Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow

Anupam Pal,1 Rohan B. Williams,2 Ian J. Cook,2 and James G. Brasseur1

1Department of Mechanical Engineering, The Pennsylvania State University, University Park, Pennsylvania 16802; and 2Department of Gastroenterology, The St. George Hospital and University of New South Wales, Sydney 2217, Australia

Submitted 17 June 2003; accepted in final form 30 June 2003

Pal, Anupam, Rohan B. Williams, Ian J. Cook, and James G. Brasseur. Intrabolus pressure gradient identifies pathological constriction in the upper esophageal sphincter during flow. Am J Physiol Gastrointest Liver Physiol 285: G1037–G1048, 2003. First published July 3, 2003; 10.1152/ajpgi.00030.2003.—Propulsion of a bolus through the upper esophageal sphincter (UES) is driven by a pressure drop in the direction of flow against frictional resisting force. Basic mechanics suggest that the axial rate of drop in intrabolus pressure (IBP), i.e., the intrabolus pressure gradient (IBPG), should be locally sensitive to abnormal constriction. We sought to quantify space-time patterns of IBP and IBPG that correlate with pathological disruption to trans-sphincteric bolus transport. High-resolution high-fidelity perfused manometry was applied concurrent with videofluoroscopy in 6 healthy controls and 10 patients with restricted UES opening and 4 bolus volumes. Pressures were interpolated spatially and displayed as space-time isocountours with bolus head and tail trajectories superimposed to identify the IBP domain. IBP and IBPG were averaged over an approximately steady period of trans-sphincteric flow. The axial location and magnitude of maximum IBP were quantified for each swallow relative to the location of the abnormal restriction. We found that average hypopharyngeal IBP and locally maximal IBPG were significantly higher in the patient group (P < 0.001), whereas the maximum IBPG was insensitive to bolus volume, and the locations of maximum IBPG in the patient group were well correlated with axial locations of maximal UES constriction (r = 0.84, P < 0.01). Space-time structure of IBP and IBPG correlated qualitatively with swallowing dysfunction. Because IBPG reflects pressure force driving the bolus against frictional force in the UES, IBPG reflects local changes in frictional resistance from pathological constriction during bolus flow. Consequently, the location and magnitude of IBPG reflect the existence and location of abnormal constriction, and IBP and IBPG structure reflect decompensation of the pharyngeal swallow.

The IMPORTANCE OF INTRABOLUS pressure (IBP) during pharyngeal deglutition and its clinical application has been previously established (1, 3, 4, 8). In these studies, IBPs measured in the hypopharynx were found to be significantly larger in the presence of pathological constriction. However, as an indirect measure of increased frictional resistance from pathological constriction, hypopharyngeal IBP can only suggest the presence or absence of abnormal constriction. On the other hand, the local rate of axial pressure drop in the direction of flow, i.e., the intrabolus pressure gradient (IBPG), quantifies the local pressure force on the bolus fluid (16), which, through Newton’s law of motion, responds directly to frictional resisting force and bolus acceleration/deceleration (i.e., inertia).

During pharyngo-esophageal (PE) bolus transport, the balance between the forces acting on the bolus changes rapidly, as shown in Fig. 1. “Phase 1” in Fig. 1 is the initial period when the tongue suddenly accelerates the bolus from rest (12, 14) and frictional resistance is minimal. During this short period, bolus inertia is balanced primarily by pressure force. As the bolus tail enters the pharynx, the upper esophageal sphincter (UES) opens, and a pharyngeal stripping wave forms, driving the bolus through the narrowed PE segment at roughly constant speed (10, 8). As explained in the Discussion, because bolus flow during this “phase 2” period (Fig. 1) is quasi-steady, local IBP force (i.e., local pressure gradient) responds to local frictional resisting force and local axial gradient in bolus fluid velocity along the lumen. The largest frictional force is associated with the narrowest luminal segment and is highly sensitive to variations in minimum diameter of pathological constriction (2). The most rapid axial change in bolus velocity is proportional to the highest axial gradient in luminal diameter and is also sensitive to minimum diameter variations (see Discussion). These mechanical considerations therefore suggest that, during the quasi-steady period of trans-sphincteric flow, IBPG should be locally sensitive to the existence and location of abnormal constriction within the PE segment.

The aims of this study were 1) to examine alterations in the space-time pressure structure of the PE segment during swallowing resulting from restricted UES open-

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: J. G. Brasseur, 205 Reber Bldg., The Pennsylvania State Univ., Univ. Park, PA 16802 (E-mail: brasseur@psu.edu).

http://www.ajpgi.org 0193-1857/03 $5.00 Copyright © 2003 the American Physiological Society G1037
is driven through an open or nearly open UES at pressure gradient. P, pressure; for the opening segment of the UES goes subatmospheric momentary high pressure in the hypopharynx. Beginning at the instant of UES opening (8), the pressure in the opening segment of the UES goes subatmospheric for −100 ms (6, 8). Phase 2 is the period when the bolus is driven through an open or nearly open UES at roughly constant speed by the pharyngeal stripping wave (10). This “quasi-steady” period is associated with a global trans-sphincteric pressure drop as shown. F, pressure; x, distance along the lumen; IBPG, intrabolus pressure gradient.

