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World J Gastroenterol 2008 May 14; 14(18): 2825-2831
World Journal of Gastroenterology ISSN 1007-9327

CLINICAL RESEARCH

Decreased postprandial gallbladder emptying in patients with black pigment stones

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Received: January 19, 2008 Revised: March 14, 2008

Abstract

AIM: To analyze gallbladder contractility in patients with black pigment stones (BPSs) and to compare this with patients with cholesterol stones (CSs) and healthy volunteers.

METHODS: The pattern of bile evacuation from the gallbladder was quantified by computer cholescintigraphy in 28 normal subjects, 22 patients with CSs and 14 with BPSs. The parameters of gallbladder contractility included ejection period (EP), ejection fraction (EF) and ejection rate (ER).

RESULTS: A significantly shorter EP was observed in patients with BPSs in comparison to those with CSs (t = 2.4, P < 0.05). EF in BPS patients significantly decreased in comparison to that in CS and normal subjects (t = 6.4, P < 0.0001; t = 2.1, P < 0.05). EF in CS patients also significantly decreased in comparison to that in normal subjects (t = -3.0, P < 0.005). Consequently, ER in patients with BPSs and CSs was significantly smaller than that in normal subjects (t = 3.1, P < 0.005; t = -3.5, P < 0.001). Moreover, in cases where postprandial reflux of a radioisotope into the common hepatic duct from the gallbladder was observed, EF and ER of either CS or BPS patients showed a significant reduction.

CONCLUSION: Bile evacuation from the gallbladder is reduced in patients with BPSs, in comparison to those with CSs and to healthy volunteers. Bile stagnation due to impaired gallbladder kinetics seems to be one of the predisposing factors for the development of BPSs.

Key words: Black pigment stone; Cholescintigraphy; Gallbladder emptying; Ejection period; Ejection fraction; Ejection rate

Peer reviewer: Sri P Misra, Professor, Gastroenterology, Moti Lal Nehru Medical College, Allahabad 211001, India

Sugo T, Hakamada K, Narumi S, Sasaki M. Decreased postprandial gallbladder emptying in patients with black pigment stones. *World J Gastroenterol* 2008; 14(18): 2825-2831 Available from: URL: http://www.wjgnet.com/1007-9327/14/2825.asp DOI: http://dx.doi.org/10.3748/wjg.14.2825

INTRODUCTION

The prevalence of gallstone disease has been increasing in Japan over the past five decades, with an increased incidence of cholesterol stones (CSs) as a leading cause[1-3]. In addition, the number of patients with black pigment stones (BPSs) has also been increasing, while the incidence of calcium bilirubinate stones is decreasing[1,2] and thus becoming less common in comparison to other Asian countries[2,3].

Much effort has been directed to identify the mechanism of gallstone formation, especially in the case of cholesterol and calcium bilirubinate stones. The supersaturation of bile, caused by an increase in cholesterol concentration or a decrease in bile salt concentration, contributes to form a liquid crystalline phase of cholesterol[4-6]. Calcium bilirubinate stones (brown pigment stones) develop as the enzyme β-glucuronidase, possibly produced by bacteria such as *Escherichia coli*, generates unconjugated bilirubin, which precipitates as a calcium salt[5,7]. Therefore, bilirubinate calcium is closely related to biliary infection[3,5,7-9].

However, the mechanism by which BPSs develop has not been fully elucidated. BPSs sometimes occur in patients with hemolytic anemia[8,10], liver cirrhosis[5,11,12], and histories of cardiac valve replacement[13] and gastrectomy[14-16], but the majority of patients have no specific background[8]. Contrary to brown pigment stones, BPSs are not associated with biliary infection and almost all occur in the gallbladder[5,8,9]. Other reports have suggested that some unique structures of the gallbladder such as the Rokitansky-Aschoff sinuses[17] and the cystic duct[18] might be predisposing factors for the formation of BPSs.

