Liquid in the gastroesophageal segment promotes reflux, but compliance does not: a mathematical modeling study

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Ghosh SK, Kahrilas PJ, Brasseur JG. Liquid in the gastroesophageal segment promotes reflux, but compliance does not: a mathematical modeling study. Am J Physiol Gastrointest Liver Physiol 295: G920–G933, 2008. First published August 21, 2008; doi:10.1152/ajpgi.90310.2008.—The mechanical force relationships that distinguish normal from chronic reflux at sphincter opening are poorly understood and difficult to measure in vivo. Our aim was to apply physics-based computer simulations to determine mechanical pathogenesis of gastroesophageal reflux. A mathematical model of the gastroesophageal segment (GES) was developed, incorporating the primary anatomical and physiomechanical elements that drive GES opening and reflux. In vivo data were used to quantify muscle stiffness, sphincter tone, and gastric pressure. The liquid lining the mucosa was modeled as an “effective liquid film” between the mucosa and a manometric catheter. Newton’s second law was solved mathematically, and the space-time details of opening and reflux were predicted for systematic variations in gastric pressure increase, film thickness, muscle stiffness, and tone. “Reflux” was defined as “2 ml of refluxate entering the esophagus within 1 s.” GES opening and reflux were different events. Both were sensitive to changes in gastric pressure and sphincter tone. Reflux initiation was extremely sensitive to the liquid film thickness; the protective function of the sphincter was destroyed with only 0.4 mm of liquid in the GES. Compliance had no effect on reflux initiation, but affected reflux volume. The presence of abnormal levels of liquid within the collapsed GES can greatly increase the probability for reflux, suggesting a mechanical mechanism that may differentiate normal reflux from gastroesophageal reflux disease. Compliance does not affect the probability for reflux, but affects reflux volume once it occurs. Opening without reflux suggests the existence of “gastroesophageal pooling” in the distal esophagus, with clinical implications.

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The pathogenesis of gastroesophageal reflux disease (GERD) is poorly understood and difficult to measure in vivo. Our aim was to apply physics-based computer simulations to determine mechanical pathogenesis of gastroesophageal reflux. A mathematical model of the gastroesophageal segment (GES) was developed, incorporating the primary anatomical and physiomechanical elements that drive GES opening and reflux. In vivo data were used to quantify muscle stiffness, sphincter tone, and gastric pressure. The liquid lining the mucosa was modeled as an “effective liquid film” between the mucosa and a manometric catheter. Newton’s second law was solved mathematically, and the space-time details of opening and reflux were predicted for systematic variations in gastric pressure increase, film thickness, muscle stiffness, and tone. “Reflux” was defined as “2 ml of refluxate entering the esophagus within 1 s.” GES opening and reflux were different events. Both were sensitive to changes in gastric pressure and sphincter tone. Reflux initiation was extremely sensitive to the liquid film thickness; the protective function of the sphincter was destroyed with only 0.4 mm of liquid in the GES. Compliance had no effect on reflux initiation, but affected reflux volume. The presence of abnormal levels of liquid within the collapsed GES can greatly increase the probability for reflux, suggesting a mechanical mechanism that may differentiate normal reflux from gastroesophageal reflux disease. Compliance does not affect the probability for reflux, but affects reflux volume once it occurs. Opening without reflux suggests the existence of “gastroesophageal pooling” in the distal esophagus, with clinical implications.

In the present study, we analyze the initiation of opening of the GES from below once myogenic tone has been inhibited by central or peripheral mechanisms. Our objective is to determine the unexplored mechanical characteristics at opening that may differentiate normal from chronic reflux (i.e., regularly occurring reflux with abnormally high frequency) when the sphincter is naturally most predisposed to opening. Because it is very difficult to experimentally measure the subtle changes in the force balance when the GES is just opening, we instead apply a mathematical model derived from Newton’s second law of physics and mass conservation in mathematical form.

Simplifications are necessary to make the mathematics solvable on a computer, but we are careful to retain in the model the essential mechanical elements that underlie opening and reflux. In particular, we include a “constitutive model” that contains a material stiffness parameter that reflects quantita-
tively GES “compliance.” We integrate this constitutive model into a Newton’s law representation of muscle force in mathematical form, coupled with a fluid flow model for liquid refluxate passing through the GES and entering the distal esophagus. We include a manometric catheter in the model, since the in vivo data we use to parameterize the model were obtained from manometry and intraluminal ultrasound studies.

Recognizing that a thin layer of liquid coats the epithelial surface, we also included in the mathematical model the existence of an “effective liquid film layer” between the mucosal surface and the catheter, which, in an average sense, represents narrow conduits of liquid between the gastric cardia and the distal esophagus. Recent studies have suggested that the presence of an acid film within the gastroesophageal sphincter in the resting state may be associated with GERD (8, 12–14, 44), and that extra liquid may be a consequence of a more distended muscularis (48, 49). We also examine the role of compliance and gastric pressure in the initiation of reflux and the ensuing refluxate volume.

MATERIALS AND METHODS

GES opening begins when the transmural pressure difference across the muscle wall of the abdominal esophagus (Fig. 1C) is high enough. However, the flow of refluxate into the esophagus is driven by the trans-sphincteric pressure difference within the fluid between the stomach and the distal esophagus (Fig. 1D). A mathematical model was developed to predict sphincter muscle deformation and the rate of gastroesophageal refluxate flow from Newton’s second law of motion, together with the principle of mass conservation for incompressible muscle written in equation form. We describe the model development in this section qualitatively. The primary mathematical equations that comprise the model are summarized in the APPENDIX; complete details of the mathematical derivations and approximations can be found in Ghosh (17).

Although it was necessary to simplify the model geometry to make it possible to solve the equations and make quantitative predictions, we were careful to retain in the model the essential anatomical and mechanical complexities that affect the opening of the GES and reflux. We include, in particular, 1) all pressures within the esophagus and stomach and outside the esophageal and gastric walls involved in opening and flow; 2) active and passive tension (technically, stress) within both circular and longitudinally aligned muscle fibers through the GES; 3) a model for net tone associated with both intrinsic (circular and longitudinal) and extrinsic (crural) muscles through the GES; 4) a model of the passive elastic stiffness that determines the increases in tension that occur in the GES muscle as it is stretched during opening; and 5) equations derived from Newton’s second law (net force = density × acceleration) and from the conservation of mass for deformable solid material (muscle) and for liquid (refluxate) from which the opening of the GES and trans-sphincteric flow can be predicted quantitatively. In the section entitled The Computer Experiments, we describe how the computer simulations from the mathematical model were carried out, and we explain the analysis methods we developed to interpret the simulation data.

The Anatomical Model

In Fig. 1, we show the modeled anatomy of the GES and the primary parameters that we specify in our mathematical model. We model the axial variations in cross-sectional area of the muscle layers, while the cross-sectional geometry is simplified as circular. The opening of the GES and the flow is therefore “axisymmetric.” In the model, we specify the primary passive material property of the muscle: the muscle stiffness. We also specify the active contribution to tension (i.e., tone) that results from neurological stimulation of sphincteric muscle fibers. The model predicts the total tensions of the longitudinal and circular muscle fibers during opening and flow. Our anatomical model (see Fig. 2, A and B) includes 1) the axial segment of the esophagus that begins at the junction between the abdominal esophagus and gastric cardia (the “gastric end” in Fig. 2), 2) a 1.5-cm segment of abdominal esophagus, 3) a 3-cm segment of sphincteric muscle, and 4) a substantial length of intrathoracic esophagus. We also felt it important to include in the model the axial thickening of the muscularis from the upper margin to the esophagocardiac junction, as measured in several cadaver and in vivo human studies (31, 45, 52). A manometric catheter (4.4-mm diameter) was included to make the model relevant to the in vivo motility studies from which the data were obtained. This also removes a concern about the effect of folding of the mucosal lining, largely absent with a catheter of this diameter (32, 36, 59).