Fig. 1. Schematic illustration of two phases of bolus motion in the normal swallow. Phase 1 is the period in which bolus flow is dominated by tongue-induced acceleration (12, 14), and the bolus encounters a (nearly) closed upper esophageal sphincter (UES), producing momentary high pressure in the hypopharynx. Beginning at the instant of UES opening (8), the pressure in the opening segment of the UES goes subatmospheric for −100 ms (6, 8). Phase 2 is the period when the bolus is driven through an open or nearly open UES at roughly constant speed by the pharyngeal stripping wave (10). This “quasi-steady” period is associated with a global trans-sphincteric pressure drop as shown. F, pressure; x, distance along the lumen; IBPG, intrabolus pressure gradient.

METHODS

Subjects

We evaluated 10 patients with dysphagia and restrictive UES opening (4 males and 6 females, 57–76 yr of age). In 7 of 10 patients, the only demonstrated abnormality of swallowing was purely mechanical restricted UES opening, specifically Zenker’s diverticulum, cricopharyngeal (CP) bar, and CP stenosis. The remaining three patients displayed significant coexistent neuromuscular dysfunction, determined radiographically and manometrically. On the basis of results of Ali et al. (1), pharyngeal motor function was considered abnormal if one or more of the following radiographic features was observed: absent pharyngeal swallow response, postswallow pooling in the pyriform sinuses, or postswallow pharyngeal wall coating of barium. Only one of these three patients had an identifiable cause of primary pharyngeal dysfunction (pharyngeal myopathy secondary to radiotherapy for cervical tuberculosis). Dysphagia in the remaining two patients was presumed to have a cerebrovascular basis.

Control data were obtained from six healthy volunteers, two males and four females, 21–25 yr of age. None of the control subjects had dysphagia or any reported medical illness. Ethical approval for the study was granted by the Human Ethics Committee of the University of New South Wales and the South-Eastern Sydney Area Health Service. All subjects gave written informed consent.

Fig. 1. Schematic illustration of two phases of bolus motion in the normal swallow. Phase 1 is the period in which bolus flow is dominated by tongue-induced acceleration (12, 14), and the bolus encounters a (nearly) closed upper esophageal sphincter (UES), producing momentary high pressure in the hypopharynx. Beginning at the instant of UES opening (8), the pressure in the opening segment of the UES goes subatmospheric for −100 ms (6, 8). Phase 2 is the period when the bolus is driven through an open or nearly open UES at roughly constant speed by the pharyngeal stripping wave (10). This “quasi-steady” period is associated with a global trans-sphincteric pressure drop as shown. F, pressure; x, distance along the lumen; IBPG, intrabolus pressure gradient.

Manometric Pressure

An 11-lumen micromanometry assembly (Dentsleeve, Wayville, South Australia) of silicon rubber (outer diameter 4 mm, lumen diameters 0.4 mm) was positioned transnasally across the UES segment. Pressures were recorded from 10 side holes spaced at 1-cm intervals. Each recording side hole was marked with aluminum markers 0.5 mm in length to permit precise radiographic localization. The central section of the catheter (side holes 3–8) had an oval cross section to force an anterior-posterior orientation when straddling the UES. All side holes faced posteriorly. The recording lumina were initially flushed with CO2 to minimize microbubble formation during perfusion and optimize recording fidelity. The manometric assembly was then perfused with degassed distilled water by a low-compliance, pneumohydraulic perfusion pump (Dentsleeve) at 0.15 ml/min. Manometric data in each channel were acquired at 200 Hz. Pressures were measured from the side holes with 10 external pressure transducers (Abbott Critical Care Systems, Chicago, IL) and were collected using a BIOPAC MP100 System (Santa Barbara, CA) with an Apple IICl computer. Perfusion and gravitational offsets were removed by zeroing the pressures during perfusion while the assembly was in a vertical position external to the body. All pressures were referenced to atmospheric by adjusting the measured pressures according to the preswallow low pressures in the pharyngeal side holes.

Videofluoroscopy

All patients and controls were studied seated in upright posture. Radiographic images were obtained in lateral and anterior-posterior projections using a 9-in. Toshiba image intensifier (Kawasaki, Japan). Fluoroscopic images were recorded on videotape at 25 frames/s in PAL by a VHS video recorder (model AG6500; Panasonic, Osaka, Japan) for later analysis. Subjects swallowed multiple boluses of 2-, 5-, 10-, and 20 ml volumes of high-density barium suspension [250% (wt/vol), E-Z-HD; E-Z-EM, Westbury, NY; density ~2 g/cm3, viscosity ~150 cP (13)] delivered in the mouth by syringe. Included in the field of view in lateral projection were the incisor teeth anteriorly, hard palate superiorly, cervical spine...
posteriorly, and proximal cervical esophagus inferiorly. Subjects held a water-filled latex glove loosely against the skin under the chin to prevent flare and enhance quality of the fluoroscopic images. Video images and pressure data were precisely correlated with a purpose-built video-timer unit (Practel Sales International, Holden Hill, South Australia), which imprinted simultaneously the elapsed time on the video images in hundredths of seconds and a signal on the pressure tracing each integral second.

