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A Model to Study the Effect on Gallbladder Stress Due to Contraction and Gallstones

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Abstract—**We introduce a mechanical model to study the correlation between geometric changes in the gallbladder and stress, particularly the impact of changes in the wall thickness, gallbladder contraction and the presence of gallstones. Collecting data on these variables could potentially support the management of diseases. For example drug delivery methods such as the introduction of nanoparticles or cells into the wall of the gallbladder for direct drainage into the portal vein and liver. In addition, data regarding these variables could potentially aid the development of a predictive model for cholecystitis. We show that neither the wall thickness nor changes in the gallbladder geometry during contraction raise the stress in the gallbladder significantly. However, there is a direct relationship between the amount of gallstones and the stress.**

I. Introduction

The gallbladder is a small organ in all vertebrates that helps in the digestion of fat and concentrates the bile produced by the liver. It is divided into four anatomic areas: fundus, corpus (body), infundibulum and neck. The fundus contains most of the smooth muscles of the gallbladder, in contrast to the body, which is the main storage area and contains most of the elastic tissue [9].

Gallstones are a prominent cause of gallbladder disease, most commonly cholecystitis [1]. Studies have shown that resistance to bile flow and bile stasis may play an important role in gallstone formation [5,8] as well as gallbladder pain. The current treatment method is removal of the gallbladder, usually performed only after symptoms are presented. Yet, the vast majority of gallstones are asymptomatic [2], and there has been scant research performed to predict whether gallstones will eventually become symptomatic in the future. Gallstones may eventually cause biliary pain and discomfort, and the ability to predict whether this change will occur could greatly decrease the incidence of emergency intervention, minimize hospital costs and improve clinical outcomes.

The gallbladder wall drains through the cystic veins into the portal vein and then into the liver. It is conceivable that this could prove to be a viable site for encapsulated islet cells and other nano- or microparticles [7] enclosed in a reservoir, noting that gallstones are usually asymptomatic[2] and the reservoir may be asymptomatic as well.

Previous models of the gallbladder have focused on pain, especially on acalculous biliary pain. Li's model [3,4] looks at the correlation between pain and stress on the gallbladder during cholecystokinin (CCK) test-induced contraction. Li's model assumes that the geometry of the gallbladder is unchanging. Although the extended three-dimensional model with patient-specific numerical methods accounts for stress due to the gallbladder's variable geometry, the model does not address the change of shape due to muscular contraction.

It has been shown that the gallbladder changes shape during contraction [10-12]; therefore, the calculation of stress in the gallbladder during contraction assumes a different geometrical configuration than the constant ellipsoid presented by previous researchers. The constant ellipsoid simplifies the estimation of stress, and it is predicted that the peak total stress in the gallbladder wall will have a strong correlation with pain, as has been shown by numerous researchers [3,4,13]. The gallbladder wall thickness is shown to vary in disease [6], and in this paper we explore a range of values of this factor to understand variations in the stress.

The role of this paper is to introduce a mathematical correlation between the geometrical changes in the gallbladder and stress, particularly in the presence of stones or space-occupying lesions such as encapsulated cells. Previous models have addressed the relationship between gallbladder geometry and stress [3,4]. They have also studied the dependence of flow rate of bile through the cystic duct on shape [8]. However, no model exists that examines the dependence on stress of multiple variables, including the contractions, wall thickness and gallstones.

II. Methods and Materials

In this manuscript a previously published mechanical model [4] is adapted and evaluated to incorporate new situations. Variations in wall thickness, the gallbladder geometry, and the presence of gallstones have been assessed in the form of a modified mathematical model. The basic physiological assumptions and the sources of data used in numerical experiments are described.

Basic Assumptions

A. Properties of the gallbladder

Prior to contraction, the gallbladder is assumed to be a thin-walled, tri-axis, ellipsoid subject to anisotropic

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contraction, with a region of compressible smooth muscle and a region of expandable tissue. The wall compliance is kept constant in this model, whereas changes are made in the thickness of the wall. During contraction, the gallbladder's shape also changes, and thus contraction necessitates modifications to the previously published model [4].

B. Muscle contraction

The gallbladder is comprised of smooth muscle, which contracts in a way similar to the smooth muscle of the bladder. However, since active contraction only involves the dome of the gallbladder (i.e., the upper third, as the lower two thirds passively distend), we assume that translation of contractions to the gallbladder will mean that equation (4) will be applied to the two parts separately, with different geometric dimensions.

