Gallbladder contractility and volume characteristics in gallstone dyspepsia

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AIM: It is difficult to differentiate gallstone dyspepsia and functional dyspepsia by clinical symptoms and signs. We hypothesized that gallstone dyspepsia was related to abnormal gallbladder motility. We aimed to differentiate gallstone dyspepsia from functional dyspepsia by measuring gallbladder motility.

METHODS: We measured gallbladder volume changes in response to gastric distension (saline 500 mL) and fatty meal in 10 normal volunteers (controls) and 62 patients with gallstones and dyspepsia before cholecystectomy. Forty cholecystectomized patients were symptom free or had improvement (group I), while the remaining 22 patients had persistent dyspepsia (group II). Gallbladder volume change and ejection fraction were analyzed and compared among the three groups.

RESULTS: In group I, there were significant decreases in gallbladder volumes 5-25 min after gastric distension, compared to fasting volumes. Compared to normal volunteers and group II, group I had significantly decreased gallbladder volumes 10-20 min after drinking 500 mL of normal saline and 10 to 50 min after eating fatty meal.

CONCLUSION: Our results support the hypothesis that increased gallbladder contraction after gastric distension or fatty meal may be related to dyspeptic symptoms in uncomplicated gallstone disease. These findings may be useful in differentiating functional dyspepsia from gallstone dyspepsia, patients with the latter disease may benefit from laparoscopic cholecystectomy.

INTRODUCTION

Laparoscopic cholecystectomy is the choice of treatment for symptomatic gallstone disease and is performed with increasing frequency. It is clear that gallstone patients with complications (acute cholecystitis, gallstone pancreatitis or jaundice) or severe biliary pain should undergo cholecystectomy. Conversely, for asymptomatic gallstone disease, no treatment should be done. Nonetheless, some patients with uncomplicated gallstone disease, once termed gallstone dyspepsia[1], suffer from mild abdominal symptoms, such as postprandial flatulence, bloating, nausea and belching. Most of these patients also undergo laparoscopic cholecystectomy, but about 20-30% of these cholecystectomized patients still complain of abdominal symptoms after surgery. These symptoms may be associated with preoperatively undiagnosed functional gut disease unrelated to gallstones[2-4]. In order to avoid unnecessary cholecystectomies, it is important to ascertain preoperatively that these mild symptoms of gallstone patients with dyspepsia are really caused by gallstones. New diagnostic methods to predict which patients will benefit from cholecystectomy are therefore necessary.

Gallstone dyspepsia and functional dyspepsia have coexisting symptoms and it is difficult to differentiate from each other based on the dyspeptic symptoms[5-7]. Despite numerous studies, the mechanism of gallstone dyspepsia has not been completely explained[8-10]. In the past, the majority of literature focused on the pathogenesis of gallstone formation. It is postulated that two distinct subgroups of gallstone patients can be identified with regard to gallbladder emptying, including “normal contractors” and “pathologic contractors” or “strong contractors” and “weak contractors”[11-14]. Therefore, we hypothesize that in these patients, gallstone dyspepsia may result from abnormal gallbladder motor activity stimulated by gastric distension or fatty meals. In this study, we investigated the difference in gallbladder contractility in response to gastric distension and fatty meals in healthy volunteers and patients with gallstones and dyspepsia. If so, preoperative assessment of gallbladder contractility with ultrasonography would contribute to better outcomes of cholecystectomy.

MATERIALS AND METHODS

Gallbladder volume was assessed in 72 subjects, including 10 healthy controls and 62 gallstone patients with symptoms of dyspepsia. None of the gallstone patients had past or present signs of complicated gallstone diseases, such as acute cholecystitis, biliary pancreatitis, jaundice or severe biliary pain. Panendoscopy and abdominal ultrasound were done to exclude esophagitis, peptic ulcer, pancreatitis or other organic diseases in all gallstone patients. After an overnight fast, the fasting gallbladder volume was measured ultrasonographically three times within 5 min, with the subjects lying supine or turned partially on their sides. The gallbladder volume was estimated using a real-time ultrasound system (MK-500, ATL, Bothell, WA) with a 3.5-MHz transducer. The largest longitudinal and transverse gallbladder images were recorded. The gallbladder volume was calculated using the computerized sum-of-cylinders method as described by Hopman et al[15]. Then, the gallbladder volume was again measured after the patient drank 500 mL of normal saline at room temperature within a 2-min period. Measurement was made at 5 min
intervals for the first 30 min, then at 10 min intervals between 30 to 90 min after drinking. On the next day, we serially measured gallbladder volumes after the patients ate a fatty meal (fried egg cake) containing protein 9.32 g, fat 20.3 g and carbohydrate 14.4 g, 277.58 Kcal, followed by 100 mL of water. After the measurements, the gallstone patients with dyspepsia underwent laparoscopic cholecystectomy and were monitored in the outpatient department at least for 1 yr after surgery. These patients were allocated to 2 groups according to cholecystectomy outcomes. Forty patients (group I) were symptom free or had improved symptoms after cholecystectomy. Twenty-two patients (group II) complained of persistent dyspepsia after cholecystectomy, with the same symptoms as their preoperative symptoms. Thereafter, we analyzed and compared the differences among the three patient groups (groups I, II and controls) for fasting gallbladder volume, volume changes and ejection fraction in response to gastric distension and fatty meal.