**Experimental Protocol**

After a fasting period of at least 4 h, the perfused manometric assembly was passed in the esophagus through a topically anesthetized nostril. The manometric assembly was passed in the esophagus through a nostril. The manometric assembly was perfused only during the period of swallow recording to minimize pharyngeal stimulation. Total fluoroscopic exposure time was limited to 2 min or less per subject.

**Correlation of Pressure and Images**

Digitized manometric pressure (P) data measured at 10 side holes spaced 1 cm were spatially interpolated along the catheter (x) using cubic splines to simulate multiple virtual ports. Local IBPGs (i.e., the local P-x slopes, dP/dx) were calculated from the interpolated P-x curves as a function of x at fixed times. The space-time structure of pressure P and pressure gradient dP/dx were displayed for each swallow as temporal plots of P and dP/dx against time at fixed x ("strip-chart" representation), as spatial plots along x at fixed times ("spatial" representation), and as space-time plots of isocontours of fixed pressure and pressure gradient values over space-time x-t ("isocontour" representation) as described previously (18).

Fluoroscopic images digitized from videotape were analyzed using custom-designed software built on Matlab 5.1 (Mathworks, Natick, MA). Pressures were measured along the manometric catheter with x = 0 cm corresponding to the most proximal side-hole marker. Pressure gradients, dP/dx, were calculated from the interpolated P-x curves as a function of x at fixed times. The space-time structure of pressure P and pressure gradient dP/dx were displayed for each swallow as temporal plots of P and dP/dx against time at fixed x ("strip-chart" representation), as spatial plots along x at fixed times ("spatial" representation), and as space-time plots of isocontours of fixed pressure and pressure gradient values over space-time x-t ("isocontour" representation) as described previously (18).

To define the catheter axis, we fitted a curve through the fluoroscopically identified catheter markers using cubic spline interpolation, and the image dimensions were calibrated using the distance between the side-hole markers. In each video frame, we recorded the locations of the bolus head and tail relative to the catheter axis. The space-time IBP domain was delineated by superimposing spatiotemporal trajectories of bolus head and tail on the isocontour plots.

To illustrate in METHODS, and to discuss later in RESULTS, we show in Fig. 2 an example of the isocontour representation of pressure and the correlation of manometry with image data for a normal swallow. Ten manometric side holes were placed across the PE segment, and the pressure data were interpolated in time using cubic spline interpolation and plotted as space-time isocontours (Fig. 2A). Figure 2, B–E, shows four radiographic images at the four time instants indicated on the isocontour plot. The locations of the bolus head and tail are shown in Fig. 2, and the space-time region between the head and tail trajectories in Fig. 2A is the IBP domain.

To relate space-time IBP structure to pathological constriction, we recorded the locations of the constrictions in the patient group relative to the catheter axis during intraesophageal flow. Specifically, we objectively determined from edge-detected digitized fluoroscopic images of the PE segment during the phase-2 periods of trans-sphincteric flow the locations of maximal rate of axial drop in luminal cross-sectional diameter (i.e., maximal negative diameter gradient) just proximal to the pathological constriction. Four examples are given in Fig. 3, where the points of maximal (negative) luminal diameter gradient can be seen. The ratio for correlating maximum pressure gradient with maximum gradient in luminal diameter is based on mechanical arguments discussed briefly in the introduction and in detail in the DISCUSSION.

To correct for catheter motion associated with laryngeal elevation (9, 10), the catheter coordinate system was updated in each frame. This was possible at all times except when the bolus obscured the side-hole markers during trans-sphincteric flow. The catheter coordinate system was therefore updated only up to the arrival of the bolus head at the side-hole just proximal to the UES. Kahrilas et al. (11) showed that the catheter ascends ~0.5 cm during the period of bolus flow through the UES, on average, in the normal swallow. Therefore, our estimates of bolus head, tail, and pathological constriction are within a precision of ~0.5 cm when plotted relative to manometric pressure during the short period that the bolus obscures the UES side-hole markers.

The period of trans-sphincteric flow likely to be most sensitive to resisting force associated with constriction is the period when the sphincter is nearly fully open and the bolus is driven through at a roughly steady rate by the pharyngeal stripping wave which, in the normal swallow, occurs with the sphincter nearly fully open. Because the normal opening period is ~600–800 ms, in the control group we defined the quasi-steady period as a 150-ms interval beginning 100 ms after the appearance of the bolus head in the sphincter segment (see, e.g., t2–t3 in Fig. 2). In the disordered swallow, the opening and trans-sphincteric flow period is much more variable, so the quasi-steady period was chosen as a 150-ms period beginning when the bolus head passed roughly 2 cm past the distal margin of the sphincter segment in the cervical esophagus. In this way, we isolated flow periods relatively unaffected by either the opening or closing of the UES and centered on a period when the UES is fully open and intrathoracic flow period tends to be roughly steady.