An important element in the model is the inclusion of a thin film of liquid between the inner wall of the mucosa and the catheter. The thickness of this “liquid film layer” (ε) was specified. This liquid film was included to represent, in an average sense, the liquid that coats the epithelial surfaces and the small pockets of liquid that lie within the mucosal folds that create narrow connecting conduits between the stomach and mediastinum. In our model, this liquid film is between the epithelium and catheter (Fig. 2A). The significance of this liquid layer will be discussed at length in RESULTS and DISCUSSION.

A “base resting state” of the GES was defined using mean anatomical measurements from in vivo studies of the resting state in normal controls. The resting state thickness of the combined mucosal layers was approximated as 2 mm and was constant along the lumen (6, 9, 39, 57). The axial variations in muscle wall thickness that were used in the model (see Fig. 2A) were obtained from in vivo intraluminal ultrasound images segmented and quantified by Ulerich et al. (57). Ulerich et al. measured a gradual thickening of the muscularis propria from 1.77 mm at the proximal margin of the GES to 2.55 mm at the distal margin of the abdominal esophagus. Cadaver measurements by other investigators (31, 45, 52) have reported a similar thickening of the muscle wall in the distal esophagus. The lengths of the abdominal and sphincteric segments were estimated from a number of studies, in addition to those already mentioned, most notably Kahrilas et al. (25).
The Physio-Mechanical Model

From the laws of mechanics in mathematical form, we derived an equation that can be programmed on the computer to predict quantitatively the spatio-temporal changes in axial geometry of the midsurface and fluid flow across the GES after the gastric pressure was increased from baseline by a specified amount (Fig. 2, A and B). We carried out a detailed study of the opening process and reflux as a function of systematic variations in gastric pressure, net muscle tone, and effective GES muscle stiffness. This was possible because Newton’s laws in mathematical form are predictive and describe the time changes in the velocity of the muscle resulting from changes in the balance between the muscle tension forces that try to keep the GES closed and the fluid pressure forces that try to open the segment (transmural pressure difference between the gastric or intraluminal fluid pressure inside and pressure outside the gastric and esophageal walls). At each time step in the simulation, the change in midsurface geometry of the muscularis is predicted. From this, the changes in the inner and outer margins of the muscularis are predicted by applying conservation of mass to the muscle layer, together with the assumption that material at each cross section moves only radially. Although we do not consider axial motions from potential shortening of longitudinal muscle of the esophagus (1, 50), the results are relevant to this issue (see DISCUSSION).

The muscle closure forces arise from “stresses” (forces per unit area) within the muscle material. At each point within the muscle, the total stresses are separated into “active” plus “passive” parts. The passive stresses quantify the purely elastic increases in tension within the muscle that resist distension and opening of the GES, with or without tone. These stresses are defined by a “constitutive” equation that relates the internal stresses within the muscle to the local “strains” (i.e., deformations) of the muscle material through a parameter that quantifies “stiffness,” the most important material property of the muscle for our application.

The active stress (tone) adds to the passive stress to create total stress. Active stresses arise from the neurological stimulation of the circular and longitudinal muscle fibers, which we modeled separately. In the sphincter, active myogenic tone maintains high levels of active stress in the resting state. These stresses are
inhibited during tLESR, which generally precedes reflux. In our computer experiments, we model the “tLESR state” as “zero circular muscle active stress,” leaving only passive circular muscle stress to resist opening. We then systematically increase the level of active stress (tone) from zero to quantify the sensitivity between opening and reflux and low levels of tone.

Longitudinal muscle fiber stress, however, is handled differently. Rather than specifying active longitudinal muscle stress, we instead specify the axial motion of the muscle, which results from total longitudinal muscle stress (for this study we specify zero axial motion), and the model predicts the total stress required. We can interpret this predicted total as active or passive. This approach has the great advantage that, although we use the same model for the passive (elastic) stress in the circular and longitudinal directions, the actual differences in stiffness in circular vs. longitudinal muscle are effectively predicted in our model calculations by the manner in which longitudinal stresses are calculated in the model.

The forces that cause opening are proportional to the difference between fluid pressure within the stomach and within the lumen of the GES, and the pressure external to the esophageal wall. The external abdominal and mediastinal pressures are specified in the model (Fig. 2D). We do not model respiratory variations in abdominal and mediastinal pressure; these pressure changes will only be relevant once opening has occurred. The pressure at the gastric end of the modeled segment (Fig. 2, A and B) is specified as a “boundary condition” to the Newton’s law mathematical equations. At baseline, gastric pressure equals abdominal pressure. In the computer experiments, gastric pressure was systematically increased from its baseline value to initiate opening and reflux.

During opening of the GES, the model also predicted the rate of flow of liquid from the stomach into the esophagus with the Newton’s law equation for the liquid combined with conservation of mass. In our simulations, we modeled reflux with the density and viscosity of water as a model of liquid reflux. Higher viscosity gastric liquid would result in less rapid rate of volume reflux once opening has occurred, but the basic conclusions obtained in this work will not change. We also have not included gravity force in our model; in effect, we model the supine position. Intragastric pressure forces the GES open, and, as the GES opens, the pressure between the stomach and esophagus forces the liquid through. As liquid moves through the GES, it changes the pressure on the inner surface of the mucosa. In the model, this changing fluid pressure at the mucosal surface is applied as a “boundary condition” to the solution of the Newton’s law equation for the muscle. Thus the two sets of equations that predict the change in muscle geometry and the motion of liquid through the GES are coupled through the pressure at the boundary between the fluid and mucosa. A qualitative description of the muscle wall model is given below. Because this is a new model, the equations are summarized in the Appendix. The basic fluid flow mathematical model, however, has been used extensively in past model studies (4, 18, 27, 28, 38, 40), so these are described only qualitatively here.

**Constitutive model for passive muscle stresses.** The mathematical model for the muscle wall was based on “finite deformation continuum mechanics,” the formal mathematical description of the relationship between deformations of a material (strains) and the stresses (forces per unit areas) within the material that cause the deformations. We apply this mathematical formalism to model the stress-strain properties of the muscularis propria. All muscle mechanics studies done in the human esophagus, except for two notable exceptions (16, 38), have assumed the esophageal wall to be “thin.” This incorrect assumption, although leading to great simplification of the mathematics, has important implications to the accuracy of predictions, so we do not make it. We use, instead, the full equations within finite deformation theory (34). Furthermore, we include both circular and longitudinal muscle fibers in our modeled muscularis; in the fully passive state (tLESR), retaining this fiber anisotropy is important to capture correctly the variable muscle properties across the mucosa and muscle layers (29, 30, 33). In contrast with the muscularis, the mucosal layer is very compliant and provides little resistance to deformation compared with the much higher stiffness of the circular and longitudinal muscle layers (19, 55).

We model the collagenous material surrounding the muscle fibers with a variant of what in the engineering literature is called the “Mooney-Rivlin” constitutive model (34, 37, 38). Our “neo-Hookean” variant is a linear mathematical relationship between the stress and strain-rate “tensors,” with the proportionality constant being the material stiffness parameter.

Qualitatively, one can think of “stiffness” as the inverse of “compliance.” However, compliance is not strictly a material property, while stiffness is. With the stiffness parameter, we model the essential passive elastic properties of the GES at a given axial location. Our stiffness parameter models the net resistance from all muscles that resist the opening of the lumen at that axial location. Thus GES stiffness is higher due to additional resistance to distension from the crux muscles, whereas stiffness proximal and distal to the GES comes only from circular and longitudinal muscle of the muscularis propria (see Fig. 2C).

Stiffness is a difficult parameter to measure in vivo, given the significant dynamic spatial and temporal variability within the GES during the respiratory cycle and the sustained active tone of the LES. Muscle stiffness of the GES was parameterized from in vivo concurrent ultrasonography with manometry studies by Schiffern et al. (49), who measured pressure vs. deformation at the hiatus during degluti
tive inhibition. Using a Newton’s law force balance with measured pressure and deformation, they estimated hoop stress and plotted stress against deformation in normal subjects and in GERD patients. The stiffness of the GES for these two subject groups, estimated by fitting a straight line through the data, was 60 mmHg for normal controls and 10 mmHg for GERD patients. We were particularly interested to evaluate, with our computer experiments, the consequences of this factor of six difference in stiffness between normal and GERD.