A change in gallbladder contractility is another possible mechanism of gallstone formation. Over the past century, many studies have been conducted to disclose a close

association with gallbladder dysmotility and gallstone diseases[11,19-29]. Previous studies, however, have yielded conflicting results. The majority of studies have reported impaired gallbladder emptying in patients with gallstones, while others have not. These conflicting results have derived in part from different methodology to assess gallbladder motility[22], and also from the fact that these studies were conducted without taking into account the chemical characteristics of the stones. To date, there have been, according to the PubMed database, very few reports that describe gallbladder motility with special reference to the pathogenesis of BPS formation.

This study analyzed the pattern of postprandial bile evacuation from the gallbladder quantitatively in patients with BPSs, using a non-invasive technique with a radioactive marker ^{99m}Tc-PMT, and compared that pattern with that seen in patients with CSs and in healthy volunteers.

MATERIALS AND METHODS

Patients

From 1991 to 2005, 694 patients underwent cholecystectomy for cholecystolithiasis at Hirosaki University Hospital, Japan. Among these, 22 patients with CSs and 14 with BPSs were included. Patients with positive bile culture obtained at the time of surgery, any sign of cholecystitis, liver cirrhosis or hepatitis, diabetes mellitus, abnormal wall thickening of the gallbladder, and/or a previous surgical history were excluded from the study. The categories of the stones were determined according to the macroscopic characteristics of the specimens and their chemical analyses. Twenty-eight healthy volunteers without any surgical history were also analyzed and included as controls. There was no significant difference in age among the three groups (52.4 ± 13.0 in CS patients, 55.8 ± 14.4 in BPS patients, and 54.8 ± 14.4 in healthy volunteers, $P = 0.74$). The male-to-female ratios were also comparable (6/16 in CS, 4/10 in PBS, and 15/13 in healthy volunteers, $P = 0.11$). The nature of the study was explained to each subject before cholescintigraphy, and informed consent was obtained under the instruction of the ethical committee for human studies, and the study was approved by the Hirosaki University School of Medicine.

Cholescintigraphy

The method was a modification of that previously described by Krishnamurthy *et al*[30]. All subjects were obliged to fast from 11:00 pm prior to the day of examination. Each subject was injected with 5 mCi 99m-Tc-N-pyridoxal-5-methyltryptophan (99m-Tc-PMT) *via* the median cubital vein in the morning. After 60 min bed rest in a semi-reclining position, a scintillation camera with a low energy, high-resolution collimator was placed on the right hypochondrium and positioned to enable the separate visualization of the common hepatic duct, common bile duct, descending portion of the duodenum, and gallbladder. The radioactivity gradually increased and reached a plateau in 60 min. Serial views of the abdomen were obtained at 1-min intervals from this point up to 60 min. The information was simultaneously digitalized and recorded in the mode on 64 × 64 computer matrices at 1 frame per 15 s. At 10 min, 200 mL Calorie Mate, which was composed of 33.4 g glucose, 6.7 g protein, 4.4 g fat, and 200 kcal (Otuka, Tokyo, Japan), was given to each patient as a test meal, and observation was continued for an additional 50 min. To avoid the effect of respiratory movement on images, each subject was instructed to breathe smoothly throughout the data collection.

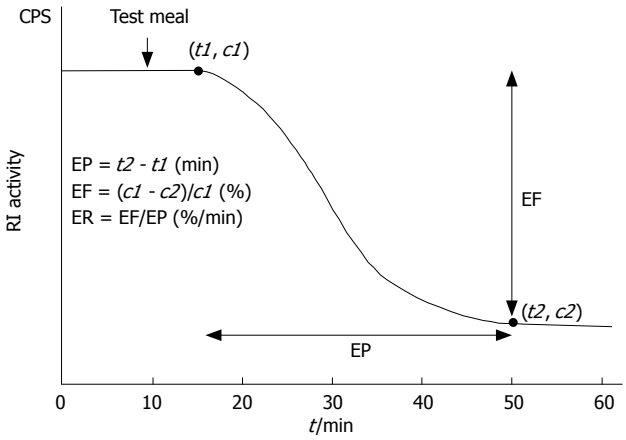

Figure 1 Definition of postprandial contractility indices of the gallbladder. Postprandial gallbladder contractility was expressed by EF, which is determined as a percentage decrease in radioactivity, and ER, which is determined by EF/EP. Radioactivity was measured in three regions of interest in the gallbladder and EP was determined as the time of decrease on the time-activity curve. CPS: Counts per second.