**Statistical Analysis**

Pressures were initially averaged over 1-cm intervals. Three-factor ANOVA was used to determine the effects of disease, bolus volume, and axial location on IBP and two-factor ANOVA to evaluate the effect of disease and bolus volume on maximum IBPG magnitude. The strength of the association between the locations of the constriction and maximum IBPG was evaluated with linear regression. An alpha value (P value) <0.05 was assumed to indicate statistical significance. All statistical calculations were performed using StatView v4.5 (Abacus Concepts, Berkeley, CA). Data are presented as means ± SE unless otherwise indicated.

*AJP-Gastrointest Liver Physiol* • VOL 285 • NOVEMBER 2003 • www.aajpgi.org
RESULTS

Normal Space-Time Pressure-Flow Relationships

We summarize in Fig. 2 the normal space-time pressure-flow relationship for subsequent comparison with the patient group. A detailed discussion of Fig. 2 and its generation is given by Williams et al. (18). In Fig. 2A, the resting state UES high-pressure zone at 1 s shows peak UES pressure at ~5.5 cm. At the initiation of the swallow, the larynx elevates and the catheter moves superiorly. However, the larynx elevates more rapidly than the catheter (9), resulting in an inferior movement of the catheter relative to the UES. This motion of the catheter relative to the UES segment is observed in the isocountour plot as an upward shift of the orange-yellow-green band between 1 s and 2 s. At time $t_1$, the bolus is just arriving at the elevated UES, which is in the process of opening (Fig. 2A and B). A drop to subatmospheric pressure because of rapid opening of the UES is visible in Fig. 2A as a transition to white isocontours from green-blue at ~2.1 s over the region 3.5–5.2 cm. Immediately after the UES opens the bolus head passes through ($time t_2$; Fig. 2C), returning the intrasphincteric pressure to supra-atmospheric values. Between $time t_2$ and $t_3$, the UES is open, and bolus fluid flows roughly steadily (Fig. 2C). The pharyngeal stripping wave is evident at 0 cm in Fig. 2A at ~2.6 s. The wave passes through the pharynx ($times t_4$–$t_5$) and enters the UES at ~2.9 s, subsequently closing the segment as the bolus tail is forced distally by the advancing pressure wave ($time t_5$, Fig. 2E). After the closure of the UES, high basal pressure is reestablished (3–4 s, 4–6.5 cm; Fig. 2A) as the bolus enters the esophagus, initiating the esophageal peristaltic contraction wave that ultimately transports the bolus tail to the stomach.

Space-Time Pressure-Flow Relationships With Restricted UES Opening

Compare the normal pressure-flow relationships in Fig. 2 with those for two patients in Fig. 4. Figure 4, A–C, is from a patient with normal pharyngeal neuro-muscular function and an isolated CP bar (apparent at $time t_3$ in Fig. 4A). Figure 4, D–F, is from an individual
with dysphagia who has an absent pharyngeal swallow response in addition to a CP bar (see time $t_2$ in Fig. 4D). These spatial locations are shown on the space-time and spatial pressure plots of Fig. 4, B, C, E, and F. We also mark the locations of maximum (negative) IBPG on Fig. 4 for comparison.

Several significant similarities and differences between the space-time pressure-flow structure between Figs. 4 and 2 are apparent. Similar to the normal space-time pressure structure, Fig. 4, B and E, displays a high-pressure band before UES opening and shows the reestablishment of resting-state sphincteric pressure after UES closure. However, many differences in the pathological pressure-flow relationship are unique to each patient, but some are often observable in multiple swallows from the same patient.

Consider, for example, the patient in Fig. 4, A–C. The isocountour plot (Fig. 4B) shows a rapid change in color from green to blue at $\sim 5.5$ cm between times $t_2$ and $t_4$, compared with Fig. 2C, for example, indicating a higher-than-normal spatial pressure gradient. This supranormal IBPG resulting from restricted UES opening is shown more clearly by the P-x curve in Fig. 4C at time $t_3$, where we have superimposed the corresponding P-x curve for the normal swallow from Fig. 2F with the two curves aligned at peak resting UES pressure. Note also that the location of maximum IBPG at 5.5 cm in Fig. 4C is in very close proximity to the CP bar for this patient (0.15 cm).

The swallow of the patient in Fig. 4, D–F, displays certain notable differences in pressure-flow relationships from both the normal swallow (Fig. 2) and the swallow of the patient in Fig. 4, A–C, that are associated with the absence of a pharyngeal swallow response in addition to a CP bar. Unlike the normal swallow, Fig. 4E does not display the upward shift of the resting-state UES high-pressure zone (between 4 and 6 cm, $t < 1$ s), indicating absent laryngeal elevation. Also, the bolus head passes through the UES well after relaxation (note time $t_1$ on Fig. 4E), much later than in the normal swallow (compare with Fig. 2C). For this patient too, the IBP in the hypopharynx is higher and has a steeper gradient than normal, as shown in Fig. 4F. Similar to the patient in Fig. 4, A–C,
the point of maximum IBPG at 4.5 cm is close to the CP bar (within 0.8 cm).