Mathematical Model

C. Gallbladder geometry

If the gallbladder is assumed to be a perfect ellipsoid under static conditions, the following equation describes its shape during the moment before contraction in Cartesian coordinates

$$\frac{x^2}{D_1^2}+\frac{y^2}{D_2^2}+\frac{z^2}{D_3^2}=\frac{1}{4}, \quad (1)$$

In polar coordinates, the same ellipsoid can be described as

$$x=\frac{D_1}{2}\cos\emptyset\cos\,\theta,\; y=\frac{D_2}{2}\cos\emptyset\sin\,\theta,\; z=\frac{D_3}{2}\sin\emptyset \quad (2)$$

where D_is are the diameters of the ellipsoid along the *x, y* and z directions respectively and the angles are in the range: $-\pi/2\le\emptyset\le\pi/2$ and $-\pi\le\Theta\le\pi$. This is shown in Fig. 1a

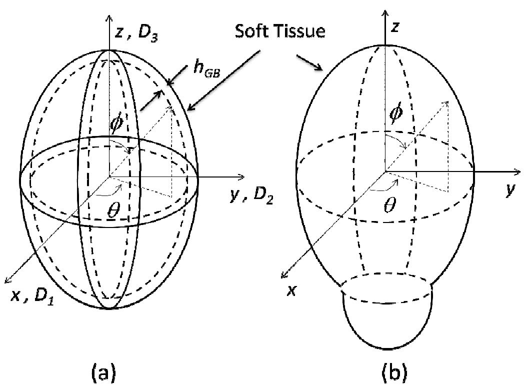

Figure 1: (a) Gallbladder just prior to, and (b) after contraction [2].

D. Stress in the gallbladder

The stresses in a thin shelled ellipsoid under uniform internal pressure load p_e are given by [4]:

$$\sigma_\theta^p=p_eF_\theta(h_{GB},D_3,k_1,k_2,\emptyset,t)\times F_n(k_1,k_2,\theta,\emptyset,t),$$

$$\sigma_\emptyset^p=p_eF_\emptyset(h_{GB},D_3,k_1,k_2,\theta,\emptyset,t)\times\frac{1}{F_n(k_1,k_2,\theta,\emptyset,t)},$$

$$\tau_{\theta\emptyset}^p=p_eF_\tau(h_{GB},D_3,k_1,k_2,\theta,\emptyset,t). \quad (3)$$

Where

$$F_\theta(h_{GB},D_3,k_1,k_2,\emptyset,t)=\frac{D_3k_1k_2}{4h_{GB}}\left(1-\frac{k_1^2-k_2^2}{k_1^2k_2^2}\cos 2\emptyset\right),$$

$$F_\emptyset(h_{GB},D_3,k_1,k_2,\theta,\emptyset,t)=\frac{D_3}{4k_1k_2h_{GB}}[k_1^2k_2^2+(k_1^2+k_2^2-2k_1^2k_2^2)\sin^2\theta+(k_1^2-k_2^2)\cos^2\theta\cos 2\emptyset],$$

$$F_\tau(h_{GB},D_3,k_1,k_2,\theta,\emptyset,t)=\frac{D_3}{4k_1k_2h_{GB}}(k_1^2-k_2^2)\cos\theta\sin 2\emptyset,$$

$$F_n(k_1,k_2,\theta,\emptyset,t)=\frac{\sqrt{k_1^2\cos^2\theta\cos^2\emptyset+k_2^2\cos^2\theta\sin^2\emptyset+\sin^2\theta}}{\sqrt{k_1^2\sin^2\emptyset+k_2^2\cos^2\emptyset}}. \quad (4)$$

In the above equations, p_e is the pressure in the gallbladder at the end of emptying. D_1, D_2 and D_3 are the diameters along the first, second and third axis in mm, and $k_1 = D_1/D_3$ and $k_2 = D_2/D_3$. For the purpose of this paper, we are interested in finding the maximum value of the stress given by: $\sigma_{max}=\max\,[\sigma_\theta,\sigma_\emptyset]$,

E. Variation in gallbladder dimensions D_1, D_2 and D_3

As can be seen from (4), D_1, D_2 and D_3, do not appear on an equal footing in the stress equations, and hence there is an inherent asymmetry in the stress. That means if we scale the three dimensions of the ellipsoid as

$$D_1\to s_1D_1,\; D_2\to s_2D_2,\; D_3\to s_3D_3,$$

the transformation will give us a completely different distribution of stress, as will be shown later in the "Results" section.

F. Gallbladder geometry during contraction

Once the gallbladder begins contraction, the shape transforms into that illustrated in Fig. 1b. This shape can be approximated as a combination of two ellipsoids with centers displaced along the z-axis. The boundary between these two ellipsoids is generally elliptical. We use (4) under the assumption that the boundary effects can be ignored. This is motivated by [4], where authors have shown that the maximum difference between a complete model and a cut-off (part of the gallbladder is flat) model done via the Finite Element Method (FEM), is approximately 2.4 percent. Also, they point out that the peak stresses computed from the ellipsoidal model are not very sensitive to small geometric deviations from a perfect ellipsoid. Hence, for this proof of concept study, we assume that the ellipsoidal model can be applied to the two parts separately.

