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Determination of membrane tension during balloon distension of intestine

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Abstract: During the last decades, it has become increasingly common to make balloons distension in visceral organs *in vivo*. In particular this is true for studies of gastrointestinal motor function and biomechanics. Balloon distension is often used for assessment of small intestinal compliance and tension based on Laplace's law for cylindrical pressure pipes. This commonly used law is valid only when the balloon-distended intestine is cylindrical. Experimentally, it is seen that the diameter of the balloon-distended intestine is not a constant, but variable in the axial direction. Hence, it is necessary to improve Laplace's law for intestinal investigation. In this paper we develop the framework for determination of the tension distribution in circumferential and longitudinal direction during balloon distension. When the radii of curvature are measured from a photograph of the intestinal profile, then the membrane stress resultants can be computed everywhere in the intestine in contact with the balloon from the equations of equilibrium. The experimental data were obtained from small intestinal segments from five pigs and three guinea pigs. Papaverine was injected before the animals were sacrificed to relax the intestinal smooth muscle. The segments were immersed in a bath with calcium-free Krebs solution with dextran and EGTA. A balloon was distended in the lumen with pressures up to 15 cmH_2O in the pigs and 10 cmH_2O in the guinea pigs and radii were measured along the z-axis. The tension in circumferential direction had its maximum approximately 25% away from the middle of the balloon. The circumferential tension was 2-3 times higher than the longitudinal tension. In conclusion when we know the shape of the intestine, we can compute the circumferential and longitudinal components of tension. The large variation in tensions along the z axis must be considered when performing balloon distension studies in the gastrointestinal tract for studying physiological and pathophysiological problems in which loading conditions are important, e.g. intestinal mechanoreceptor studies in order to obtain accurate description of the biomechanics and the stimulus-response function.

keyword: Intestine, balloon distension, tension.

1 Introduction

Balloon distension is a commonly used technique in visceral organs. Research studies take advantage of this technique for studying organ physiology, e.g. for investigating the force-deformation relationship (Gregersen, Jørgensen and Dall, 1992) and various receptors that respond to mechanical stimulation (Gregersen and Kassab, 1996). Balloon distension is also used for diagnostic purposes, e.g. in the diagnostics of non-cardiac chest pain (Rao, Gregersen, Hayek, Sommers, Christensen., 1996) and for treatment of diseases such as coronary plaque formation in atherosclerosis (Bonnet, 1988), bleeding oesophageal varices due to liver disease and lower oesophageal sphincter dilatation in achalasia (Goyal, 1994). In a biomechanical analysis it is important to know the force-deformation (stress-strain) relationship of the tissue. If the wall thickness is measurable and the intestine remains in cylindrical shape, then the average stress in the tissue can be determined according to Laplace's law. However, often the thickness is not measurable and the shape of the balloon-distended intestine is not exactly a cylinder, then the force exerted on the tissue is expressed in terms of tension, and the Laplace's law must be improved to remove the cylindrical shape restriction. Several studies have evaluated the tension in circumferential direction in visceral organs corresponding to the mid-balloon location (Villadsen, Petersen, Vinter-Jensen, Juhl, Gregersen, 1995; Gregersen, Jørgensen, Dall., 1992; Juhl, Vinter-Jensen, Djurhuus, Gregersen, Dajani., 1994). However, to the best of our knowl-