In the isocontour representation of pressure for the patient in Fig. 4E, there is no indication of a stripping wave between 0 and 2 cm (compare with Fig. 4B), suggesting the absence of a pharyngeal swallow response. The remnant of a stripping wave appears in the hypopharynx at 2–3 cm, a reflection of the neurogenic pathology in this patient. However, the existence of a late-forming hypopharyngeal stripping wave is not apparent in the radiographic images (Fig. 4D) and, for this reason, this patient was previously diagnosed as completely absent of pharyngeal response. In this case, the space-time isocontour representation of high-resolution pressure data provides additional useful detail, producing a different conclusion from that obtained radiographically. Because of the absence of an upper pharyngeal pressure wave, the patient’s swallow in Fig. 4F does not show as strong an IBPG as does the patient in Fig. 4C, reflecting a weaker pressure force driving the bolus through the UES constriction.
Comparison of IBP and IBPG Between Normal and Restricted Trans-sphincteric Flow

IBP is averaged in time over 150-ms quasi-steady periods $t_{2}$-$t_{3}$ in Figs. 2 and 4. Figure 5 shows the axial variations in average IBP for each bolus volume in normal subjects (Fig. 5A) and in patients with restricted UES opening (Fig. 5B), where individual time-averaged IBP curves from each swallow were aligned to match the superior-anterior corners of the subglottal air columns $(x = 0 \text{ cm})$ before calculating the group mean IBPs. The magnitude of the IBP is highly dependent on axial location ($P < 0.0001$) and swallowed bolus volume ($P < 0.0001$) and is much greater in patients than in controls ($P = 0.0007$). For comparison of IBP between healthy normal subjects and patients with restricted UES opening, in Fig. 5B we show the average IBP range for normal swallows by the gray patch along with the individual curves of average IBP vs. $x$ for patients in each bolus volume group. The hypopharyngeal IBP in the patient group is significantly higher compared with the normal group for each bolus volume. However, the IBP in the cervical esophagus is similar between the patient and control groups, resulting in an increase in overall pressure gradient through the PE segment as a whole in the group with restricted UES opening ($P < 0.0009$, disease-bolus volume interaction term; $P < 0.0002$, disease-axial location interaction term).

The IBP curves in Fig. 5B, averaged relative to an anatomic reference for patients in the different volume groups, suggest that the axial location of maximum IBP changes with bolus volume. Assuming that the pathological constriction in the patients is responsible for the elevated IBPG, this change in location of IBPG with bolus volume might be explained by differences in relative locations of constriction among the patients and the consequent loss of localization of the maximum pressure gradient. To test this hypothesis, in Fig. 5C we average the individual IBP curves after first aligning along the maximum gradient point $(x = 0 \text{ cm})$. On each average pressure curve in the patient group, we plot the average locations of the pathological constrictions with corresponding SE bars. Similar to Fig. 5B, comparison between the realigned gray patch (normal controls) and the realigned patient IBP curves in Fig. 5C again shows the drastic change in IBPG associated with restricted UES opening. Furthermore, the average locations of the pathological constrictions are within $0.5–0.8 \text{ cm}$ of the maximum IBPG, on average, for all bolus volumes. To further confirm the hypothesis, we realigned the individual IBP curves to the pathological constriction locations $(x = 0 \text{ cm})$ and plotted on the pressure curves the locations of maximum IBPG. The resulting plot (not shown) is very similar to Fig. 5C except that curves are shifted down relative to $x = 0$. The relative distances between $x = 0$ (the constriction) and maximum IBPG locations are the same as in Fig. 5C, suggesting a strong correlation between maximum IBPG location and pathology.

To quantify the correlation between the locations of pathological constriction and maximum IBPG, we plot in Fig. 6 the locations of pathological constriction against the locations of maximum IBPG relative to the superior-posterior corner of the subglottal air column for each swallow. Figure 6 confirms a high linear correlation between pathology and maximum IBPG ($r = 0.84, P < 0.01$), with 71% of the variance in location of maximum IBPG accounted for by location of the maximal constriction. Furthermore, both the locations of pathological constriction and the maximum IBPG are grouped by individual in different locations over a $3 \text{ cm}$ region of the sphincter segment. Thus, although the locations of pathology and maximum IBPG vary from patient to patient, the correlations between the two remain localized for individual subjects with restricted UES opening.

Figure 7 compares the average maximum IBPG magnitudes of healthy controls and patients with restricted UES opening in each volume group. When compared to

![Fig. 5. Group mean intrabolus pressure through the open sphincter in controls (A) and in patients (B and C). In A and B, averaging are done referenced to the superior margin of the subglottal air column, whereas in C the averaging is referenced to the location of the maximum IBP. Gray patches in B and C show the intrabolus pressure range for the normal swallow. Filled triangles in C give the average locations of the pathological constrictions. IBP, intrabolus pressure.](http://ajpgi.physiology.org/)
with controls, the maximum IBPG in patients with restricted UES opening is significantly higher ($P < 0.001$). Interestingly, however, the maximum IBPG was not bolus volume dependent ($P = 0.65$).