Computer data analysis

Serial images were created by a data-analyzing computer. Four regions of interest on a composite image were chosen. The first included the entire gallbladder; the second, the common hepatic duct; the third, the descending part of the duodenum; and the fourth, the liver as a background. Time-activity curves were generated for each region, background counts were subtracted, and net count decay was corrected and normalized. In a similar manner, time–radioactivity curves were obtained.

Next, the times when the gallbladder began ejecting (*t1*) and when the gallbladder stopped ejecting (*t2*), and their corresponding counts (*c1, c2*) were set (Figure 1). The ejection period (EP), ejection fraction (EF) and ejection rate (ER) were calculated according to the formulae below: EP = *t2* - *t1* (min); EF = (*c1* - *c2*)/*c1* (%); ER = EF/EP (%/min).

Statistical analysis

For statistical examinations an analysis of variance, Student's *t* test, χ^2 test and linear regression analysis were all used appropriately, and the SPSS 11.0J software program for Windows was used for the analysis. The continuous variables were reported as the mean ± SD. $P < 0.05$ was considered to be significantly different.

RESULTS

Gender did not affect EP, EF and ER in all three groups (Table 1). Age also showed no correlation with EP, EF and

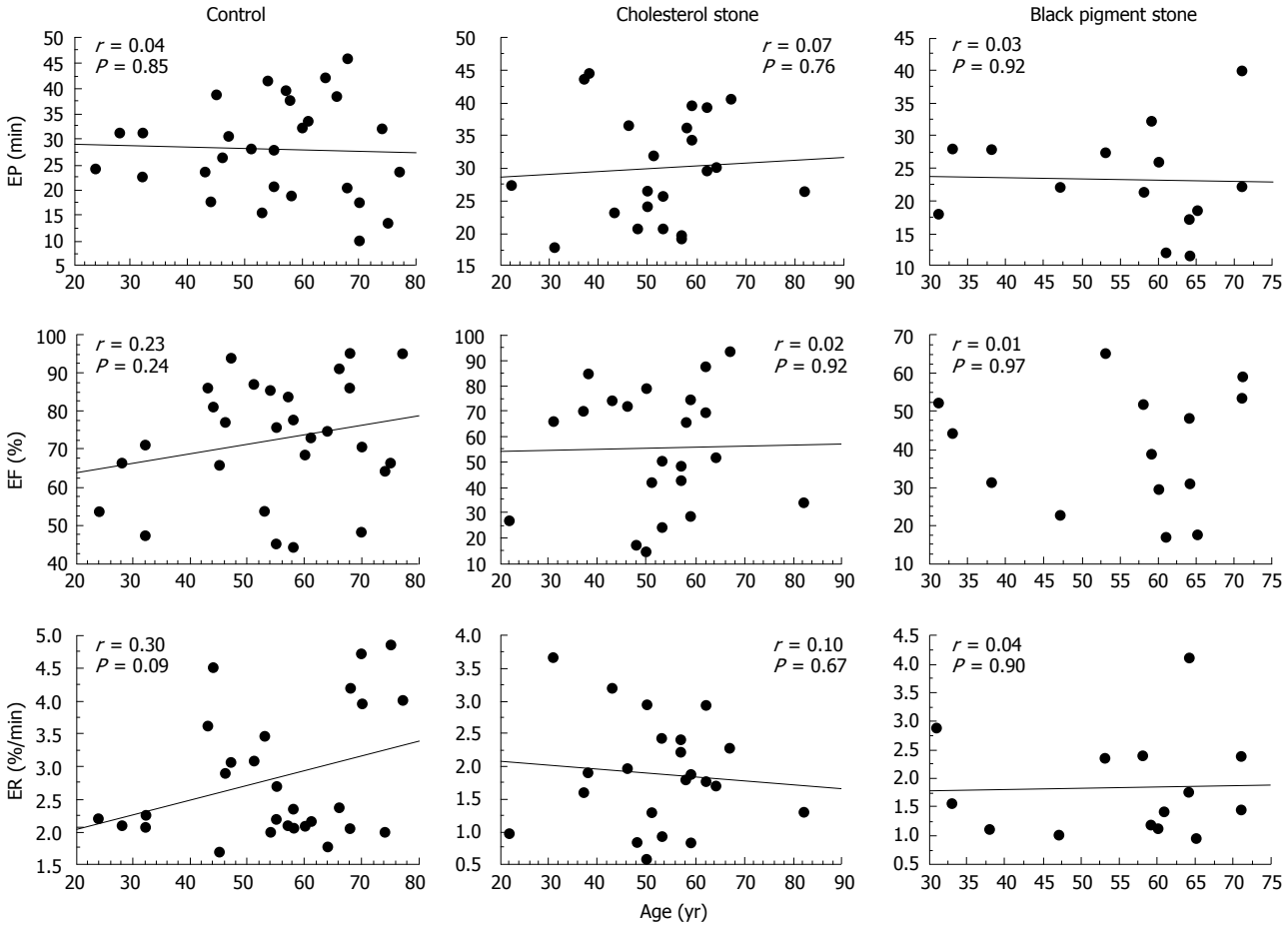

Figure 2 Correlation of age with contractility indices of the gallbladder. There was no correlation between age and EP, EF and ER in all three groups.

ER (Figure 2). Moreover, the size and the number of the stones correlated with none of the indices in either group with CSs or BPSs (Figures 3 and 4).