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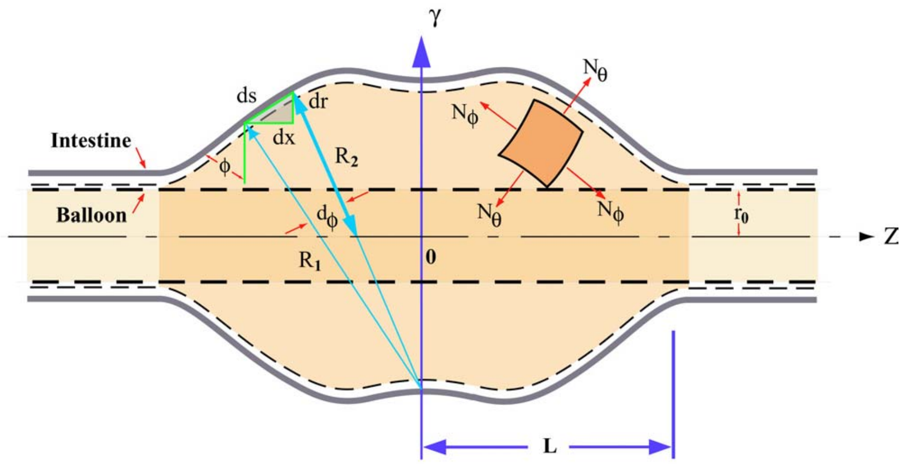

Figure 1 : Schematic drawing of the distended segment of an intestine. Coordinates with z as the longitudinal axis, r as radial axis, θ the polar angle, ϕ the latitudinal angle. θ and ϕ form a set of curvilinear orthogonal coordinates. Membrane stress resultants are $N_{\theta,}N_\phi$, the circumferential and longitudinal membrane stress, respectively. Definitions of these coordinates and stress resultants are given in the appendix.

edge no study so far evaluated the distribution of tension in circumferential and axial direction everywhere in the balloon-distended area.

In this study we develop the framework for determination of the circumferential and longitudinal components of tension during balloon distension. The basic message is that when we know the shape of the intestine, we can compute the circumferential and longitudinal components of tension. The theory will help to get insight into understanding the mechanical properties of visceral organs in health and disease and the stimulus exerted by balloons during distension. Data are obtained during distension of the small intestine to illustrate the usefulness of the development.

2 Methods

2.1 Development of theory and principles for determination of tensions during balloon distension

The theory outlined below can be used in any hollow visceral organ *in vitro* or *in vivo* as long as the geometric data and the balloon pressure can be measured. In this paper data are obtained from the pig small intestine *in vitro.* Bending forces and moments are neglected. It is assumed that the balloon and intestine form a tube of revolution, that the structure and deformation are axisymmetric, that the zero-stress state of the balloon has a diameter larger than that of the distended intestine and that its length is sufficiently longer than the intestinal segment in contact. The intestine resists the pressure imposed through the balloon. We assume also that the shear stress (friction) between the balloon and intestine is negligible. At places where the balloon is in contact with the intestine during distension, we treat the tissue and balloon together as a membranous structure. Coordinates as shown in Fig. 1 are used, with z as the longitudinal axis, r as radial axis, θ the polar angle, ϕ the latitudinal angle. θ and ϕ form a set of curvilinear orthogonal coordinates. Membrane stress resultants are $N_{\theta,}N_\phi$, the circumferential and longitudinal membrane stress, respectively. Definitions of these coordinates and stress resultants are given in the appendix. For an oversized balloon we can assume that $N_\theta = N_\phi = 0$ for the balloon.

The boundary condition for stress in intestine is $N_\theta = 0 = N_\phi$ when $z \to \infty$. The shear $N_{\theta\phi}$ is zero for axisymmetric deformation. The radius of curvature of the longitudinal section is r_1. The radius of curvature of the intestinal surface in a normal section orthogonal to the longitudinal direction is r_2. Fig. 1 shows the following geometric relationships:

$$r = r_2 \sin\phi, \qquad ds = r_1 d\phi \tag{1}$$

$$dz = r_1 \sin\phi d\phi, \qquad dr = r_1 \cos\phi d\phi \tag{2}$$

The equations of equilibrium are

$$\frac{N_\phi}{r_1} + \frac{N_\theta}{r_2} = p, \tag{3}$$

$$\frac{d}{d\phi}(rN_\phi) - r_1 N_\theta \cos\phi = 0 \tag{4}$$

where p is the pressure in the balloon.