The three-dimensional model performed by Li [4] accounted for the flattened top of the gallbladder due to its position next to the liver, but it did not consider the changing shape of the gallbladder during contraction. Using the contracted gallbladder model presented in Fig. 1b and using the same stress equations for both parts, estimation of the various variables can be considered.

G. Gallstones

Evaluating the effect of gallstones in the gallbladder requires certain assumptions. The ellipsoidal model is still valid but the total pressure inside the gallbladder now includes a factor coming from gallstones:

$$p_{corrected}=p_e+\frac{\rho gV}{133.32\,A} \quad (6)$$

where ρ = density of gallstones in Kg/m^3, g = 9.8 m/s^2, V = volume of gallstones in m^3, and A = surface area on which these stones are applying pressure, in m^2. The factor of 133.32 is needed to convert pressure units from Pascal to *mmHg*.

H. Clinical data

To make sensible estimates of the stress, the dimensions of the gallbladders of real patients/volunteers are needed. The geometrical data for the gallbladder have been collected in [4] for 51 patients, and we use it to estimate stress. Characteristics of this data set are shown in Table 1:

TABLE 1: Characteristics of gallbladder geometry data taken from [4].

	Mean (mm)	SD (mm)	Min (mm)	Max (mm)
D_1	23.6	5.1	14.4	37.8
D_2	29.5	4.6	17.2	37.8
D_3	67.0	9.7	45.8	92.3

Additionally, we use the following data for our numerical studies: h_{GB} = 2.5 mm [6], and p_e = 11 mmHg (gallbladder internal pressure while emptying) [4,8,19]. To estimate the density of gallstones, we use the published data for their masses and sizes [16,17] to get a range of density values from 1000 to 4000 Kg/m^3.

III. Results

In this section, we study the impact on gallbladder stress coming from changes in different variables. The distribution of passive stress, with h_{GB} = 2.5, using (4) (see also Ref [4]) is given in Table 2.

TABLE 2: Stress range in the data set taken from [4].

Stress in mmHg	**Number of subjects**
Stress ≤ 100	24
100 < Stress ≤ 125	5
125 < Stress ≤ 150	4
150 < Stress ≤ 175	9
Stress > 175	9

A. Variation in stress due to variations in h_{GB}

The gallbladder wall thickness h_{GB} is varied from 1.250mm to 3.750mm in steps of 0.625mm, or ±50% around the middle value of 2.5mm. We assume the shape remains as shown in Fig. 1a. The combined results for all 51 patients are shown in Table 3.

TABLE 3: Variation of stress with wall thickness

h_{GB} (mm)	Average stress (mmHg)	SD (mmHg)	Min (mmHg)	Max (mmHg)
1.250	220.0	105.8	102.6	562.9
1.875	146.6	70.6	68.4	375.3
2.500	110.0	52.9	51.3	281.5
3.125	88.0	42.3	41.0	225.2
3.750	73.3	35.3	34.2	187.6

As can be seen, the peak stress (averaged over all patients) decreases with increasing wall thickness. The table shows that by doubling the wall thickness from 1.250 to 2.500 mm, the stress reduces to half its original value (110.0mmHg from 220.0mmHg). Hence, the stress goes on decreasing if we increase the wall thickness. On the other hand, the stress increases with decreasing wall thickness and quickly crosses the pain threshold of 175mmHg when h_{GB} is 50% less, or just 1.250 mm.

B. Variation in stress due to variations in the dimensions

For the model shown in Fig. 1b, we assume that wall thickness of the one-third contracted part varies as before, whereas the un-contracted part maintains a wall thickness of 2.5 mm. For the lower (contracted) part, we assume that the dimensions reduce by 50% along the two minor axes and by 20% along the major axis. For the un-contracted part, which retains the original size, the stress values also remain the same, as in Table 3. For the contracted part, stress reduces from 40.2mmHg with a 1.250mm thick wall to 13.4mmHg with a 3.750 mm wall. Details are shown in Table 4.