The stiffness of the esophageal body was estimated from the in vitro muscle strip studies of Tøstrup et al. (55), who estimated a stiffness of 15 mmHg in normal subjects for stretch ratios (distended radius divided by resting radius) <2, and 157 mmHg for stretch ratios >2. We included in our model a smooth transition from low to high stiffness near a stretch ratio of 2. Anatomically, the GES was defined as a 3-cm-wide region with a middle third region of high stiffness (60 mmHg) and reducing to the stiffness of the esophageal body (15 mmHg) on either side (Fig. 2C).

**MUSCLE DAMPING.** GES opening occurs over a short period of time (<1 s). If the GES and esophagus were purely elastic, opening would be followed by elastic oscillations similar to a ball suspended on a spring. Ghosh et al. (18) measured GES opening during deglutition and found that, on average, the lumen diameter overextended before settling to a maximum opening diameter, suggesting the existence of elastic energy with rapid frictional damping from the muscle microstruc
ture and/or the viscous nature of the trans-sphincteric fluid flow. In preliminary studies with our model, we found that fluid damping was minimal, indicating that damping should be included in the muscle equations. This was done in a simple way by adding a “damping term” to the Newton’s law equation for the muscle. This term contained a damping coefficient (called $\gamma$ in Appendix Eq. A5). Based on the results of Ghosh et al. (18), we chose the damping coefficient to be just high enough for the predicted opening of the GES to include, at most, a single oscillation (18). The damping coefficient varied from

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1 The resting state esophageal muscle wall has a thickness-to-radius ratio of −0.6, which far exceeds the requirements for the “thin-wall” approximation to be valid. It has been shown that the thin wall approximation fails for all physiological deformations of the esophageal wall (53).
simulation to simulation, depending on the chosen parameters for that computer experiment.

The Computer Experiments

The model was parameterized with accurate anatomical and physiological data, as described above. These parameters were systematically varied in a series of computer experiments. The base state was defined as the average physiological resting state of the normal GES. Muscle wall thickness and stiffness were determined as described above. We specified the pressure external to the esophagus, consistent with a transition from atmospheric pressure (760 mmHg) in the mediastinum to 5 mmHg above atmospheric pressure in the abdominal cavity; the transition in pressures was modeled with a smooth sinusoidal curve over the 3-cm GES, as shown in Fig. 2D. At baseline, the modeled pressures within the stomach and esophageal lumen were set equal to the external pressures. The net active component of hoop stress in the GES was specified using an approximate force balance between stress and intraluminal pressure (38). Active stress (and its corresponding pressure) was modeled with a smooth curve that peaked at the center of the GES and was zero at the boundaries of the GES. This model is consistent with Ref. 6, which measured separately the active contributions to intraluminal pressure from the intrinsic smooth muscle and extrinsic cranial muscle components of the sphincter. We defined the tLESR state as “zero active stress.”

Figure 2 illustrates the process of GES opening as calculated from the equations that comprise our mathematical model. In Fig. 2, A and B, the muscle and mucosal layers are in the base and deformed states, respectively. The opening process is initiated by a sudden increase in gastric pressure above the baseline with the external pressures (Fig. 2D) held fixed. In our computer experiments, we model a refluxate with the density and viscosity of water. We show in Fig. 2, A and B, thick lines in the base and deformed states at a single cross section at z1. These represent lines of material in the mucosal and muscle layers and illustrate the model approximation that the material line in the mucosa does not shear, and we approximate the shearing of the muscle layer as linear. We approximate shearing of the muscle layer as perpendicular to the muscle midlayer.

Computer experiments were performed to study the initiation and space-time details of opening and reflux in response to the changes in the force balance between opening and closing forces initiated by an assumed increase in gastric pressure (Fig. 2B). Because opening and reflux were very slow at small gastric pressure increases, we discovered that a distinction must be made between GES opening and gastroesophageal reflux. We defined “GES opening” as occurring whenever the radius of the GES lumen increased with time, regardless of the speed of opening. The existence of gastroesophageal reflux, however, depends on the rate at which refluxate enters the esophagus. After experimenting with several definitions for “reflux,” we settled on the definition that “at least 2 ml of refluxate must enter the esophagus within 1 s.” This would occur only when the balance of forces was such for GES opening to proceed at a sufficiently rapid rate that a significant volume of refluxate enters the esophagus over a relatively short time. The definition is consistent with conclusions from concurrent impedance and high-resolution manometry that 1) reflux is a rapid event, and 2) not every tLESR event is followed by reflux (7, 15, 47, 51, 56).

Gastroesophageal reflux may occur either in the setting of a hypotonic LES or a tLESR. Therefore, we quantified opening and reflux first with a completely relaxed GES, and then we systematically increased sphincter tone in small increments until first reflux, and then opening, were blocked. In this way, we were able to determine the boundaries between the parameter combinations of gastric pressure rise vs. sphincter muscle tone (quantified as “sphincter augmentation pressure”) that lead to opening vs. reflux. The boundaries were different, owing to the different definitions that determine under what parameter combinations opening vs. reflux occur. These boundaries in parameters were determined as a function of different thicknesses of the liquid film layer. Thus, in the plots that follow, we distinguish between “opening” and “no opening,” and between “reflux” and “no reflux” within the space of variations among three parameters: 1) increase in gastric pressure above the base state; 2) sphincter augmentation pressure, representing tone; and 3) liquid film thickness.

RESULTS

Opening vs. Reflux

In Fig. 3, we plot four pairs of two curves from the mathematical model predictions. Below the solid curves, the combinations of mechanical parameters are such that the GES is predicted to open; above the solid curves the parameter combinations maintain closure. Figure 3 indicates, that for any increase in gastric pressure above baseline, the segment will eventually open if there is complete absence of sphincteric muscle tone, or zero “sphincter augmentation pressure.” However, the addition of sphincteric tone can maintain closure. Consider, for example, the pair of curves with liquid film thickness of 0.4 mm. According to the model, when gastric pressure increases by ~1 mmHg, the sphincter will open in the presence of sphincteric muscle tone unless active sphincteric muscle tension produces augmentation pressure >3 mmHg. Similarly, sphincteric augmentation pressure must increase to >4 mmHg when gastric pressure increases to ~2 mmHg to maintain GES closure. Interestingly, the model suggests that increases in gastric pressure >2 mmHg require relatively small increases in sphincteric augmentation pressure to maintain closure.

As discussed in MATERIALS AND METHODS, because “reflux” depends on how rapidly the GES opens and refluxate passes into the esophagus, we defined the criterion for “reflux” as “at least 2 ml of gastric liquid entering the esophagus within 1 s.” Using this definition, the combination of parameters that lead to reflux is given by the regions below the dashed curves in Fig. 3. While, above the dashed curves, the sphincter either does not open or opens sufficiently slowly that reflux does not occur.
occur (<2 ml in 1 s). For example, with a 1-mmHg increase in gastric pressure, reflux occurs when sphincter closure pressure is \( \leq 1 \) mmHg for liquid film thickness of 0.4 mm.

The mix of parameters in the shaded regions between the solid and dashed curves in Fig. 3 produces GES opening, but at an insufficient rate for \( \geq 2 \) ml of gastric liquid to enter the esophagus within 1 s. Thus opening is a necessary precursor for reflux, but does not imply the existence of reflux. Four pairs of curves are given in Fig. 3, for average GES film layer thicknesses \( \varepsilon = 0.2, 0.4, 0.6, \) and 0.8 mm. In Fig. 3, the tLESR state is given by the \( x \)-axis (where sphincter augmentation pressure = 0). We find that a tLESR is always accompanied by GES opening; however, a minimum increase in gastric pressure is required for reflux. This minimum level is sensitive to the effective thickness of the film layer, as will be discussed.