Solving Eq. 3 for N_θ and substituting the result into Eq. 4 and reducing, we obtain

$$\frac{d}{d\phi}(rN_\phi) + r_2\cos\phi N_\phi - p r_1 r_2 \cos\phi = 0 \tag{5}$$

On multiplying by sin ϕ and using Eq. 1, we obtain

$$\frac{d}{d\phi}(r_2 N_\phi \sin^2\phi) = p r_1 r_2 \cos\phi \sin\phi \tag{6}$$

Hence,

$$N_\phi = \frac{1}{r_2 \sin^2\phi}\int p r_1 r_2 \cos\phi \sin\phi \, d\phi \tag{7}$$

Using the geometric relationships in Eqs. 1 and 2, we obtain

$$N_\phi = \frac{1}{r\sin\phi}\int_{r_o}^{r} pr\,dr = \frac{p(r^2 - r_o^2)}{2r\sin\phi} \tag{8}$$

where r_o is an integration constant. Since N_ϕ tends to zero when $z \to \infty$, we see that r_o is the radius of intestine sufficiently far away from the balloon. An alternative expression for N_ϕ as a function of z is:

$$N_\phi = \frac{1}{r\sin\phi}\left[p\int_0^z r_2\cos\phi\, dz + C\right] \tag{9}$$

where C is an integration constant.

If at a large distance z = L_o, r = r_{Lo}, $\phi = \pi/2$, $N_\phi = N_\phi^{(\infty)}$, total longitudinal force = $2\pi r_\infty N_\phi^{(\infty)}$ = T, then

$$T = 2\pi\left[p\int_0^{L_o} r_2\cos\phi\, dz + C\right] \tag{10}$$

Of special interest is the case in which T = 0, i.e. the longitudinal tension in the intact intestine is zero. Then

$$C = -p\int_0^{L_o} r_2\cos\phi\, dz \tag{11}$$

With this C, we can then compute the value of $N_\phi^{(0)}$. This gives the longitudinal tensile stress resultant N_ϕ at the centre section z = 0

Using Eq. 8 or 9 in Eq. 3, we have

$$N_\theta = r_2(\rho - \frac{N_\phi}{r_1}) \tag{12}$$

Combining with Eqs. 8 or 9 we obtain

$$N_\theta = r_2 \text{ p } (1 - \frac{r^2 - r_o^2}{2rr_1\sin\phi}) \tag{13}$$

Hence, if the radii of curvature r_1, r_2 are measured from a photograph of the intestinal profile, then the membrane stress resultants N_θ, N_ϕ can be computed everywhere in the intestine in contact with the balloon.

2.2 Experimental protocols

2.2.1 Animal preparation

Five normal LY pigs (a mixture of Danish Country breed and Yorkshire), approximately 40 kg, and three guinea pigs, 700-800 grams, were used in the study during balloon distension of the distal small intestine. The experiments were carried out in accordance with national guidelines and approval of the protocol was obtained. The pigs were fasted overnight and premedicated with 4.8 mg kg^{-1} azaperone and 0.6 mg kg^{-1} midazolam (i.m.). Etomidate (0.4 mg kg^{-1}) was administered intravenously thirty minutes later, and the pigs were intubated and ventilated on a respirator. Anaesthesia was maintained by continuous intravenous infusion of 10 mg kg^{-1} h^{-1} ketaminol, 0.6 mg kg^{-1} h^{-1} midazolam and 0.12 mg kg^{-1} h^{-1} parvulon. The calcium antagonist papaverine was given intravenously to relax the smooth muscle. Following the attainment of surgical anaesthesia, the abdomen was opened in the midline and the distal ileum was identified. The distal ileum was selected because it appears straighter than the remaining part of the small intestine. An approximately 10-cm-long segment of the distal ileum was dissected free from its mesenterium, cut proximally and distally and excised after the vessels were clamped. After flushing the lumen it was quickly placed in a small organ bath with calcium-free Krebs solution containing 6% dextran and 2 mM EGTA in order to relax the smooth muscles. No contractile activity was observed in the intestinal segment *in vitro*. The solution was aerated with a gas mixture of 95% O_2-5% CO_2 at pH 7.4. Any remaining mesenterium was carefully removed and the surface cleaned. The guinea pigs were anaesthetised with ketamine (25 mg kg^{-1} im) and xylazine (0.25 mg

kg^{-1} im). The guinea pigs' intestine was prepared using a similar protocol.