TABLE 4: Variation in maximum stress for the contracted ellipsoid.

h_{GB} mm	Average stress (mmHg)	SD (mmHg)	Min (mmHg)	Max (mmHg)
1.250	40.2	6.8	26.1	58.4
1.875	26.8	4.5	17.4	39.0
2.500	20.1	3.4	13.1	29.2
3.125	16.1	2.7	10.5	23.4
3.750	13.4	2.3	8.7	19.5

C. Variation in stress due to gallstones

In order to use (6), the volume of the gallstones and surface area on which they are applying pressure is needed, as well as the gallstone density. However, the amount of gallstones in the gallbladder is a patient-dependent quantity. To study a broad range, calculations were made by filling the gallbladder to 33% (one third of the gallbladder contained stones) and 66% (two thirds of the gallbladder contained stones). The assumption was made that the wall thickness remained the same throughout the gallbladder; therefore, the un-contracted model of Fig. 1a was used. To calculate the maximum pressure change, the minimum cross-sectional surface area was needed; that was obtained from the dimension of the two smaller axes of the ellipsoid (i.e., $\pi D_1 D_2$). Finally, we vary the density of gallstones in the range mentioned in section H to incorporate the effect of gallstones of varying density. The statistical measures of stress values are tabulated in Table 5.

TABLE 5: Stress calculated for all patients including the effect of gallstones. The population minimum and maximum are also shown.

Quantity of Gallstones	Density of Gallstones (Kg/m^3)	Average Stress (mmHg)	SD (mmHg)	Min (mmHg)	Max (mmHg)
1/3rd	1000	113.5	54.9	52.6	293.2
	2000	117.1	56.8	54.0	304.9
	3000	120.6	58.8	55.3	316.6
	4000	124.1	60.7	56.6	328.3
2/3rd	1000	117.1	56.8	54.0	304.9
	2000	124.1	60.7	56.6	328.3
	3000	131.2	64.7	59.3	351.6
	4000	138.3	68.6	62.0	375.0

To elaborate on the amount of changes in stress, we take the 3000 Kg/m^3 as a sample value from Table 5 and compare results of stress with gallstones to stress without gallstones. The average value of stress increases to 120.6 mmHg for one third of the gallbladder filled with stones and 131.2 mmHg for two thirds filled with stones. Compared with the stone-free value of 110.0mmHg, that is an increase of 9.6% and 19.3%, respectively. The maximum increase corresponds to density of 5000 Kg/m^3 and becomes 16.1% and 32.2% for one-third and two-thirds gallstone fillings, respectively.

IV. Discussion and Conclusions

Creating a mathematical model of the gallbladder that can be used to evaluate the effect of various variables is important because it may aid the prediction of disease, such as symptomatic gallstone disease. It may also aid in the prediction of the effects of altering the wall thickness, for instance, by incorporating cells such as encapsulated islets into the wall [20]. The model also helps determine the effect on gallbladder contraction to ensure that the primary function (contraction) is minimally, if at all, impaired. A reservoir for islet cells, when implanted into the gallbladder, may also serve as a therapeutic site of implantation of islet cells to treat diabetes.

Symptomatic gallstone disease is among most common causes of non-injury abdominal pain in the emergency room [14], and the visits have increased by 31.8% by 2008 [15]. Emergency cholecystectomy is the second most-common type of emergency surgery (emergency room to operating room) [14]. For all these reasons, a reliable predictive model of biliary pain both with and without calculous disease would potentially have the effect of reducing emergency surgeries, reducing the workload of physicians (reducing sleep deprivation), reducing hospital costs and improving patient outcomes.

Physiologically, gallbladder tone is regulated by spontaneous muscle activity, hormones and neurotransmitters released into the muscle from intrinsic neurons and extrinsic sympathetic nerves. Methods to explore gallbladder smooth muscle function *in vitro* include CCK receptor-binding studies and contractility studies. The interplay between contraction and relaxation of the gallbladder muscularis leads to appropriate gallbladder emptying and refilling during fasting and postprandially [10]. Therefore, for the model proposed in this paper, we assumed that the actions of the fundus and the corpus differed, with the fundus mainly contracting, while the corpus is the main site of distention. Previous models have attained an accuracy rate of up to 75% at predicting pain [4]; however, these models assumed an unchanging shape, whereas the proposed model does not, by varying the wall thickness and the contraction of a part of the gallbladder by using a double ellipsoid.

Our results show that both the variables (i.e., the increase in the wall thickness and the decrease in the dimensions of the ellipsoid due to contraction) work in favor of reduced stress. Previous studies have shown that stress is correlated with the pain as reported by patients and have documented a success rate of about 76% [4] for CCK-induced pain. We note that in the presence of gallstones the pressure, and hence the passive stress, increases. That in turn makes it possible for stress to cross the threshold of 175mmHg. As shown in Table 2, 9 out of 51, or 18%, of subjects have a starting stress that is already above the threshold. A 30% increase in the stress will push another 9 subjects to above pain threshold values. Future work will involve creating a three-dimensional model that tracks the gradual transformation of the changing pressure within the gallbladder during contraction.

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