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A model of gallbladder motility

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ABSTRACT

Impaired gallbladder motility leads to some clinical manifestations associated with its muscle contraction and/or the rate of filling with bile. To gain a better understanding of the possible reasons for different filling/emptying patterns we developed a mathematical model of the gallbladder that takes into account the kinetics of its filling and emptying and changes in the concentration of the accumulated bile. The model is based on four parameters responsible for the maximum speed of bile evacuation (M_g), pulsation of contractions (ω), the kinetic filling rate (k_g) and the maximum bile mass accumulated in the gallbladder (m_{total}). The model results were fitted to different clinical results describing gallbladder motility depending on the meal composition, patient's age and health condition (obesity and gallstones). Compatibility of the model results with the experimental data allows us to draw physiological conclusions. We found that different gallbladder emptying patterns may result from differences in the amplitude of contraction of gallbladder muscles (e.g. for various meal composition), differences in the rate of bile inflow (e.g. for obese patients during filling), and differences in gallbladder muscle pulsations (e.g. for lean patients during early gallbladder emptying). The model of gallbladder motility can facilitate identification of causes of disorders, help to explore complicated physiological pathways, and can be applied in etiology analysis or studies of observable clinical indicators.

1. Introduction

Despite the fact that the gallbladder is not essential for life, it is one of the most important elements in bile enterohepatic circulation. The gallbladder is responsible not only for proper bile evacuation, but also for its storage, concentration and composition. Disturbances in gallbladder functioning lead to bile circulation disorders, which strongly influence lipid balance in the organism and can lead to many diseases [1]. Consequently, gallbladder disorders, such as gallstone formation, have a strong effect on health condition [2–4]. For instance, cholecystectomy increases the risk of colorectal cancer, due to increased concentration of the secondary bile acids, indicating the importance of the gallbladder [3,5,6]. The solution of the previously developed two-compartment ordinary differential equation (ODE) model of cholesterol homeostasis [7–9] indicated a significant effect of cholesterol circulating with bile. The results show that the gallbladder must be included in the model as an important element of enterohepatic circulation. Here, we present a mathematical model of gallbladder motility in reference to clinical data for healthy and obese subjects.

1.1. Gallbladder physiology

The liver daily secretes from 600 to 1000 ml of liver bile [10]. It flows distally into the common bile duct. Approximately 75% of the liver bile enters the gallbladder. The remaining part flows directly into the duodenum. Liver bile consists mainly of water (about 97.5%) and bile salts (about 1.1%). During enterohepatic circulation, the composition of bile changes. In the gallbladder, processes associated with liver bile concentration change the proportions of bile components. The composition of liver and gallbladder bile is shown in Table 1.

After a meal, the gallbladder releases up to 75% of its content [11]. Emptying occurs in the form of multi-stage gallbladder wall muscle contractions and is accompanied by simultaneous refilling, which follows from its volume fluctuations [12,13]. Gallbladder filling is a continuous

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Table 1
Liver and gallbladder bile main components [10].

component	bile [g/dl]	
	liver	gallbladder
water	97.50	92.00[a]
bile salts	1.10	6.00
bilirubin	0.04	0.30
cholesterol	0.10	0.30–0.90
fatty acids	0.12	0.30–1.20
lecithin	0.04	0.30
others	1.10	0.80

[a] Other source: 82% water, 18% dry components [32].

process, due to the enterohepatic circulation [14]. During the fasting state, the gallbladder is not a passive bile pool – it is partially emptied and refilled (with about 10% of its volume) [3]. However, after a meal, due to evacuation of larger amounts of bile, gallbladder refilling increases. In the first 40 min after a meal, refilling is slow, but it increases afterwards [14]. Both emptying and refilling processes are performed through the same way – a cystic duct. Therefore the gallbladder refilling pattern is complementary to the emptying scheme [14].

Gallbladder contraction depends among other factors on the meal composition, due to secretion of different amounts of cholecystokinin. For instance, a fat-free meal causes less than 50% fasting volume gallbladder contraction, while in the case of a pure-fat meal this value increases to 85% [15]. Similar results were obtained by Kossena and co-workers: maximal gallbladder contraction (about 70% of the fasting volume) was obtained after ingestion of a meal containing 10–25 g of lipid. A low dose of long chain lipids and a low dose of short chain lipids give similar results (contraction from 30% to 50%) [16].