2.2.2 Balloon distension experiments

For the pig studies a 15F probe containing a six-cm-long non-compliant 25-micrometer-thick polyurethane balloon was used. For the guinea pig studies an 8F probe containing a two-cm-long balloon of the same material was used. The maximum diameters of the balloons were 5 and 2 cm without stretching the balloon. Hence, the balloons were large compared to the degree of distension obtained in these studies. The tube was inserted in the small intestinal segment and the balloon could be inflated by fluid to various pressures by varying the height of a level container. Before running the actual tests, the segments were preconditioned by loading and unloading the segment in the selected pressure range (see below) until the stress-strain relation became reproducible. The pressure steps in this study ranged from 0 to 15 cmH_2O in the pigs and from 0 to 10 cmH_2O in the guinea pigs, i.e. the transmural pressure difference was controlled. When a balloon is distended in the intestinal lumen, its geometry is shown in Fig. 1. The radius was determined optically by using a CCD camera and a frame grabber.

2.3 Data analysis

The photographs were analysed using image analysis software (Sigmascan Pro 4.0, Jandel Scientific, Germany). The data needed for the analysis were obtained from the digitised images during the balloon distension tests. One quadrant of each intestinal sample was measured due to the axi-symmetry during balloon distension. From the images of the intestinal specimens we measured the radii along the z-axis. A cubic polynomial was fitted to the measured radii using a least square fit. Good agreement was demonstrated between the measured and computed radii with a correlation coefficient of 0.98-0.99. The circumferential and longitudinal membrane tensions were computed in accordance with the equations outlined in the methods section. ANOVA was used for statistical analysis.

3 Results

Fig. 2 shows an intestinal segment during balloon distension with a pressure of 10 cmH_2O (1 kPa). The radii obtained at different pressure levels as function of z is shown in Fig. 3 for one of the pig experiments (top graph) and for one of the guinea pig experiments (bottom graph). For the ease of interpretation, only a limited number of the pressure levels is shown. A similar pattern was seen in all experiments. Fig. 4 shows N_ϕ, N_θ and T_L as function of z at the same pressure levels as shown for the pig experiment in Fig. 3 (the tension T_L was computed according to Laplace's law, T_L = p r for comparison with N_θ). N_ϕ increased with the pressure, was highest at the mid-balloon location and fell towards the end of the balloon. N_θ increased with the pressure applied and was in general 2-3 times higher than N_ϕ, At the highest pressure applied in the pigs, the maximum N_θ was located 22% (12-31%) away from the middle of the balloon (the middle and end of balloon defined as 0 and 100%, respectively). The location of the maximum was independent of the pressure (ANOVA, $p<0.5$) and was similar using the smaller balloon in the guinea pigs. N_θ at the location of maximum was approximately 230 cmH_2O mm (0.023 kPa m) in the pigs and it remained rather high towards the end of balloon where it decreased rapidly. The values in guinea pigs were correspondingly smaller due to the smaller radii at comparable pressures. N_θ at the middle balloon was 86% (71-95%) of the maximum N_θ.

T_L exceeded N_θ from 0 to about 70% away from the middle of the balloon. Only at the location of maximum N_θ was N_θ and T_L similar. At about 80% away from the middle of the balloon N_θ became higher than T_L. Fig. 5 shows the comparison of N_θ and T_L from one pig experiment at a pressure 15 cmH_2O. The same pattern was found at lower pressures and using the smaller balloon in

Figure 2 : A photograph of an intestinal segment during balloon distension with a pressure of 10 cmH_2O. z is in the direction of the longitudinal axis of the segment (approximately horizontal in this image). The radii normal to the z-axis were measured from the images and used for the computation of tensions.

guinea pigs.