Note from Fig. 3 that, at increasing levels of sphincter muscle tone, greater increases in gastric pressure are required to initiate opening or reflux. The distinction between opening and reflux changes at these higher levels of sphincter muscle tension and gastric opening pressures. However, the difference between opening and reflux is generally less with a thicker liquid film layer. The reduced distinction between opening and reflux is particularly strong in the absence of sphincter muscle tension (tLESR). According to the mathematical model, when the liquid film layer is greater than roughly 0.8 mm, opening and reflux are both virtually assured for any increase in gastric pressure. This is not the case with thinner liquid films.

**Effect of the Liquid Layer on Opening and Reflux**

Figure 3 indicates that, once opening occurs, the probability for reflux is greater with a thicker effective liquid film in the GES. This is shown explicitly in Fig. 4. In Fig. 4A, we plot the augmentation in sphincteric muscle tone that is required to suppress reflux as a function of the liquid film thickness within the GES for a specific increase in gastric pressure. Reflux is suppressed above and to the left of each curve. We find that reflux occurs at higher sphincter augmentation pressures when the liquid film is thicker. Because the curves in Fig. 4A change smoothly and gently with decreasing film thickness, we can extrapolate these curves to film thicknesses below the lowest film thickness computed with the mathematical model (0.4 mm) with good precision. We have carried out these extrapolations down to sphincter augmentation pressure of zero (tLESR) using spline fits to the five calculated points on each curve, as shown by the dashed curves in Fig. 4A. The extrapolated values are the dashed parts of the curves in Figs. 4 and 5 and were used to generate the curves in Figs. 3 and 6 when \( \varepsilon < 0.4 \) mm.

In Fig. 4B, we plot gastric pressure against film thickness at fixed sphincter augmentation pressure (tone); each curve separates the combination of parameters that produce reflux from those that do not. From a clinical perspective, the tLESR curve is particularly significant. We find that, when the sphincter has no tone or residual tension, the level to which gastric pressure must increase to generate reflux rapidly increases as the thickness of the liquid film in the GES decreases. The model predicts that, when there is no liquid film at all in the sphincteric segment, reflux cannot occur, whereas the existence of even a thin film of liquid across the collapsed GES can substantially increase the probability for reflux. Our mathematical model predicts that gastric pressure must rise above \( \sim 4 \) mmHg to trigger reflux when a liquid film of effective thickness \( \sim 0.01 \) mm exists in the GES. When the film thickness is \( \sim 0.1 \) mm, gastric pressure must rise above \( \sim 2 \) mmHg to trigger reflux. However, when the liquid film thickness is \( \sim 0.5 \) mm, the rise in gastric pressure to trigger reflux is only \( \sim 0.5 \) mmHg, virtually assuring reflux.

Figure 5 is similar to Fig. 4B but shows the curves that separate opening from no opening rather than reflux from no reflux. Opening is triggered at lower increases in gastric pressure than is reflux, and, theoretically, opening always occurs in the absence of sphincter muscle tension. At lower gastric pressure increases, the opening of the sphincter occurs at a rate too low for sufficient flow into the esophagus to define the event as reflux. For tLESR in particular, although the model predicts opening at all increases in sphincteric tone, only with sufficient levels of liquid within the GES is flow into the esophagus rapid enough to classify as reflux (Fig. 3).

Comparison of Figs. 4 and 5 suggests that the reduction in reflux protection by the existence of liquid in the GES is particularly serious in the presence of sphincter muscle tone. This result is shown explicitly in Fig. 6, where the increases in
sphincter augmentation pressure required to suppress reflux are plotted against gastric pressure rise for different liquid film thicknesses. According to the model, when the film thickness is <0.2 mm, a few millimeters of mercury of tonic pressure are sufficient to ensure protection against reflux for realistic increases in gastric pressure. However, even with the added protection of 5- to 6-mmHg tonic pressure, effective liquid layer thicknesses of <0.4 – 0.6 mm are sufficient to ensure reflux when gastric pressure rises only a couple millimeters of mercury. Greater levels of liquid within the GES require much higher levels of sphincteric tone to maintain protection against reflux.

Role of Muscle Compliance in Opening and Reflux

We examined the parameters that control the degree of reflux after reflux has been initiated. We do this by quantifying the change in the degree of reflux from a refluxing “base state,” which we chose to be the tLESR reflux event shown on Fig. 3 with a solid circle at 2-mmHg elevation in intragastric pressure with 0.4-mm liquid film thickness. The degree of reflux can be reduced either by increasing the time required to initiate reflux, or by reducing the opening diameter after reflux has begun. A lower increase in gastric pressure will move the solid circle to the left along the abscissa of Fig. 3 in the direction of the open circle and should, therefore, reduce reflux. However, compliance of the GES muscle has also been implicated as a mechanical parameter that determines sphincteric competence (2, 35, 43). We compare the sensitivities to stiffness vs. gastric pressure rise in level of reflux using the mathematical model, relative to the base state defined by the solid circle in Fig. 3 with baseline stiffness of 60 mmHg (Fig. 2) and effective film thickness of 0.4 mm. For this study, we define “reflux initiation time” as the time at which the rate of refluxate flow rate into the esophagus reached 2 ml/s.

Figure 7 shows the effect on the reflux initiation time of varying GES stiffness (curve A) and gastric pressure rise (curve B) during a tLESR. For this model experiment, the gastric pressure rise was varied from 4 to 1 mmHg (the open circle in Fig. 3). GES stiffness was varied from 10 to 80 mmHg, consistent with the work of Schiffner and colleagues (48, 49), who measured a reduction in effective stiffness from 60 mmHg in normal subjects to 10 mmHg in a GERD group. We find that, while reflux initiation time changed only slightly when GES stiffness was varied, GES opening was very sensitive to changes in gastric pressure increase. A 50% increase in gastric pressure rise (from 2 to 4 mmHg relative to intra-abdominal pressure) resulted in a 40% decrease in reflux initiation time, whereas a 50% reduction in gastric pressure rise increased the time to reflux initiation by over 250%. In contrast, Fig. 8A shows that the maximum radius of GES opening with reflux was equally sensitive to relative changes in stiffness or gastric pressure rise. From Fig. 8B, where we plot the predictions of refluxate volume that entered the esophagus after 1 s, we find that the degree of reflux was very sensitive to both muscle stiffness and gastric pressure rise. For example, the volume of reflux nearly doubled when stiffness was reduced by 82%, the level measured in GERD patients by Schiffner et al. (48, 49).
In the “relaxed” state, but before opening, the normal GES is effectively sealed, and intragastric fluid pressure does not communicate with intragasophageal fluid pressure (3, 5). GES opening results from a change in the balance between an opening force proportional to the difference between gastric fluid pressure (liquid or gas) and abdominal pressure external to the stomach, and a closing force proportional to the summation of active and passive tensions within the sphincteric muscles. When the force balance has changed so that opening force outweighs closing force at the point of closure, the opening process begins at the esophago-cardiac junction and progresses proximally toward the mediastinum (Fig. 1C). When the entire GES has filled with gastric fluid, a new force balance comes into play that drives flow across the sphincteric segment and into the esophagus (Fig. 1D). The driving force for flow is proportional to the pressure difference in the fluid between the stomach and esophagus, while the resisting force is friction within the flow. This frictional force is very sensitive to the minimum dimension of the lumen as liquid passes through the hiatus (18, 41), so that the rate of flow into the esophagus, and, therefore, the existence of reflux, depends both on sphincter opening and on the trans-sphincteric pressure difference.