Postprandial changes in gallbladder contractility are summarized in Figure 5. The EP values of normal subjects (28.2 ± 9.5 min) and CS patients (30.0 ± 8.4 min) were comparable but the value in BPS patients (23.3 ± 7.8 min) was significantly shorter than that in CS patients ($P < 0.05$). The EF of CS patients (55.5% ± 24.0%) was significantly smaller than that of normal subjects (72.5% ± 15.5%, $P < 0.05$), and the value of BPS patients (40.2% ± 15.5%) was significantly reduced in comparison to that of CS patients ($P < 0.05$), and to that of normal subjects ($P < 0.0001$). Consequently, the ER in the CS group (1.9% ± 0.8%/min) and in the BPS group (1.9% ± 0.9%/min) significantly decreased in comparison to that of normal subjects (2.8% ± 1.0%/min, $P < 0.001$, $P < 0.005$). The ER values were comparable between the CS and BPS groups.

Postprandial bile reflux from the gallbladder to the common hepatic duct was observed in 22/28 (76%) normal subjects, 11/22 (50%) CS patients, and 8/14 (57%) BPS patients. Comparisons between the cases with and without reflux are summarized in Figure 6. In normal subjects, EP and ER were comparable between 22 reflux (28.5 ± 9.5 min, 3.0%/min) and six non-reflux cases (27.0 ± 10.0 min, 2.3% ± 1.0%/min), while EF was significantly larger in the reflux group (76.3% ± 13.6%) than in the non-reflux group (58.4% ± 14.3%, $P < 0.01$).

Table 1 Effects of gender on postprandial motility indices of the gallbladder

	Male	Female	*P*
Normal subjects (*n*)	15	13	
EP (min)	26.6 ± 10.3	30.1 ± 8.4	0.34
EF (%)	68.7 ± 14.6	77.1 ± 15.9	0.16
ER (%/min)	2.9 ± 1.2	2.7 ± 0.7	0.51
CS (*n*)	6	16	
EP (min)	29.1 ± 6.1	30.4 ± 9.2	0.76
EF (%)	54.3 ± 27.1	56.0 ± 23.7	0.89
ER (%/min)	1.9 ± 1.0	1.9 ± 0.8	0.99
BPS (*n*)	4	10	
EP (min)	22.4 ± 5.6	23.6 ± 8.7	0.80
EF (%)	39.3 ± 10.9	40.6 ± 17.6	0.89
ER (%/min)	1.9 ± 0.8	1.9 ± 1.0	0.99

In CS patients, EP was significantly longer in 11 reflux cases (33.5 ± 7.4 min) than in 11 non-reflux cases (26.6 ± 8.1 min, $P < 0.05$). EF and ER were comparable between reflux and non-reflux groups. In BPS patients, EP, EF and ER were comparable, despite reflux state.