**DISCUSSION**

This study derives conceptually from Newton’s second law of mechanics applied to bolus fluid motion, which can be written as a balance between the acceleration $a$ of a small mass element of bolus fluid and the sum of all forces per unit mass acting on the small bolus mass in the local direction of bolus flow ($16$)

$$a \approx f_{\text{pressure}} - f_{\text{friction}}$$  \hspace{1cm} (I)

Newton’s law states that, as an element of bolus liquid moves through the PE segment, IBP force $f_{\text{pressure}}$ drives the bolus element through the segment against frictional force $f_{\text{friction}}$ arising from frictional resistance to bolus flow through the narrowing UES. We use an approximation in Eq. 1 because, in principle, the weight of the bolus fluid element ($f_{\text{gravity}}$) adds to bolus acceleration but is negligible in practice ($15$). Our study is based on the fact that the pressure force $f_{\text{pressure}}$ driving the bolus through the PE segment is proportional to the spatial gradient in IBP ($16$), the pressure gradient being the slope in the pressure vs. distance ($P$-$x$) curve at a given position $x$ within the bolus fluid at a given time. The pressure gradient is a quantity that can be measured approximately with high-resolution manometry.

$$\alpha \approx f_{\text{pressure}} - f_{\text{friction}} \hspace{1cm} (I)$$

During the period when the sphincter is at near peak apogee ($3, 11$) and bolus fluid is driven through the fully opened sphincter by the pharyngeal stripping wave at roughly constant speed ($10$), Newton’s law force balance equation (Eq. 1) states that the local IBPG is approximately proportional to local frictional force (per unit mass) minus local fluid acceleration (i.e., $f_{\text{pressure}} \sim f_{\text{friction}} - a$). Both contributions, $f_{\text{friction}}$ and $a$, to IBPG therefore warrant further consideration.

The contribution to IBPG from frictional force $f_{\text{friction}}$ is proportional to $Q/D^5$ ($2$), where $Q$ is the rate of volume flow through the segment (approximately constant along the lumen during the quasi-steady phase 2 period), and $D$ is the average luminal diameter at axial location $x$ (no assumption about cross-sectional shape is made). Thus, during the phase 2 period, the frictional contribution to IBPG is greatest near minimum luminal diameter and, because of the high-power 4 on $D$, will tend to localize to the largest value of $1/D^5$ and therefore the smallest luminal diameter. Furthermore, this highly nonlinear relationship between frictional resisting force and local luminal diameter implies high sensitivity between the frictional contribution to the IBPG and differences in minimum constriction diameter.

On the other hand, the contribution to IBPG from bolus fluid acceleration $a$ during the quasi-steady transport period is approximately proportional to $Q^2/D^5 \times \Delta x$, where $Q$ and $D$ are again the rate of volume flow and the average luminal diameter, and $\Delta x$ is the “axial gradient of $D$ at $x$,” that is, $G_{\Delta x} = dD/dx$ is the rate at which the luminal diameter changes along the lumen at the location $x$. \(^1\) Whereas $1/D^5$ is maximal

\(^1\)This is because fluid acceleration is proportional to $dV^2/dx$ when the flow is steady, where $V$ is the average fluid velocity at lumen location $x$ ($16$), given by $V = 4Q/mD^2$. By conservation of mass ($16$), $Q$ is approximately constant along the bolus-filled lumen during the

**Fig. 6.** Scatter plot of maximum IBPG vs. location of pathological constriction (see METHODS and Fig. 3) relative to the superior margin of the subglottal air column. Each patient is shown with a different symbol indicating that the location of the constriction varied over a 3-cm region from the upper margin of the sphincteric segment. In a few random swallows, the reference catheter location was not discernable, precluding an updating of the catheter position and determination of the relative maximum IBPG and constriction locations. The locations of pathological constriction and maximum IBPG were highly correlated ($r = 0.84, R^2 = 0.71, P < 0.01$).

**Fig. 7.** Comparison of magnitudes of maximum IBPG within the pharyngo-esophageal (PE) segment during the quasi-steady period of bolus flow (METHODS). The magnitude of maximum IBPG is significantly higher in the patient group ($P < 0.001$) but independent of bolus volume ($P = 0.6$).
at the point of minimum diameter, $GDX$ is maximal near to, but just above, the point of minimum diameter (see Fig. 3). Thus the contribution to IBPG from fluid acceleration is expected to be largest close to but slightly above the minimum diameter of the constriction, where the diameter $D$ is small and the rate of change in the diameter (i.e., $GDX$) is large. It was for this reason that we quantified the constriction location in the patient group as the point of maximum rate of change in diameter just proximal to the constriction (see METHODS). Furthermore, the high power of 5 on $D$ implies that, like frictional resisting force, the contribution to IBPG from bolus fluid acceleration is sensitive to differences in minimum constriction diameter and will localize close to the most occluded portion of the constriction.

These mechanics-based arguments suggest that IBP force should localize near the most constricted location in the PE segment and should be sensitive to an abnormally constricted UES during the phase 2 transport period. Although neither viscous force nor fluid acceleration can be measured easily in space-time in vivo during trans-sphincteric flow, pressure force can be estimated both along the lumen and in time by measuring the local IBPG with sufficiently well-resolved intraluminal manometry. The primary objective of this study, therefore, was to evaluate the hypothesis that pathological constriction of the UES can be identified, localized, and quantified using high-resolution perfused manometry with 1-cm-spaced side holes combined with quantitative analysis algorithms sufficiently accurate to estimate local IBPGs in space-time during bolus flow through a nearly fully opened UES.