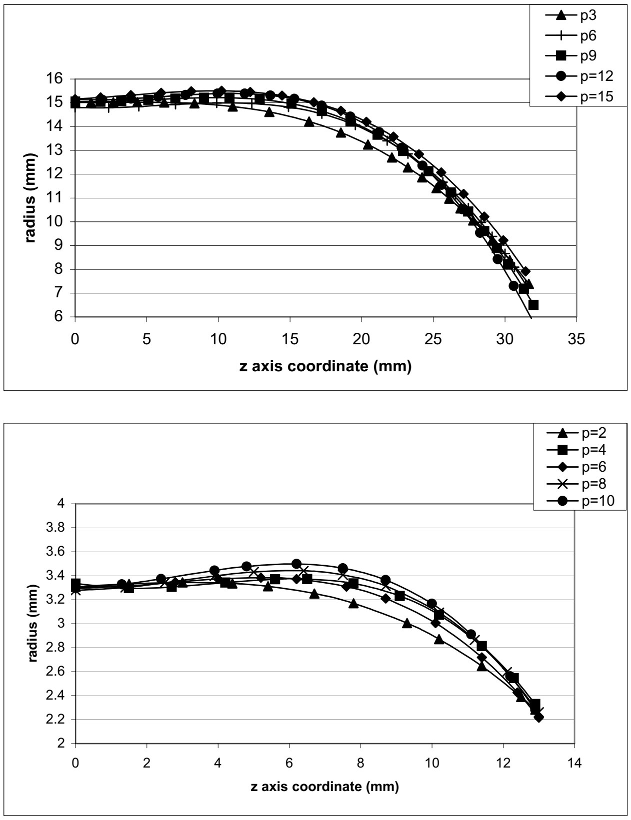

Figure 3 : Representation of radii obtained at pressure levels up to 15 cmH_2O as function of z for one of the pig experiments (top graph) and for one of the guinea pig experiments (bottom graph). For the ease of interpretation only a limited number of the pressure levels is shown.