In a subgroup analysis limited to patients with postprandial bile reflux from the gallbladder to the common hepatic duct, EF and ER in the BPS CS groups were significantly smaller than those in normal subjects. EP in the BPS group was also significantly shorter than that in the CS group (Figure 6).

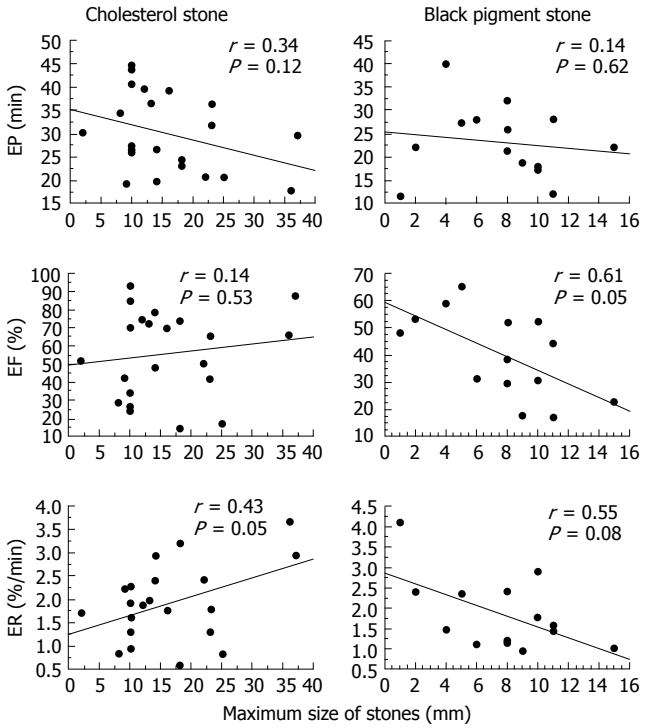

Figure 3 Correlation of the size of stones with contractility indices of the gallbladder. There was no correlation between stone size and EP, EF and ER in all groups.

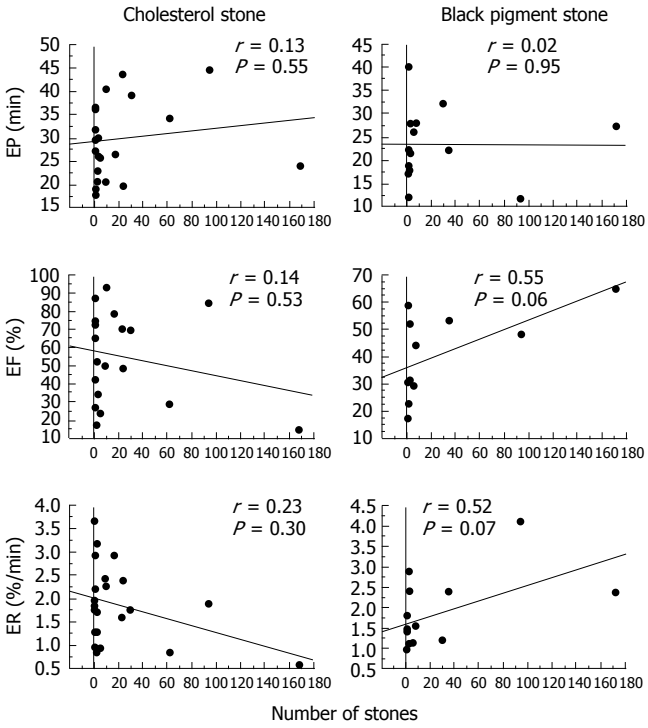

Figure 4 Correlation between the number of stones with the contractility indices of the gallbladder. There was no correlation between the number of stones and EP, EF and ER in all groups.