We have shown that, unlike previous studies where pressures were measured at a few widely spaced manometric ports (1, 4, 5, 17), 10 manometric side holes spaced 1 cm from the pharynx in the cervical esophagus provided sufficient spatial resolution to localize the highest pressure gradients within the PE segment when quantified using cubic spline interpolation (Figs. 2 and 4). We further show that low-compliance perfused manometry has a sufficiently high frequency response to capture the primary short-duration time-local events such as the rapid drop to subatmospheric pressure at the instant of UES opening in the normal swallow (Fig. 2) and the propagation of high-pressure-amplitude stripping waves through the PE segment (Figs. 2 and 4).

In the isocontour plots of Figs. 2 and 4, the high-pressure regions most apparent to the eye generally reside outside the intrabolus domains defined by the head and tail trajectories and reflect muscle-generated contact forces applied directly to the catheter (2). The lower-pressure regions in Figs. 2A and 4, B–E, during trans-sphincteric flow contain the pressure forces that drive the bolus through the PE segment and the vari-

atations in these forces associated with pathological constriction.

Bolus flow dynamics change rapidly between the phase 1 period (Fig. 1A), when the cricopharyngeus muscle relaxes and the UES is pulled open by the thyro-hyoid traction forces generated with laryngeal elevation (8), and phase 2 (Fig. 1B), when the bolus is driven through a nearly fully opened UES by the pharyngeal stripping wave. The normally sudden opening of the UES during phase 1 creates a transient subatmospheric pressure drop in the UES (8) illustrated schematically in Fig. 1A and evident in Fig. 2, A and B. This transient subatmospheric period quickly disappears as the bolus is driven in the UES (8) and the pharyngeal stripping wave applies high pressure at the tail of the bolus, forcing the bolus through the narrowed UES segment against frictional resistance (Fig. 2, E–I). Figure 2, E–F, shows a short “quasi-steady” period of bolus motion at peak UES opening during which the IBPG (fpressure) is most sensitive to frictional resistance (ffriction).

In the normal swallow, the axial IBP variations ($P_x$) display a relatively gentle negative slope through the UES (Fig. 2, C and D), and bolus motion and space-time variation in pressure are stereotypic (18). However, with swallowing dysfunction, there are multivariate deviations from the normal pressure-flow pattern of bolus motion described above and in RESULTS in context with Figs. 1 and 2. These deviations from normalcy, particularly apparent in well-resolved space-time pressure-flow patterns plotted as isocontours, reflect specific pathology (Fig. 4).

The manometric data displayed in Fig. 4E for a patient with neurogenic dysfunction is an example of the level of detail contained in well-resolved space-time pressure structure potentially useful for clinical evaluation. A standard fluoroscopic examination for this patient (Fig. 4D) suggested complete absence of the pharyngeal swallow response. However, the pressure isocontour plot of Fig. 4E shows that a stripping wave does exist but is not initiated until the distal hypopharynx (2.5–4.0 cm, $t > t_s$) rather than the oropharynx, as is normal. Furthermore, Fig. 4E makes clear a much-delayed initiation of peristalsis in the cervical esophagus. Neither radiography nor standard low-resolution manometry can provide this level of clinically relevant detail. The highest level of diagnostic understanding is obtained from combined space-time analysis of high-resolution manometry concurrent with imaging.

Previous studies of Ali et al. (1), Cook et al. (4), and Dantas et al. (5) showed supranormal hypopharyngeal IBPs in patients with Zenker’s diverticulum and CP bar when measured at a single spatial location, leading to the postulates that hypopharyngeal IBP with CP bar is a predictor of abnormal CP disruption (1, 5) and that increased hypopharyngeal IBP with Zenker’s diverticulum reflects reduced compliance of the UES (4). Both conclusions suggest an indirect relationship between pathological constriction and a global increase in resistance to trans-sphincteric flow. Our analysis confirms the mechanical arguments for a direct relationship.