The fasting gallbladder volume was calculated as the mean of three values before meal intake. The postprandial gallbladder volume was expressed as a percentage of the fasting volume. Results are expressed as mean±SE. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software. Comparisons among the three groups were analyzed using the χ² test. Differences between means were considered significant at \( P<0.05 \).

RESULTS

Patient characteristics are shown in Table 1. The fasting gallbladder volume tended to be larger in the two groups of patients with gallstones than in healthy volunteers during either test (Table 1).

### Table 1 Characteristics of subjects (χ² test)

|               | Normal (n=10) | Group I (n=40) | Group II (n=22) | P value |
|---------------|---------------|----------------|-----------------|---------|
| Age (yr)      | 61.2±12.3     | 59.5±15.1      | 62.5±13.4       | NS      |
| Sex (M:F)     | 4:6           | 14:26          | 9:13            | NS      |
| Weight (kg)   | 60.9±5.7      | 59.8±3.8       | 57.6±9.8        | NS      |
| BMI           | 27.8±3.8      | 24.8±7.4       | 24.4±5.7        | NS      |
| Fasting       | 26.3±7.4      | 32.6±14.1      | 33.9±10.7       | <0.05   |
| gallbladder volume (mL) | | | | |

BMI, body mass index. \( P<0.05 \) was considered statistically significant.

In normal volunteers and group II gallstone patients after drinking 500 mL normal saline, the gallbladder volume did not significantly change from the basal fasting level throughout the 90-min observation period (Figure 1). In contrast, in group I patients, within 5 to 25 min after drinking 500 mL of normal saline, there was a significant decrease in the gallbladder volume from the basal fasting volume (\( P<0.05 \)) (Figure 1). The gallbladder volume change (10-20 min) in group I patients was significantly larger than that in healthy volunteers and group II patients (\( P<0.05 \)) (Figure 1).

After the fatty meal, there were significant decreases in gallbladder volume in healthy volunteers and the two groups of gallstone patients throughout the 90-min study period (Figure 2). Group I patients had larger gallbladder volume changes (\( P<0.05 \)) than the other two groups during the early phase (10-50 min) of testing, the lowest residual volume was detected at the 40th min. We also found that the gallbladder volume change was significantly smaller (\( P<0.05 \)) in group II during the early phase (10-40 min) than in healthy volunteers in response to fatty meal (Figure 2). The ejection fraction was significantly greater (\( P<0.05 \)) in group I than the other two groups 10-50 min after the fatty meal (Figure 3).
DISCUSSION

It is clear that complicated gallstone diseases, such as acute cholecystitis, obstructive jaundice, gallstone pancreatitis and severe biliary pain, are good indications for cholecystectomy. With the technical improvements in laparoscopic surgery, many patients with uncomplicated gallstone disease termed gallstone dyspepsia underwent laparoscopic cholecystectomy for only mild gastrointestinal symptoms such as postprandial flatulence, bloating or belching. However, the benefit of cholecystectomy for gallstone patients with dyspepsia has remained debatable[16]. Only about one half of patients were symptom free after cholecystectomy[17,18]. About 20-30% of cholecystectomized patients still complained of dyspepsia, which might have been associated with preoperatively undiagnosed functional gut diseases unrelated to gallstones[2-4].

Because gallstone dyspepsia and functional dyspepsia had coexisting symptoms, it is difficult to differentiate them based on dyspeptic symptoms[8]. In order to avoid unnecessary cholecystectomies, it is important to ascertain preoperatively that the symptoms of gallstone patients with dyspepsia are truly caused by gallstones.

Even with numerous studies, the mechanisms underlying gallstone dyspepsia could not be completely explained[6-10]. Some investigators believed that dyspepsia was associated with functional gut diseases such as antral duodenal reflex and irritable bowel syndrome, rather than with gallstone disease[19,20]. However, Johnson[21] suggested that an association existed between flatulent dyspepsia and gallbladder disease, although it had no direct relationship. In the past, the majority of literature focused on the pathogenesis of gallstone formation rather than on the association of gallbladder motility and clinical symptoms. Using different techniques, investigators showed decreased[20-12], normal[23] or even increased[24] gallbladder contractility compared to normal controls. Moreover, it has been postulated that two distinct subgroups of gallstone patients could be identified with regard to gallbladder emptying, including strong and weak contractors[24,25]. Perhaps the mild abdominal symptoms were related to abnormal gallbladder motility. We identified two distinct groups of patients with gallstones and dyspepsia in terms of gallbladder contractility.