DISCUSSION

Many studies have reported a high incidence of BPSs in patients with hemolytic jaundice[8,10], heart valve replacement[13], liver cirrhosis[5,11,12] and a previous history of gastrectomy[14-16]. The first two are primarily due to bilirubin overproduction, while the latter are not. However, despite similar biochemical and clinical features, many patients with hemolytic anemia do not develop BPSs. Moreover, Portincasa *et al*[10] have reported that impaired gallbladder motility is observed in patients with β-thalassemia major, and have suggested that hemolytic hyperbilirubinemia and dysmotility might contribute to the process of pigment stone formation. In patients with liver cirrhosis, Acalovshi *et al*[11] have reported that gallbladder contractility is impaired and hypomotility is proportional to disease severity. A close relationship between high incidence of gallstones and changes in gallbladder kinetics after gastrectomy has also been described[15]. Taking into consideration that BPSs also occur without these complications[17], impaired gallbladder function may be associated with BPS formation. However, there have so far been very few reports on gallbladder kinetics and the mechanism of stone formation with special reference to BPSs.

In this study, biliary scintigraphy was used to analyze the postprandial dynamics of bile flow in patients with BPSs in comparison to those with CSs and normal subjects, because it was essentially risk-free, with very slight radiation exposure and yielded a precise assessment of the ejection fraction of the gallbladder motility, as previously reported[22,30]. First, the effects of age, gender and the characteristics of the stones on gallbladder contractility were analyzed, because there have been some previous studies on the effects of age and sex on gallbladder emptying[21,31]. In all groups, age and gender, and size and number of stones did not affect EP, EF and ER. Other studies have also found that size and number of stones have no influence upon postprandial gallbladder emptying[11,27]. Therefore, gallbladder contractility was analyzed without taking these backgrounds into consideration.

It has been reported that EF in normal subjects is 80% in response to postprandial intrinsic loading of cholecystokinin (CCK)[19], and it ranges from 50%-80% in response to extrinsic administration of CCK[24,27]. In patients with gallstones, the contractility is reduced to 52% by intrinsic[19] and to 32%-50% by extrinsic stimulus of CCK[24,27]. These reports, however, included all kinds of gallstones with different etiology, while also neglecting the presence or absence of acute or chronic inflammatory processes, such as gallbladder-wall thickening. In this study, gallbladder contractility was analyzed according to the predominant chemical component of the gallstones. Patients with any sign of cholecystitis, liver cirrhosis or hepatitis, diabetes mellitus, abnormal gallbladder-wall thickening, and/or previous surgical history which might affect contractility were excluded from the study.

In BPS patients, EP was significantly shorter than that in CS patients. Simultaneously, EF was reduced significantly in BPS patients, in comparison to those with CSs and healthy volunteers. These findings suggested that bile clearance from the gallbladder was significantly reduced in patients with BPSs. Krishnamurthy *et al*[24] have reported that there is no difference in EP between