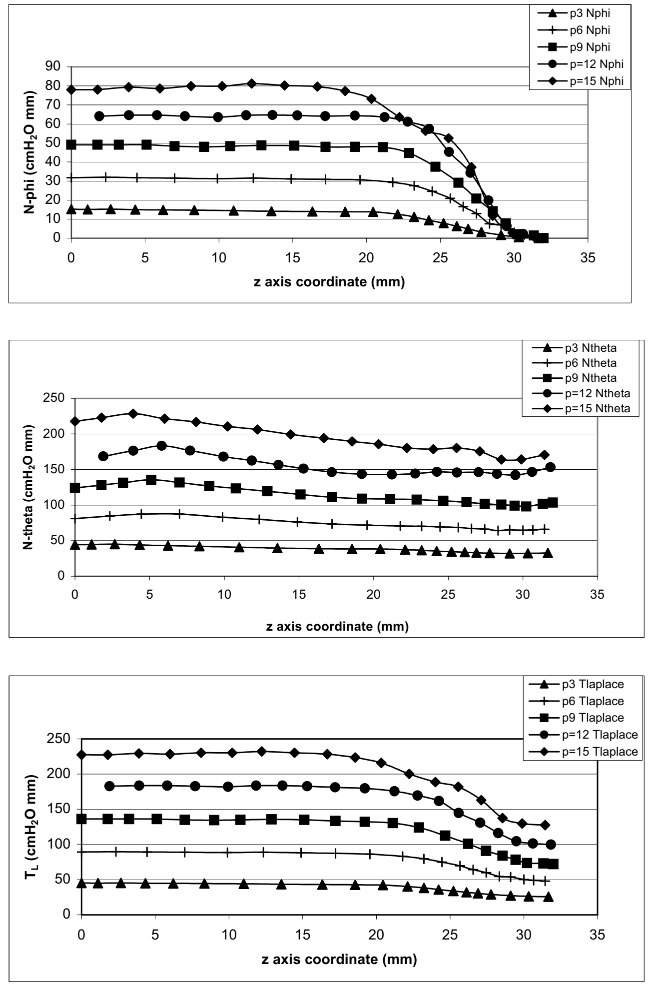

Figure 4 : N_ϕ, N_θ and T_L as function of z at the same pressure levels as shown for the pig experiment in figure 3. N_ϕ and T_L are seen to resemble the shape of the radii shown in figure 3 whereas N_θ has a local maximum 20-30% away from the middle of the balloon.

4 Discussion

Assessment of tension in visceral organs has attracted more and more interest. This is especially true in gastroenterology. The function of the gastrointestinal tract is to a large degree mechanical and mechanical data are significant in the study of tone, peristaltic reflexes, mechanoreceptor kinematics, and fluid transport. The wall of the gastrointestinal tract is stretched passively in the vicinity of a bolus (Ehrlein, Schemann, Siegle.,1987), indicating that the elastic properties of the small intestine determine the capacitance and thereby the resistance to flow. Furthermore, mechanical stimulation is needed for the determination of the interaction between stimulus, electrical responses in neurons and the mechanical behaviour of the gut. Investigation of biomechanical properties is also important from a clinical perspective because several diseases are associated with growth and mechanical remodeling of the GI tract. For example, prestenotic dilatation, increased collagen synthesis, dysmotility, and altered distensibility are common features of obstructive diseases in the gastrointestinal tract (Tung, Schulze-delrieu, Shirazi, Noel, Xia, Cue., 1991; Ravinder, Ren, McCallum, Shaffer, Sluss., 1990; Gabella 1975). Currently, compliance derived from pressure-volume or pressure-cross-

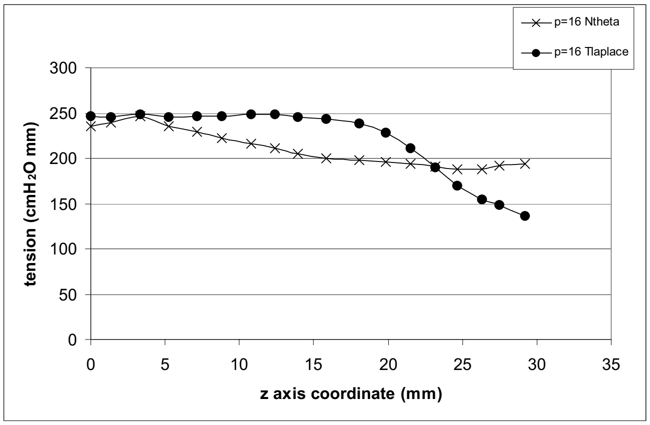

Figure 5 : Comparison of T_L and N_ϕ in a representative pig experiment at pressure 15 cmH_2O. Only at the location of maximum N_θ were N_θ and T_L similar. At about 80% away from the middle of the balloon N_θ became higher than T. The same pattern was found at lower pressures and using the smaller balloon in guinea pigs.

sectional area relations and tone are by far the most commonly used measures of gastrointestinal distensibility (Rouillon, Azpiroz, Malagelada., 1991; Madoff, Orrom, Rothenberger, Goldberg.,1990, Schulze-Delrieu, 1991). However, the mechanical properties of the small intestine remain poorly understood and great variations in physiological responses to balloon distension have been found between studies using different distension techniques. It is important to express the tissue forces in terms of tensions and stresses. The rationale behind this study is to provide a method for determination of tensions in the distended area on basis of knowing the shape of the distended region.