The primary closing force component, within the force balance that decides opening of the GES, is myogenic tone of sphincteric muscle. Thus the inhibition of tone during tLESR mechanically predisposes the GES to opening and reflux. Yet reflux is not guaranteed during tLESR, implying a level of subtlety associated with the details of the initial opening process, details that are difficult to measure experimentally. We, therefore, applied a sophisticated mathematical model of the combined fluid-muscle interaction process that results from specified increases in transmural gastric pressure difference (i.e., opening force). The great advantage of the mathematical model is its ability to quantitatively predict the systematic responses to specified changes in the force balance as a function of precisely controlled variations in muscle tone, geometry, and sphincter muscle stiffness (or compliance), at the most critical time: the initiation of reflux. Although the mathematical model of the GES cannot represent all details of the complex interrelationships that separate normal from chronic liquid reflux (i.e., occurring with abnormal frequency), we designed a model that includes a sufficient level of complexity to predict the essential responses to the physiomechanical changes that underlie GES opening and reflux. In doing so, we have discovered a previously unknown contributor to GES opening that could play a role in the demarcation between normal reflux and GERD.

The baseline model was parameterized with anatomical data of muscle and mucosal thickness determined in vivo from endoluminal ultrasound (57), net stiffness of the passive stress-strain response of the GES as a whole from analysis of in vivo data (49), and abdominal and mediastinal pressures. Net sphincteric tone was specified in terms of its contribution to intraluminal pressure as measured manometrically, and a manometric catheter was included in the model. The existence of liquid within the mucosal folds and coating the epithelium was modeled as an effective “lubrication film layer” between the catheter and mucosa with specified “film thickness.” The liquid film should be interpreted as a model for those pockets of liquid within the mucosal folds that form fluid conduits between gastric liquid and the esophageal lumen (8, 13, 14, 44, 50). With specified intrathoracic and abdominal pressure, we systematically varied gastric pressure from baseline, net sphincter...
tone, net sphincter muscle stiffness, and the effective liquid film thickness. Potential axial movement of the sphincter relative to the pressure inversion point (50) was not explicitly modeled, although, as we shall discuss, the results are relevant to this issue.

The results in Fig. 3 make it clear that opening and reflux are not necessarily the same event. The model predicts that, in the absence of tone and residual tension, the sphincter will open in response to any transmural gastric pressure increase at the point of closure (Fig. 5). However, opening may be so slow that insufficient gastric content passes into the esophagus during the period of gastric pressure elevation to qualify as "reflux." Whereas reflux cannot occur without opening, opening does not guarantee reflux. The passage of sufficient volume of gastric content into the esophagus for reflux to have occurred depends not only on the existence of opening, but also on the rapidity and extent of opening. Thus the parameter combinations that separate reflux from no reflux are different from those that separate opening from no opening (Fig. 3).

In this study, we defined a "reflux event" as one in which at least 2 ml of liquid enters the esophagus within 1 s. As shown in Figs. 5 and 6, sphincteric muscle tone (parameterized as manometrically measured "augmentation pressure") can suppress opening and/or reflux. It is not surprising that the level of tone required to suppress sphincter opening or reflux increases with the degree of gastric pressure rise driving reflux. However, we also discovered that the level of tone required to prevent opening or reflux is strongly dependent on the thickness of the liquid layer between the catheter and mucosa. As effective film thickness decreases, so does the level of sphincter tone necessary to maintain closure or to prevent reflux. Similarly, during tLESR, the separation between the parameters that define opening vs. reflux is much greater when the film thickness is thinner. As shown in Fig. 3, when the lubrication film is sufficiently thick, reflux is guaranteed to follow from opening; however, when the liquid film is very thin, opening does not guarantee reflux. With a very thin liquid film, the level of gastric pressure increase that is required for reflux is much greater than that required for opening.

In fact, the model predicts that, when there is no liquid within the mucosal folds (film thickness = 0), reflux will never occur (Fig. 4), and GES opening is blocked by any level of muscle tension, no matter how small (Fig. 5). This can be explained from mechanical principles as a consequence of theoretically infinite frictional resistance to flow of fluid into the GES as the gap between mucosa and catheter (cross-sectional area available for flow) shrinks to zero. In reality, of course, there is always some liquid lining the closed sphincter, with or without a catheter. Indeed, the very high sensitivity between reflux and liquid film thickness displayed in Fig. 4 reflects the high sensitivity between frictional resistance to gap flow and gap thickness when gap thickness is "thin." The consequence is a high sensitivity between retrograde flow and gap thickness for given gastric pressure rise (shown in Fig. 3 by the increasing distance between the solid and dashed lines with decreasing film thickness when sphincter augmentation pressure is zero), and between gastric pressure rise and film thickness for given retrograde flow (Fig. 4).

From functional and clinical perspectives, Figs. 3–5 indicate that the existence of abnormally high levels of liquid within the GES, perhaps associated with an abnormality in the anatomy of the GES, is a controlling element that distinguishes normal opening from pathological opening and reflux. Studies comparing GERD groups with controls have shown that, when the relaxed sphincter is opened, the opening diameter of the hiatus is higher in the GERD groups (43, 54). A recent study by Schiffrin et al. (48, 49) has shown that, in GERD patients without an obvious HH, the higher level of distension observed after opening could be traced back to an abnormally high radius to the circular muscle in the resting state and that, during opening, the muscularis continues to distend abnormally. When fully open, the difference was ~2.1 mm, consistent with a 2.5-mm difference between a normal and HH group at maximum mechanical distension of the GES and a 2.1-mm difference at maximum opening during reflux between a normal and GERD group as measured by other investigators (43, 54). However, Schiffrin et al. (48, 49) found that, in the resting state, the average radius to the inner surface of the circular muscle was ~1.2 mm greater in the GERD group compared with that in normal controls.

It appears that a characteristic that distinguishes the normal controls from the GERD patients in the above studies is a muscle layer that is more distended than normal in the resting state, and, therefore, there is the potential for higher levels of liquid within the GES at the initiation of opening. In fact, recent studies have identified the existence of acidic liquid within the GES in the normal sphincter and covering the entire segment in GERD groups (8, 13, 14). A recent study has also measured the upper margin of an acidic liquid layer in the resting state to extend 1.3 cm above the upper margin of the high-pressure zone of a mild HH GERD group, compared with 3 cm below in normal controls, consistent with a more distended GES and thicker liquid film layer with GERD (44).

The results of the present study show that, because of subtle balance in fluid mechanical forces at opening, even slightly higher than normal levels of liquid in the GES can reduce significantly the degree to which gastric pressure must rise to cause opening and reflux. Combining the predictions from the present model study with the result of Shiffner et al. (48, 49), that the radius of the muscularis in their GERD group was 1.2 mm higher than normal, we can show that the distinguishing effect of an abnormally thick effective liquid layer can be very strong. The higher radius to the muscle layer of 1.2 mm implies additional space for liquid to reside within the GES by some reasonable fraction of 1.2 mm. For illustrative purposes, let us assume an increase in the effective liquid film thickness of one-third of 1.2 mm, or 0.4 mm. To determine how this additional 0.4 mm of liquid affects the probability for reflux, consider the model predictions of Fig. 4 in the tLESR state. Since respiration may increase gastric and abdominal pressures by 2–4 mmHg, let us assume that the normal sphincter requires an increase in gastric pressure relative to abdominal pressure of ≈3 mmHg to trigger reflux. Then, from Fig. 4, we would specify the normal sphincter film thickness to be roughly 0.05

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2 In the limit of the gap spacing shrinking to zero, the frictional force resisting the pressure force that drives the flow becomes proportional to \( QD^2 \), where \( Q \) is the volumetric rate of flow through the gap, and \( D \) is the gap spacing [see discussions in Pal et al. (41) and Brassard and Dodds (5)]. The \( 1/D^2 \) creates a high sensitivity at small enough gap spacing between the driving pressure force required for flow (the \( x \)-axis in Fig. 5) and the film thickness (the \( y \)-axis in Fig. 5). When the gap spacing is driven to zero, frictional resistance and the driving force required to overcome frictional resistance are driven to infinity, as shown in Fig. 4B.
mm. Now consider the abnormally distended sphincter containing additional liquid with increased effective film thickness of 0.4 mm, so the total film thickness is 0.45 mm. Then, from Fig. 4, we would conclude that, in the abnormally distended sphincter, a gastric pressure increase of only 0.7 mmHg would be sufficient to stimulate reflux, compared with 3 mmHg in the normal sphincter. Consequently, the abnormally distended sphincter would reflux much more frequently in the presence of tLESR than would normally occur.