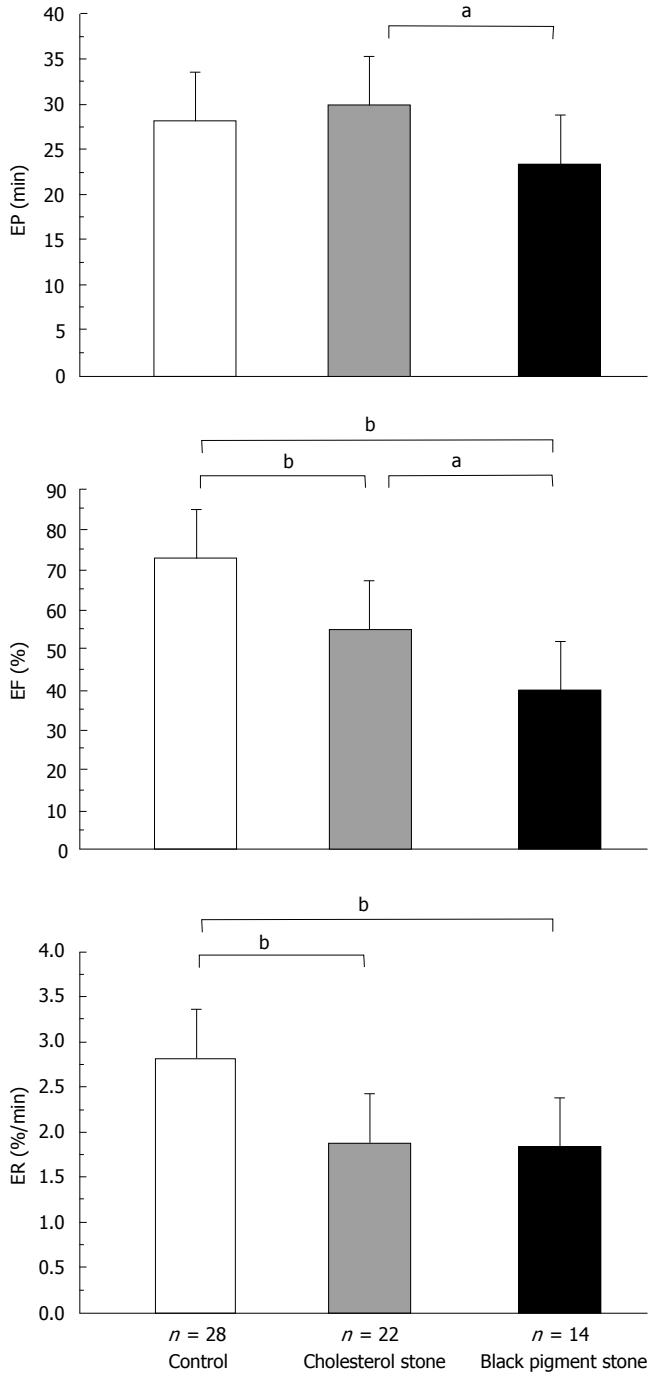

Figure 5 Postprandial contractility indices of the gallbladder. A significantly shorter EP was observed in patients with BPSs than in those with CSs. EF in BPS patients was significantly decreased in comparison to that in CS patients and normal subjects. EF in CS patients also significantly decreased in comparison to that in normal subjects. Consequently, ER in patients with BPSs and CSs was significantly smaller than that in normal subjects. $^{a}P < 0.05$, $^{b}P < 0.01$.