In our study, patients with gallstones and dyspepsia had significantly larger fasting gallbladder volumes, which were similar to a previous report[26]. The symptoms experienced in gallstone patients were traditionally believed to arise from gallbladder spasm, and normal gallbladder contractility was thought to be a prerequisite for the development of symptoms. Heaton reported that gallstones were prone to cause symptoms in younger patients and cited the explanation that younger people perhaps had stronger gallbladder contractions[27]. We also found that group I patients had larger gallbladder volume changes and stronger gallbladder contractions during the early phase of observation in response to 500 mL of normal saline and fatty meals, although there was no significant difference in age among them. We found that in group I patients, symptoms improved after cholecystectomy, that is, patients who had stronger gallbladder contractions in response to gastric distension and fatty meal benefited from cholecystectomy. However, group II patients with impaired gallbladder contractility did not benefit from cholecystectomy because their symptoms were perhaps unrelated to gallbladder motility.

In 1979 Debas et al found that antral distension initiated a cholinergic pyloro-cholecystic reflex causing gallbladder contraction in dogs[28]. Intact vagus nerves and cholinergic pathways were required for this reflex. Vagal stimulation via mechanoreceptors in the stomach initiated gallbladder contraction independently of meal composition[29]. Yamamura et al found that gastric distension following ingestion of 400 mL of water induced a maximum gallbladder evacuation of 25%, compared with a maximum gallbladder contraction of 44% after ingestion of fatty meal in humans[30]. However, in our study, the gallbladder response to gastric distension following ingestion of 500 mL of normal saline in healthy volunteers and group II gallstone patients was not significantly different from fasting gallbladder volumes. In group I gallstone dyspepsia patients, after drinking 500 mL of normal saline, the lowest gallbladder residual volume (13%) occurred at 15 min, with progressive recovery to the fasting volume thereafter. This saline water induced gallbladder early net emptying most prominently between 5 and 25 min in group I patients. In contrast, after fatty meal, there were significant decreases in gallbladder volumes both in healthy volunteers and the two groups of gallstone patients throughout the study period. The group I gallstone patients had the largest gallbladder volume change at the 40th min of the study. The ejection fraction was significantly increased in group I patients compared to the other two groups 10-50 min after fatty meal, but not thereafter.

Our study showed that gallbladders of group I gallstone dyspepsia patients had greater motility than those of normal individuals and group II patients in response to both gastric distension and fatty meal, which is important for elucidating the pathophysiology of gallstone dyspepsia. To our knowledge, these findings have not been previously reported. The greater motility might have been caused by hypersensitivity of the gallbladder wall to neural stimuli and hormone or by increased serum hormone levels in patients with gallstone dyspepsia. We do not know if gallbladder hypermotility precedes the development of gallstones, accompanies their development or is a relatively late sequel of their appearance. The finding that not all gallstone patients have gallbladder hypermotility also suggests there may be mechanisms for hypermotility other than the gallstones themselves. The primary mechanism is still debated and may indeed differ among individual patients. The gallbladder hypermotility phenomenon requires further studies.

In our study, more patients (34%) did not benefit from cholecystectomy than those in other studies (20-30%). We consider that the difference in the study populations may explain this phenomenon. Previous studies included more patients with acute cholecystitis or severe biliary pain who are better candidates for cholecystectomy[2-4]. The patients in our study were selected because of their relatively mild symptoms of postprandial distress without fever, chills, transient jaundice or severe biliary pain. This is one reason that might explain why others reported better cholecystectomy results.

Most studies of gallbladder motility in the presence of gallstones have shown impaired gallbladder contractility. Thus, our findings have also been noted by others[22,23]. Our study indicated that increased gallbladder contraction was the prerequisite for the development of dyspepsia symptoms. Previous studies included more asymptomatic patients with decreased gallbladder contractions in response to gastric distension and fatty meals.

Increased gallbladder contractility in patients with gallstone dyspepsia may be useful in identifying patients with atypical mild symptoms or possibly with early acalculous cholecystitis. The studies we conducted were noninvasive, inexpensive and within the capability of conducting ultrasonography in modern hospitals. The findings of promptly increased gallbladder contractility in response to intake of 500 mL of normal saline and fatty meal may lend support to including gallbladder contractility studies as part of the dyspepsia differential diagnosis.

Postprandial gallbladder volume changes and relative ejection fraction, determined sonographically, seem to be able to discriminate gallstone dyspepsia from functional dyspepsia.
In clinical practice, this type of diagnostic study may help to determine the appropriate treatment for gallstone patients with dyspepsia.

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