The loss of protection from the additional liquid in the GES, however, is even more severe than the above argument suggests. Figures 4 and 5 show quantitatively how the addition of tone to sphincteric muscle increases the protective function by increasing the levels of gastric pressure rise required to trigger opening and reflux. As shown in Fig. 6, this protective function of sphincteric muscle is very strong with a very thin film thickness, but weakens a lot with higher, but still small, levels of liquid within the GES. Consider, for example, how much tone (sphincter augmentation pressure) would be required to suppress reflux with a rise of 1 mmHg in gastric pressure above the trigger pressure in the normal vs. distended sphincter from the discussion above. According to Fig. 6, in the normal sphincter (ε = 0.05 mm), only a very small level of tone, equivalent to 0.5 mmHg, would suppress reflux when the gastric pressure increases by 1 mmHg above the trigger pressure of 2.7 mmHg, enough to trigger reflux in the abnormal sphincter described above, but not enough to trigger reflux in the normal sphincter. The model predictions indicate that, to prevent reflux in the normal sphincter (film thickness = 0.05 mm) from a 3–4 mmHg rise in gastric pressure, only a small level of sphincter tone equivalent to augmentation pressure of <0.5 mmHg would be required. However, in the distended sphincter with a film thickness of 0.4 mm, ~3 mmHg of tone augmentation pressure would be required to prevent reflux from a 1-mmHg increase in intragastric pressure above the trigger pressure of 0.7 mmHg. Consequently, the protection against reflux afforded by low levels of tone is severely diminished in the presence of abnormal levels of liquid in the GES within an abnormally distended GES.

We conclude that the existence of abnormal levels of liquid, arising potentially from abnormal distension of sphincter muscle, is a potentially important distinguishing characteristic between normal and chronic reflux. What is the role of compliance? The studies by Pandolfino et al. (42, 43) argued that compliance of sphincter muscle may be relevant to GERD. “Compliance,” traditionally defined as the slope of distending pressure against the distending volume or area, is an experimental (inverse) measure of muscle stiffness. Stiffness, however, is a well-defined parameter in our model, so we asked the question, “if the GES were in a severe reflux part of the parameter space in Fig. 3, to what extent would changes in stiffness reduce the probability and level of reflux?” To address this question, we compared changes in reflux to the base state given by the solid circle in Fig. 3 with film thickness of 0.4 mm and stiffness of 60 mmHg. We found that the compliance of the sphincteric muscle did not affect significantly the probability for the occurrence of reflux, especially compared with reducing the level of gastric pressure rise driving reflux (Fig. 7). However, once reflux has occurred, the compliance of the sphincter has a significant impact on the degree of reflux, as measured by reflux volume and opening diameter.

We conclude that liquid in a distended GES enhances the probability for reflux, but compliance does not. Abnormal distension is a natural consequence, for example, of hiatal hernia (HH) but, based on recent studies, may be a general feature of GERD (43, 48, 49, 54). A recent study has concluded that the sphincter components include an overlapping intrinsic and extrinsic component, as well as a third component at the gastro-cardiac junction (6), and has suggested that this third component may be absent in HH (25). The present study suggests that the reduction of tonic protection afforded by this missing sphincteric component would compound susceptibility to chronic reflux when combined with the additional liquid that would reside within a more flaccid GES from HH.

We further conclude that, within the events that classify as reflux, the less stiff (more compliant) sphincter will open wider and reflux a greater volume of gastric content. To reduce the frequency of reflux, however, surgical procedures should strive primarily to reduce the level of liquid within the GES. Thus, whereas the level of reflux as a consequence of a flaccid sphincteric segment is reduced by increasing stiffness via a fundoplication wrap (42) or by endoscopic suturing (48, 49), the reduction in sphincter compliance will not change the probability of reflux through mechanical means, unless the wrap also reduces the average thickness of residual liquid in the GES that connects the stomach cavity to the mediastinal esophagus. A natural consequence of such a procedure will likely also be to increase the stiffness of the GES, giving the additional benefit of reducing reflux level when reflux does occur.

Three additional clinically relevant observations may be made from this mathematical modeling study. The first we shall call “gastroesophageal pooling,” by which we mean the accumulation of gastric liquid within the distal esophagus from continual slight ejections of small volumes of gastric liquid across the GES into the region just proximal to the high-pressure zone. Consider opening vs. reflux in Fig. 3 (solid vs. dashed lines) with an increase in gastric pressure of 2 mmHg during a tLESR (the solid circle) with liquid film thickness = 0.2 mm. According to Fig. 3, the sphincter would open, and reflux would occur. However, a gastric pressure increase of only 1 mmHg would not cause reflux, but would cause opening (according to our criterion for reflux). The fact that there is opening implies that some small amount of liquid is passing through the GES into the distal esophagus over the period of the tLESR. In a normal sphincter with minimal liquid within the GES, the rate of volume flow into the esophagus with each 1-mmHg rise in intragastric pressure would be negligible. However, within an abnormally distended GES containing abnormal levels of liquid within the GES, there may exist continual repetitive ejections of small amounts of acidic liquid into the distal esophagus during repetitive, small increases in gastric pressure. Fig. 3, for example, suggests that, with an effective liquid film of thickness 0.45 mm (the GERD case discussed previously), a small volumetric ejection of gastric

3 A longer and/or tighter fundoplication wrap, for example, may reduce the level of liquid in the gastroesophageal sphincter that connects the stomach to the esophagus. However, a modeling study of impaired esophageal emptying with fundoplication by Ghosh et al. (18) suggests that a longer wrap is less detrimental to swallowing and, therefore, may be preferable to a tighter wrap to reduce the connecting conduits of liquid within the GES.
Liquid into the distal esophagus would occur with each respiration cycle. Such small volumes would be insufficient to stimulate a stretch-induced contractile reflex in the distal esophagus, so that low levels of acidic liquid might be continually present and contribute to the deterioration of the epithelium.

The second observation is the potential role of residual tension in the protective function of the gastroesophageal sphincter. Studies done with esophageal muscle from animals have shown that, when axial slices of passive esophageal muscle are cut along its circumference, it tends to open (16, 29, 33). The “opening angle” is a qualitative measure of “residual tension,” the level of circularly oriented passive tension that would be required to re-close the gut segment and return muscle to its precut state. A nonzero opening angle from dead muscle tissue may imply the existence of residual passive tension in vivo. These experiments have not been carried out with sphincteric tissue; however, the results of this mathematical modeling study suggest that, like small levels of tone, small levels of residual tension can enhance significantly the protective function of the gastroesophageal sphincter. Similar to the protective function of sphincter muscle tone discussed above, the effectiveness of residual tension would be greatly compromised with abnormal levels of liquid within the GES.

A final observation may be made concerning recent research that may indicate low levels of shortening of longitudinal muscle in the esophageal body and upward motion of the LES preceding some opening and reflux (50). The current mathematical model did not explicitly include the changes in anatomy that would accompany an upward pulling on the GES. However, our study may be relevant, since the conformational changes of the GES associated with an upward pulling would likely cause the collapsed portion of the distal esophagus to shorten axially. Axial shortening of the closed segment would likely increase the liquid in the connecting conduits between the stomach and distal esophagus and, therefore, the thickness of the effective liquid film layer. Thus, from a mechanical perspective, the shortening of longitudinal muscle of the esophagus could enhance the potential for GES opening and reflux post-LLESR.