The main purpose of this paper is to provide a method to determine tensions during balloon distension provided that the shape of the distended area is known. The longitudinal tension (N_ϕ) and T_L behaved much as expected with maximum values at the middle of the balloon. However, N_θ had its maximum app 25% away from the middle of the balloon. This was true for most pressures and both for small and large animals (guinea pigs and pigs). The reason why the intestine conforms to this shape during distension lacks an explanation but energy considerations may be important. The analysis implicates that tension computed directly from Laplace's law does not provide very accurate measures of circumferential tension.

The basic equations for the two-dimensional tension analysis are provided and the functionality of the analysis is illustrated on intestinal samples *in vitro*. The *in vitro* setup was chosen because it allowed clear video imaging of the segments during distension, facilitating the measurement of radii along the z-axis. In the analysis it is assumed that friction between the balloon and the intestinal wall is negligible at steady state pressures. Considering the wet environment and the morphology of the mucosa, this assumption seems very reasonable. The balloon-probe system was identical to that used in previous *in vivo* studies where it was found that the influence of the balloon itself were negligible (Villadsen, Petersen, Vinter-jensen, Juhl, Gregersen., 1995; Storkholm, Villadsen, Jensen, Gregersen., 1995). It is important to ensure that the applied pressure is properly transmitted to the tissue by using a sufficiently large balloon. However, balloon-intestine coupling is never completely attained in volume measurements in the intestines, and the balloon may elongate while distending the intestinal wall. This phenomenon is in fact what often lead to overestimation of compliance in pressure-volume measurements. It should be emphasised that close to the ends there may be a slip between the balloon and the intestinal wall, i.e. the tension in that region should be interpreted with caution. In the current study radii are measured on the exterior surface of the intestine. For a fairly thin-walled organ there is not much difference between the internal and external radii but for a thick-walled organ, this may be a matter of issue. We regard the intestine as a thin-walled organ during distension (thickness-to radius ratio $<<$ 10%). The theory presented can be applied to the *in vivo* situation as long as the shape and the pressure can be obtained. Balloon distension with pressure-volume measurement cannot provide such data. However, there are several other ways to obtain the data *in vivo*. Impedance planimetry can provide measures of the balloon cross-sectional area at various locations on the z-axis (Scheel *et al*. Yet unpublished data) and assuming circularity the internal radii can be computed (Gregersen, Jørgensen, Dall, 1992). X-ray is another way to provide the geometric data (see for example Fig. 2 in Villadsen, Petersen, Vinter-Jensen, Juhl, Gregersen, 1995). New imaging techniques, however, call for attention. B-mode ultrasound or 3D-ultrasound, multi-slice CT-scanning and NMR scanning can all provide a threedimensional profile of the distended area. Another advantage with these techniques is that the wall thickness can be measured, i.e. the stress rather than tension can be computed in the two directions. For the ultimate *in vivo* application, aspects such as determination of the transmural pressure difference (solutions are presented in Gregersen and Kassab, 1996), the resolution and sensitivity of the method used, tethering between organs, etc., needs to be evaluated and errors to be estimated.

In this study the active muscle tension was relaxed by using calcium-free solution containing EGTA to chelate intracellular calcium stores under otherwise physiological experimental conditions. We believe that passive conditions were obtained because no contractile activity was observed during the studies. However, due to the in vivo application of this method it is of interest to discuss the method of handling the muscles and their tension in more detail since active contraction of muscles is the most important feature of the peristaltic movement of the intestine. The "three element model" of Nobel Laureate A.V. Hill (1970) was developed for this purpose. The model considers the tissue as a composite of a "contractile element" connected with a "series elastic element" to describe the active contraction of the muscle, and a "parallel element" to describe the connective tissue. This model has been applied extensively to the mechanics of the heart, lung, and blood vessels. The present article deals with the parallel elements exclusively. Applying the model to the physiology of the gastrointestinal tract, we consider the mucosa, submucosa and the quiescent muscles as "parallel elements" whereas the contractile and series elastic elements belong to the active muscles. Continuum mechanics connects the elements together. The effect of the balloon distension on physiological responses may not be obvious until the full Hill's model is analysed. However, it is clear that the tensions determined in this study are a fundamental feature of the parallel element. The function of the contractile element depends on the parallel element, e.g. the length of the muscle cell depends on the strain of the parallel element.