1.2. Obesity

One of the main risk factor of cholelithiasis is obesity. Obesity increases gallbladder fasting volume – up to 33.0 ± 2.0 ml (normal weight: 22.2 ± 0.7 ml) [17]. Also, the gallbladder residual volume is significantly higher than in normal-weight patients (obese: 8.0 ± 0.8 ml, normal weight: 5.8 ± 0.3 ml) [17,18]. In lean patients the gallbladder evacuates about 75% of its content after a meal [17]. In obese patients in comparison to lean patients, the evacuated bile volume is similar or smaller (depending on the obesity level) [17,19,20]. Depending on BMI, age and other individual features [12,21], parameters describing gallbladder motility for obese patients slightly differ according to the research [12,17,19,20]. In these studies, the greatest differences can be observed in fasting volume, residual volume and emptying/refilling times. Therefore, in this paper, we refer to an example gallbladder emptying pattern for obese patients [17]. Studies demonstrate that in both lean and obese patients, the gallbladder starts to refill at the same time [17]. Additionally, in both cases, gallbladder contraction occurs almost immediately after a meal, and the gallbladder empties quickly in the first 30 min [17]. Nevertheless, gallbladder emptying patterns show other significant differences between normal-weight and obese subjects. In obese patients the emptying rate is about 0.46 ml/min, while in normal-weight patients, it is only about 0.3 ml/min [17]. In lean subjects the minimal gallbladder volume is achieved in the first 15 min, and afterwards the slow refilling phase begins. In obese patients the emptying rate decreases significantly (approximately to 0.06 ml/min) in the first 75 min [17]; gallbladder volume continues to decrease with lower speed in order to achieve the minimal volume after 105 min postprandially [17]. Moreover, refilling, after attaining the minimal gallbladder volume in obese patients, is more rapid compared to lean patients [17,19].

Both the meal composition and disorders have a huge impact on gallbladder motility. All these processes and disorders associated with gallbladder functioning are essential for lipid balance. They demonstrate the undeniable role of the gallbladder in the enterohepatic cycle which we also observed during analysis of the two-compartment model. Therefore in our current work we pay special attention to modeling the gallbladder and its disorders.

1.3. Gallbladder disorders

There are numerous disorders of the gallbladder which can cause disturbances in motility. Because of the specific innervation there is a high possibility of a change in the gallbladder contraction pattern. This can induce numerous diseases associated with the gallbladder wall or lumen, which influence the rate of bile release or inflow into the gallbladder [22]. Cholecystitis is the most common type of gallbladder disease. It presents as either acute or chronic inflammation of the gallbladder mostly caused by gallstones. Gallstones may become lodged in the neck of the gallbladder or in the bile ducts. When the gallbladder is plugged in this way, bile cannot exit. This may lead to the gallbladder becoming inflamed or distended. The plugged bile ducts will further prevent bile from traveling from the liver to the intestines. Gallstones are a common risk factor for gallbladder cancer. Gallbladder cancer can spread from the inner walls of the gallbladder to the outer layers and then on to the liver, lymph nodes, and other organs.

Acalculous gallbladder disease is inflammation of the gallbladder that occurs without the presence of gallstones. Presence of a significant chronic illness or serious medical condition can be caused by numerous factors including severe physical trauma, abdominal surgery, severe burns, autoimmune conditions such as lupus, blood stream infections when receiving nutrition intravenously (IV), and significant bacterial or viral illnesses [23,24].

Another disease is biliary dyskinesia, which occurs when the gallbladder has a lower-than-normal function. This condition may be related to ongoing gallbladder inflammation. Symptoms can include upper abdominal pain after eating, nausea, bloating, and indigestion. Eating a fatty meal may trigger symptoms. There are usually no gallstones in the gallbladder with biliary dyskinesia. Ongoing inflammation and damage to the bile duct system can lead to scarring. This condition is referred to as sclerosing cholangitis. However, it is unknown what exactly causes this disease. Nearly half the people with this condition do not have any symptoms [25].

Gallbladder polyps are lesions or growths that occur within the gallbladder. They are usually benign and have no symptoms. However, it is often recommended to have the gallbladder removed for polyps larger than 1 cm. They have a greater chance of being cancerous [26].

Gangrene of the gallbladder can occur when the gallbladder develops inadequate blood flow. This is one of the most serious complications of acute cholecystitis. Factors that increase the risk of this complication include diabetes. Abscess of the gallbladder results when the gallbladder becomes inflamed with pus. Pus is the accumulation of white blood cells, dead tissue, and bacteria [26].

2. Materials and methods

In this section we describe the gallbladder motility model, which includes the kinetics of gallbladder filling/emptying and the bile concentration process. The model is based on the literature data described in detail in the *Introduction* section.

Here, it is important to note that two experimental techniques are most commonly used for examination of gallbladder motility: ultrasonography (USG) and scintigraphy. However, each method gives a different pattern of gallbladder filling. Scintigraphy allows one to study changes in time of mass of the chosen bile component, whereas USG determines gallbladder volume changes and the results depend on water resorption and gallbladder bile concentration.

2.1. Filling process

We model the process of gallbladder filling by the Verhulst equation