APPENDIX: MATHEMATICAL MODEL DEVELOPMENT

Here we summarize the mathematical formulas of the combined muscle wall and fluid flow model developed for the computer experiments. Many of the features of the mathematical formulation are borrowed from Nicosia and Brasseur (37, 38). However, whereas Nicosia and Brasseur modeled the esophageal wall in the static state, in our application the dominant term in the Newton’s law expression for the sphincter muscle is the acceleration term, from which the space-time changes in wall radius are computed after two integrations in time. The resulting mathematical model is the first finite-deformation, fluid-structure interaction model of tube opening with a first-order inertial term and the first finite-deformation model of muscular-flow interactions in the gastrointestinal tract.

The mathematical equations describe the dynamic relationships among the forces that drive the time-dependent deformations of the esophageal wall from the esophago-cardiac junction into the thoracic cavity. The mathematical descriptions of these forces may be separated into two distinct predictions, both of which couple Newton’s second law of mechanics with the law of mass conservation for incompressible matter: 1) prediction of the changes in geometry of the muscle and mucosal layers; and 2) prediction of the flow of liquid from the stomach through the GES and into the esophagus. The fluid and muscle models are coupled by equating fluid pressure with normal mucosal stress at the interface between the mucosa and fluid. In the resting state, an “effective film layer” extends throughout the GES to model the liquid coating the epithelium and small pockets of liquid within the mucosal folds, as described in MATERIALS AND METHODS. The model geometry includes a manometric catheter with diameter from the in vivo studies used to parameterize the model.

We simplified the anatomy to an axisymmetric muscularis of mixed circular and longitudinal muscle fibers and collagen embedded within an elastic isotropic cellular matrix connected to an axisymmetric layer of mucosal tissue. We assumed that the loose cellular structure of the mucosa could not support shear stress, so radial pressure from its inner boundary was transferred directly to the inner surface of the muscularis. The total stress within the muscularis was modeled as a summation of passive plus active stress components, with the active component further decomposed into circular and longitudinal muscle fiber components. The passive component was modeled with a linear constitutive relationship between local stress vs. strain in the absence of tone. We used a variant of the anisotropic Mooney-Rivlin linear stress-strain constitutive model for finite deformations of incompressible elastic materials (34), with the proportionality being the net muscle stiffness. Sphincteric tone was modeled as net stress in the circular and longitudinal directions, with the circular component specified in the model as an added “tonic pressure”, as might be measured manometrically. The longitudinal contribution was calculated by specifying local longitudinal motions of the muscle areas. In the present experiments, we assumed no longitudinal motion of the muscularis; that is, we assumed no local longitudinal shortening. Because we parameterize the active circular muscle stress and passive elastic stiffness with in vivo endoluminal ultrasound and manometry data, the additional stresses from the extrinsic crural muscles are included indirectly through the data. Thus the parameterized mathematical equations should be interpreted as modeling the net effects in the circular and longitudinal directions of the sphincter muscle.

The mathematical details, including the derivations of the equations summarized here, may be found in the PhD thesis of Ghosh (17). These developments borrowed from the muscle model of Nicosia and Brasseur (37, 38). Additional details of the fluid flow model may be found in Ghosh et al. (18) and Li et al. (27, 28).

The Muscle Deformation Model

The undeformed GES was modeled as a thick-walled distensible axisymmetric cylindrical tube with axially varying thickness and model parameters. The deformed state is described using the cylindrical coordinates \((r, \theta, z)\) with unit vectors \((\hat{r}, \hat{\theta}, \hat{z})\). The reference configuration \((R, \Theta, Z)\) corresponded to a tube collapsed onto the manometric catheter as shown by the “base state” of Fig. 2A. As shown in Fig. 2B, we defined a locally orthogonal coordinate system to quantify the force-deformation relationship in the local longitudinal \((\xi)\) and azimuthal \((\eta)\) directions. The transformations in derivatives between the two coordinate systems is:

\[
\frac{\partial}{\partial r} = \cos \alpha \frac{\partial}{\partial \xi} - \sin \alpha \frac{\partial}{\partial \eta}, \quad \frac{\partial}{\partial z} = \sin \alpha \frac{\partial}{\partial \xi} + \cos \alpha \frac{\partial}{\partial \eta} \quad (A1)
\]

The law of mass conservation for incompressible muscle implies that muscle volume is conserved between the reference and deformed configurations. \(\xi_s\) and \(\xi_e\) are, respectively, the locally radial coordinates of the inner and outer surfaces of the muscle layer. Thus \(\xi_e = \xi_s + \tau_M\), where \(\tau_M\) is the thickness of the muscle wall. The mathematical statement is:

\[
\frac{\partial}{\partial r} \left( r \frac{\partial Z}{\partial r} \right) - \frac{\partial}{\partial z} \left( r \frac{\partial Z}{\partial z} \right) = r \quad (A2)
\]

The force balance equations of the muscle wall in the radial and
longitudinal directions are described by Newton’s second law of motion,
\[ \rho a_{\mu} = \nabla \cdot F_T + F_d \quad (A3) \]

where \( a_{\mu} = a_{\mu} + \dot{e}_\mu \), \( a_{\mu} \) is the acceleration of a muscle wall particle, and \( T \) is the Cauchy stress tensor. Because passive muscle response is viscoelastic, we include the effects of viscous damping with a damping force \( F_d \) in Eq. A3. Gravity forces were not included, since these are either zero in the supine position or negligible otherwise. Most biological tissue, gastrointestinal smooth muscle is nonlinear, elastic, and anisotropic. The Cauchy stress \( T \) was modeled using a fluid-fiber-collagen decomposition into fiber and background components \( S_f \) and \( S_b \) (22, 23, 38):
\[ T = -I I + S_f + S_b \quad (A4) \]

where \( e = -\sin \alpha \cos \beta \hat{e}_x + \cos \alpha \cos \beta \hat{e}_y \) is a unit vector in the longitudinal muscle fiber direction, and \( e = e_0 \) is a unit vector in the circular muscle direction. \( F_1 \) and \( F_2 \) are components to the total stress associated with longitudinal and circular muscle fibers, respectively. \( I I \) is a “hydrostatic” stress that is necessary to satisfy incompressibility when mass conservation is applied (\( I I \) is the Lagrange multiplier). The background stress tensor \( S_b \) is modeled using a linear Mooney-Rivlin constitutive model between \( S_b \) and the Eulerian finite strain tensor strain \( e \). \( \mu_M \) is a stiffness coefficient (qualitatively, the inverse of compliance). Stress contributions from the circular diaphragm are embedded into the model for \( F_2 \).

The local radial force balance equations were integrated in \( \zeta \) across the muscularis to produce equations for average muscle layer stress that were identified with the midsurface of the muscle layer (Fig. 2, A and B). The damping term in Eq. A3 was modeled as proportional to the local velocity of the material element (a dashpot) with damping coefficient \( \gamma \). The integrated radial equation is:
\[ \frac{\partial u_{\text{ML}}}{\partial t} = \int_{l_i} \left[ -\cos \alpha \frac{\partial I}{\partial \zeta} + \cos \alpha \frac{\partial S_{\mu \mu}}{\partial \zeta} - \sin \alpha \sin \alpha \frac{\partial I}{\partial \eta} + \sin \alpha \frac{\partial S_{\mu \mu}}{\partial \eta} + \frac{S_{\mu \mu} - S_{in}}{\cos \alpha \cos \alpha} \right] \delta \zeta - \gamma u_{\text{ML}} \quad (A5) \]

where \( u_{\text{ML}} \) is the radial velocity of the midlayer surface, and \( S_{in} \) are the components of the total stress tensor that include both active and the passive components (Eq. A4). \( \alpha \) is the local angle of the midlayer to the horizontal, defined as the angle between the positive directions of the \( z \) and the \( \eta \) axes (Fig. 2B).

