31</sup> Cholinergic stimulation accentuates the abnormalities, possibly further exaggerating changes induced by insufficient inhibition—even in regions typically less affected by cholinergic control.<sup>20,32</sup> The clinician presently is disillusioned by the poor utility of detecting these abnormalities in symptomatic patients. As our understanding of their pathogenesis continues to evolve, clues to the underlying mechanisms responsible for functional esophageal syndromes may surface, ultimately leading to better management approaches.

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