quasi-steady period when the sphincter is nearly fully open. During this phase 2 period, therefore, $a \propto (\Delta V/\Delta x) \propto (Q^2/D^5)(dD/dx) \approx$ approximately.
Fig. 8. Example of swallow failure resulting from motor events during swallowing of a 20-ml bolus in a patient with an early Zenker’s diverticulum and CP bar. This example shows “decompensation” of the swallow because of the demands of a large bolus volume and extremely high resistance at the PE segment despite two ineffective pharyngeal closure waves (PC1 and PC2). A: 6 sequential videoradiographs from $t_1 = 1.80$ s to $t_6 = 3.46$ s. B: isocontour representation of interpolated space-time-pressure with image times $t_1$–$t_6$ shown by vertical dashed lines. $t_1$. The pressure plot suggests that at time $t_1$ the sphincteric muscle has relaxed while the image indicates that the bolus head is just entering the sphincteric segment, delayed by $\approx 200$ ms from the normal swallow (Ref. 8 and Fig. 2). $t_2$. The UES is open, the CP bar is visible, and some trans-sphincteric flow exists in the presence of synchronous isobaric pressure along the length of the pharynx between 1.8 and 2.0 s. The magnitude of the intrabolus pressure at this time (93 mmHg) is supranormal, and the rapid pressure rise from 2.8 to 3.6 cm forces bolus fluid retrograde. $t_3$–$t_4$. At time $t_3$ a weak pharyngeal contraction PC1 is initiated at 2 cm in the midpharynx and progresses to 4.4 cm at time $t_4$. The images indicate that this contraction wave is never lumen occluding and never progresses into the UES, which remains open. $t_5$. After failure of this swallow attempt, a second pharyngeal swallow is triggered just before $t_5$ with posterior motion of the tongue base (large arrow on left of image), again giving rise to supranormal intrabolus pressure (3.0–4.6 cm), distension of the lumen (small arrows on right of image), retrograde bolus flow, and some sporadic trans-sphincteric flow. This is soon followed by a second, more impressive, pharyngeal contraction wave (PC2) initiated at 1.4 cm, progressing partly in the UES and culminating in temporary closure at time $t_6$. A third and final pharyngeal contraction wave PC3, delayed from the initiation of UES opening by $\approx 1.7$ s compared with normal subjects, finally clears the residual bolus and closes the PE segment as it traverses the UES normally.
between local frictional resisting force and pressure force and local sensitivity between pathological narrowing of the PE segment and abnormally high IBP.

Figure 5B shows that IBP in the cervical esophagus is unaffected by pathological constriction within the UES. This result, when combined with global friction-induced increases in trans-sphincteric pressure gradient graded by bolus volume ($P < 0.0001$), explains the observed volume-graded increases in proximal hypopharyngeal pressure ($P < 0.001$). In contrast, the local maximum IBP during phase 2 trans-sphincteric flow is independent of bolus volume, both in the presence and in the absence of restricted UES opening (Fig. 7). The magnitude of maximum IBP, on the other hand, is highly sensitive to the existence of pathological UES constriction (Figs. 5C and 7, $P < 0.001$). Thus IBP has diagnostic power at all bolus volumes as a clinically useful indicator of sphincteric obstruction.

As important, we confirm the spatial localization of maximum IBP near the abnormal constriction. Figure 6 shows that, although the proximal margins of the pathological constrictions in the patient group were spread from 0 to 3 cm below the superior margin of the subglottal air column, the correlation between the locations of abnormal constriction and maximum pressure gradient was high ($r = 0.84$, $P < 0.01$, Fig. 6).

However, the relative positions of the manometric catheter and images could be updated only up to the arrival of the bolus head at the UES while the catheter ascends an average of 0.5 cm relative to the larynx during the period of normal trans-sphincteric bolus flow (11). Thus, if similar ascension occurs with obstruction, the estimate of 0.5–0.8 cm as the average distance between maximum pressure gradient and constriction should be reduced by ~0.5 cm, supporting the mechanical arguments for close spatial proximity between the maximum IBPG and the proximal margin of the constriction.

Although the maximum IBP was found to be independent of bolus volume in patients, we observe in Fig. 7 an increase of almost 40% with a change in bolus volume from 10 to 20 ml. Whereas swallows in the normal group generally move the 20-ml bolus smoothly through the pharynx and PE segment in a single stereotypic swallow (18), many individuals in the patient group found it much more difficult to swallow 20-ml boluses compared with 10 ml, requiring multiple swallows for final clearance. The dramatic increase in the maximum IBP for the 20-ml bolus volumes with pathology (Fig. 7) may reflect the generation of additional contractile events in the 20-ml swallow that were generally absent in the 2- to 10-ml swallows.

For example, in Fig. 8 we show videoradiographs and a corresponding isocontour plot for a 20-ml bolus swallow from a patient with a prominent CP bar and early Zenker’s diverticulum demonstrating swallow failure when IBP exceeds pharyngeal closure pressure. The resistance induced by bolus flow through the narrowed PE segment is so great that the pharynx is unable to accommodate the largest bolus volume and IBP exceeds the pharyngeal closure pressure as a result. Although some sporadic flow events across the PE segment do occur (Fig. 8, $t_{6}$), non-peristaltic pharyngeal contractile events force bolus fluid retrograde, and subsequent peristaltic contractions ($PC_{1}$, $PC_{2}$) are too weak to occlude the pharyngeal lumen because of excessive frictional resistance in the restricted segment, resulting in “swallow failure.” The delayed time at which a successful pharyngeal stripping wave $PC_{3}$ is ultimately generated, the contraction-wave strength, and its transport characteristics are apparent in the isocontour plot (Fig. 8B). Bolus clearance and UES closure, delayed by ~1.7 s compared with the normal swallow, takes place during this period (3.8–4.4 s).

From a clinical perspective, the isocontour representations of space-time pressure structure obtained with high-resolution manometry provide useful detail of muscle squeeze behavior not available through fluoroscopy or low-resolution manometry. By combining basic principles of mechanics with well-resolved manometry concurrent with videofluoroscopy, we have shown that IBP force reflects locally the existence of UES constriction, suggesting potential applicability of pressure gradient as a useful clinical physiological measure for the identification and localization of pathologically restricted UES opening.

REFERENCES