As discussed in MATERIALS AND METHODS, Ghosh et al. (18) measured GES opening during swallowing and found that the elastic response to opening is rapidly damped by muscle viscoelasticity. Consistent with their results, we chose \( \gamma \) in each computer experiment by limiting the elastic response to, at most, a single oscillation during opening from below and requiring that the maximum amplitude of the oscillation be, at most, 10% of the steady-state radius. The solution must be independent of the damping coefficient in the steady-state limit. We were careful to choose \( \gamma \) so that the system was damped only to the extent necessary to limit the number of oscillations to one; particular care was taken to prevent overdamping. The maximum amplitude of the oscillation was, on average, 5.3% of the steady-state radius, and we ensured that the steady state was independent of the damping coefficient.

The equations above were integrated and reduced to a final form amenable to computer simulation with a couple additional minor approximations (see Ref. 17 for details). As mentioned above, the mucosa transmits normal stress (pressure) directly to the inner muscle surface. The boundary conditions for the final form of Eq. A5 were obtained by requiring continuity of total stress at the mucosa-fluid interface. The result is a relationship between the hydrostatic and nonhydrostatic stresses \( I \) and \( S \) in Eq. A4 with fluid pressure \( P \):
\[ I(r_{in}, z) = P_m(z) + \beta (r_{in}, z) \quad (A6) \]

where
\[ \beta(r_{in}, z) = S_{in}(r, z) \cos^2 \alpha(z) + S_{out}(r, z) \sin^2 \alpha(z) + 2S_{in}(r, z) \sin \alpha(z) \cos \alpha(z) \quad (A7) \]

Similarly, the boundary condition at the outer wall is given by
\[ I(r_{out}, z) = P_m(z) + \beta (r_{out}, z) \quad (A8) \]

where \( P_m \) is the extramural pressure as specified in Fig. 2C. Because the outward normal at the inner and outer surfaces of the muscularis is always perpendicular to the circular and the longitudinal muscle layers, the stresses in Eq. A7 are strictly passive.

In our model, the tonic circular fiber stress \( F_c \) is specified through an equilibrium force balance between \( F_c \) and “muscle augmentation pressure.” The longitudinal fiber stress component \( F_l \), however, is predicted from the longitudinal component of the Newton’s law force balance, \( E q. A3 \), and the specification of local axial motions of the muscle layer cross sections. In this way, we retained the ability to parameterize longitudinal shortening of the muscle layer. The longitudinal force balance equation is given by
\[ \frac{\partial F_l}{\partial l} + F_c \theta_1 + \phi_2 = 0 \quad (A9) \]

where
\[ \phi_1 = -2 \tan \alpha \frac{\partial \alpha}{\partial r} + (1 - \tan^2 \alpha) \frac{\partial \alpha}{\partial r} + \tan \alpha \quad \text{or} \]

\[ \phi_2 = -\frac{\rho}{\cos \alpha} \frac{\partial^2 \rho}{\partial \alpha} \frac{1}{\cos \alpha} \frac{\partial^2 \rho}{\partial \zeta^2} + \frac{1}{\cos \alpha} \frac{\partial S_{z \zeta}}{\partial \zeta} \quad (A10) \]

The subscript, \( m \), implies passive component of the stress. In the computer experiments carried out in this work, we did not study the potential role of local longitudinal shortening and assumed that the cross sections did not move axially. Recent research (50) suggests that some reflux events may be preceded by low-level shortening of longitudinal muscle. For the boundary condition, a prespecified longitudinal stress of 75 mmHg based on prior physiological studies was applied based on estimates by Nicosia and Brasseur (37, 38) and based on data by Tottrup et al. (55).

The Fluid Flow Model

The fluid flow model for gastroesophageal reflux of liquid was based on Newton’s second law, combined with conservation of mass for incompressible Newtonian fluids (here, water). We do not include gravitational forces in the model. The model described here is a generalized version of the mathematical model of Li and Brasseur (27), subsequently applied to antegrade esophageal emptying by Ghosh et al. (18). The Navier-Stokes equations for incompressible fluids are written in cylindrical coordinates and reduced for using “lubrication theory” for friction-dominated flows with low wall curvature. The model is generalized by including an approximation for
the inertial term left out in the classical lubrication theory approximations. We have verified that this term is generally small in our simulations. The approximation of gentle wall curvature has been shown to capture the volumetric flow accurately (10), while reducing the complexity of the mathematical solution. For example, a consequence of this approximation is that pressure depends only on the axial coordinate, $z$.

Conservation of mass for incompressible fluids requires a relationship between the local flow rate $Q(z,t)$ through a cross section of the lumen at axial location $z$ and time $t$ and the time changes in lumen radius $r_{\text{lum}}(z,t)$:

$$Q(z,t) = -2\pi \int_0^z r_{\text{lum}}(z',t) \frac{\partial r_{\text{lum}}(z',t)}{\partial t} \, dz' + Q_0(t)$$

where $Q_0(t) = Q(0,t)$ is the volume flow rate at the gastric margin of the lumen (see Fig. 2B). The axial Navier-Stokes equation (Newton’s law) with the approximations described above and applying the no-slip boundary condition for fluid velocity at the lumen boundary reduces to the following equation for fluid pressure $P(z)$:

$$-\frac{\partial P(z,t)}{\partial z} = 16\mu \frac{1}{\gamma(z,t)} \int_0^z r_{\text{lum}}(s,t) \frac{\partial r_{\text{lum}}(s,t)}{\partial t} \, ds$$

$$+ \frac{8\mu}{\pi \gamma(z,t)} Q_0(t) + I(z,t)$$

where

$$\gamma(z,t) = r_{\text{lum}}^4(z,t) - R_c^4 - \frac{r_{\text{lum}}^4(z,t)}{R_c^4} \quad \text{and} \quad I(z,t) = -\frac{1}{2} \frac{d(\alpha U^2)}{dz}$$

$R_c$ is the radius of the catheter, $\alpha$ is the “kinetic energy correction factor” as described in textbooks on fluid mechanics (58) and depends only on the shape of the velocity profile (here $\alpha \approx 2$). The intraluminal pressure variation is obtained by integrating Eq. A12, which gives:

$$P(z,t) = 16\mu \int_0^z \frac{1}{\gamma(z',t)} \int_0^{z'} r_{\text{lum}}(s,t) \frac{\partial r_{\text{lum}}(s,t)}{\partial t} \, ds \, dz'$$

$$+ \frac{8\mu}{\pi} Q_0(t) \int_0^z \frac{1}{\gamma(z',t)} \, dz'$$

$$+ P_0(t) - \frac{1}{2} \left[ p(\alpha(z)U^2(z) - \alpha(0)U^2(0)) \right]$$

where $P_0(t) = P(0,t)$ is the gastric pressure and $U$ is the axial velocity averaged over the lumen cross section. To force fluid velocity to zero at the upper margin of flow domain, we set the axial pressure gradient to 0 at the esophageal end of the tube ($z = L$). The esophageal segment $L$ is chosen large enough that the upper end of the flow does not affect the flow though the LES.

Algorithm for Solution of the Model Equations

The solution algorithm employed for the computer simulations is as follows: time $t = 0$ is defined by the base state (Fig. 2A) with zero velocity at the fluid-mucosa interface. To move to the next time step, the intraluminal pressure variations (Eq. A13) and the intramural stress tensor (Eq. A4) are calculated. Active circular muscle stress is specified, and passive circular stresses are calculated from the constitutive relationship in Eq. A4. The longitudinal stresses are then calculated from Eqs. A9 and A10, completing the total stress tensor in Eq. A4. Equation A5 is then integrated using a second-order Runge-Kutta method to predict the velocity of the muscle midlayer. A second integration using Runge-Kutta produces the change in shape of the midlayer at the next time step. The conservation of mass relationship, Eq. A2, is then used to identify the inner and outer boundaries of the muscularis and the inner surface of the mucosa. The stress tensor for the new deformed state is then calculated, and the updated geometry is used to determine intraluminal pressure gradients at the next time step. A time step of 0.001 s was found to be adequate for the simulations.

GRANTS

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REFERENCES