The method presented will be useful for studying the mechanical properties of the tissue. Our goal is to measure the stress-strain relationship. Elastic moduli in the two directions can be computed if the strains are also measured. We are currently implementing the strain analysis. Assuming the intestinal constitutive equation is similar to that of other soft tissues, then we shall use the method outlined in Fung and Liu (1995) to derive the full non-linear constitutive equation. Previous studies have shown a great variation in physiological responses to balloon distension. The disadvantages of the compliance parameter (dv/dp) and differences in length of the balloons used can explain some of the variation. We suggest, on the basis of the data in this study, that the full range of tensions or stresses along the length of the balloon is implemented in any analysis of physiological responses to balloon distension. For example in experiments where balloon distension is used to stimulate afferent nerve activity or pain, the variation in the measured response can possibly be reduced by considering the length of the distended segment and knowing the tensions, stresses or strains over the full balloon range.

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Appendix

Definitions of the curvilinear coordinates and membranes stresses used in this article

To analyse the tension in the intestine as the balloon is inflated, we have to describe the geometry and define the notions of the stresses. Fig. 1 shows a sketch of the intestine and balloon. Two systems of coordinates are convenient. (1) the 3-dimensional cylindrical polar coordinates (r, θ, z). (2) the two-dimensional latitude-longitude coordinates (ϕ, θ) on the surface of the intestine, similar to the one we use for our globe in geography. The latitudinal angle ϕ is defined as the angle between the normal vector to the intestinal surface and the axis of symmetry z. The longitudinal angle θ is the angle of rotation of the meridianal cross-section about the z axis. Now there exists a normal vector at any point P on the surface with coordinate ϕ and θ. At a point neighbouring to P, with coordinates (ϕ+dϕ and θ) there is another normal vector. These two normal vectors will intersect at a distance r_1 from the surface. This r_1 is *a principal radius of curvature of the surface* in the longitudinal cross-section. On the other hand, the normals at (ϕ, θ) and (ϕ+dθ and θ) will intersect at a distance r_2 from the surface. r_2 is also a principal radius of curvature of the surface. It can be shown that the radius of curvature of the curve of intersection of any other normal plane at P lies between r_1 and r_2. So the curvature of the intestinal surface is defined by r_1 and r_2.

The stresses of interest in an axi-symmetric tube subjected to axi-symmetric load are those lying in the wall, acting on normal cross-sections of the wall. In Fig. 1, a rectangular element with sides dϕ and dθ is shown, similar to a sphere on our globe with a small latitudinal and longitudinal difference. The stresses $\sigma_{\phi\phi}$ and $\sigma_{\theta\theta}$ can be much larger than the pressure in the balloon, p. When the shear stress between the balloon and intestine is ignored, and the bending stresses are ignored because the intestinal wall thickness is small compared with the radii of curvature, then $\sigma_{\phi\phi}$ and $\sigma_{\theta\theta}$ are uniformly distributed throughout the intestinal wall. Multiply the uniform stresses $\sigma_{\phi\phi}$ and $\sigma_{\theta\theta}$ by the wall thickness, h, we obtain

$$N_\phi = \sigma_{\phi\phi}\, h, \qquad N_\phi = \sigma_{\theta\theta}\, h$$

which are called *membrane tensions* in cross-sections whose normal vectors lie in the direction of ϕ and θ axes, respectively. The units of N_ϕ, N_ϕ are force per unit length, N/m, like those of surface tension, while the stresses have units N/m^2. Some authors call N_ϕ, N_ϕ *stress resultants* or *membrane stress resultants* to recognise the fact that they are the integrals of stresses throughout the thickness of the membrane wall. In this paper, it is shown that if we know the pressure in the loose balloon and measure the shape of the intestine, then we can compute the membrane tension in the intestinal wall.