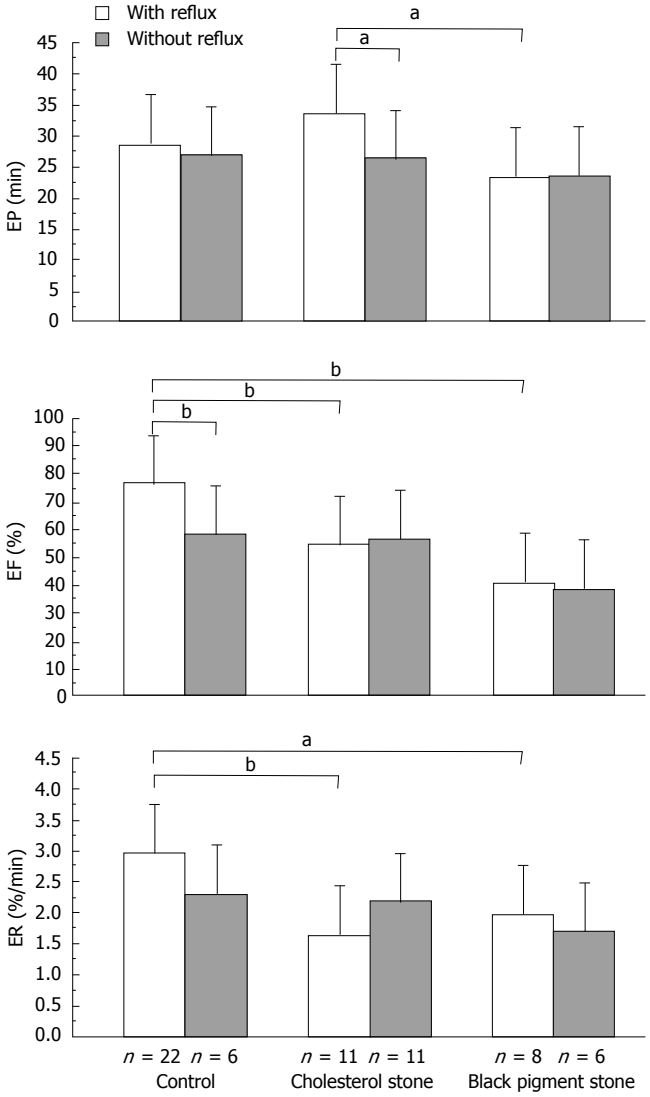

Figure 6 Postprandial contractility indices of the gallbladder according to the reflux state of a radioisotope into the common hepatic duct. In normal subjects, EF was significantly larger in patients with reflux. In a subgroup analysis of such patients, EF and ER in those with either CSs or BPSs showed a significant reduction in comparison to those in normal subjects. $^{a}P < 0.05$, $^{b}P < 0.01$.

gallstone patients and normal individuals, but they do not distinguish patients according to the chemical characteristics of their stones. Such results may come from an increased proportion of CSs in their study, because the EP of normal subjects and gallstone patients did not differ in the current study. Portincasa *et al*[28] have conducted a comparative analysis of gallbladder contractility in patients with BPSs or CSs, and observed an increased fasting volume of the gallbladder in CS but not in BPS patients. Postprandial emptying was delayed and incomplete in both CS and BPS patients in comparison to control subjects. However, these observations were made based on the findings of ultrasonography, and not by biliary scintigraphy.

It has been demonstrated that CCK simultaneously induces contraction of the gallbladder and relaxation of the sphincter of Oddi, which facilitates secretion of the bile duct into the duodenum. If this contraction-relaxation coordination fails, bile reflux from the gallbladder to the common hepatic duct may occur because of transient resistance of the sphincter. Itoh *et al*[32] have reported that this phenomenon is observed in patients with chronic pancreatitis and that the degree of reflux is proportional to disease progression. This means that one of the causes of such reflux is relative stenosis of the distal bile duct. Bile reflux, however, was observed in half of the patients with gallstones, in whom EF was significantly reduced in comparison to that in healthy volunteers. This phenomenon

suggests that minute discordance of gallbladder emptying and relaxation of the sphincter of Oddi predisposes to bile reflux and thus causes bile stagnation in the gallbladder.

Chemically, the structure of BPSs is polymerized bilirubin with copper, ion, calcium and other metals, and almost all the stones are formed in the gallbladder[33]. Therefore, an environment suitable for the formation of BPSs comprises conditions that allow chemical polymerization with sufficient time. In fact, EF was reduced in patients with gallstones, especially with BPSs in the present study. Moreover, bile reflux from the gallbladder to the common hepatic duct may cause subclinical transient bile stagnation, thereby contributing to stone formation.

In conclusion, bile evacuation from the gallbladder is reduced in patients with BPSs, in comparison to those with CSs and healthy volunteers. We therefore postulate that impaired gallbladder motor function and discordance of bile evacuation is not the result of the presence of gallstones, but instead it is considered to precede the development of BPSs.

ACKNOWLEDGMENTS

The authors thank Professor R Hada and Emeritus Prof. M Konn, Hirosaki University Graduate School of Medicine, for their many and varied contributions throughout the study.

COMMENTS

Background

The incidence of BPSs and CSs is increasing in Japan. However, the mechanism of BPS formation is still not completely understood. The authors hypothesize that reduced motor function of the gallbladder and dysfunction of bile evacuation is associated with BPS formation.

Research frontiers

To date, there have been very few reports that describe gallbladder motility with special reference to the pathogenesis of BPS formation. The authors found impaired gallbladder kinetics in patients with BPSs, in comparison to those with CSs and to healthy volunteers.

Innovations and breakthroughs

The authors strictly selected the patients without any background diseases such as cholecystitis, liver cirrhosis or hepatitis, diabetes mellitus, abnormal gallbladder-wall thickening, and/or a previous surgical history, and then analyzed physiological patterns of bile evacuation from the gallbladder quantitatively by a less-invasive method of computer cholescintigraphy.

Applications

This research is expected to contribute to understanding the pathogenesis of gallstone diseases.

Peer review

The authors analyzed gallbladder contractility in patients with BPSs in comparison to those with CSs and healthy volunteers. The study is very interesting.

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