

# The role of cholescintigraphy in demonstrating delayed post prandial gallbladder motility in cirrhotic patients

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## Abstract

**Objective:** The purpose of this study was to investigate the postprandial gallbladder motility of cirrhotic patients using cholescintigraphy by technetium-99m-ethylhydroiminodiacetic acid (<sup>99m</sup>Tc-EHIDA). **Subjects and Methods:** Sixty two cirrhotic patients (Child-Pugh A: 28 patients; Child-Pugh B: 21 and Child-Pugh C: 13 patients) and 24 normal subjects were included in this study. All patients underwent cholescintigraphy. Mean gallbladder ejection fraction (GBEF) and mean ejection period (EP) were acquired by the region of interest method. In order to evaluate gallbladder contractility of cirrhotic patients, their mean GBEF and EP were compared with the same tests of normal subjects using an independent sample t test. **Results:** The mean GBEF of cirrhotic patients was lower and their mean ER was longer than that of normal subjects. The means of GBEF and EP of cirrhotic patients were different among different Child-Pugh grade groups. All these differences showed statistical significance. **Conclusions:** This study suggests that post prandial cholescintigraphy by <sup>99m</sup>Tc-EHIDA demonstrated slower gallbladder motility in cirrhotic patients. The ejection period of cholescintigraphy by <sup>99m</sup>Tc-EHIDA can be used as an index of abnormal gallbladder motility.

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## Introduction

The evaluation of gallbladder (GB) motility by cholescintigraphy is a valuable technique for detecting gallbladder dysfunction [1]. Functional gallbladder scintigraphy is performed after the intravenous (i.v.) administration of iminodiacetic acid agents. Measurement of gallbladder ejection fraction (GBEF) by i.v. infusion of exogenous cholecystokinin (CCK) is a well-established technique for the diagnosis of chronic acalculous cholecystitis, biliary dyskinesia, gallbladder spasm, cystic duct syndrome, functional gallbladder disease, or chronic acalculous gallbladder disease [2, 3]. However, there have been some major concerns and issues regarding CCK cholescintigraphy, such as the proper infusion methodology for CCK, including the amount of the total dose administered, the duration of infusion, the time of quantification, and the actual absence of normal values. A fatty meal, which is used to release endogenous CCK, has been used as a stimulant to empty the gallbladder [4]. Cirrhotic patients have increased prevalence of gallstones, when compared with the general population, by 29% to 59% [5, 6]. The pathogenesis of this phenomenon is still not fully clarified. Gallbladder dyskinesia, has been proposed to explain the increased prevalence of gallstones in cirrhotic patients [7]. The aim of this study was to investigate the postprandial gallbladder motility in cirrhotic patients using cholescintigraphy.

## Subjects and Methods

Twenty four normal control subjects, 16 female and 8 male, aged 36.2-70.1 years, and 62 patients, 40 female and 22 male, aged 30.2-77.4 years, with liver cirrhosis were included in this study. The etiologies of liver cirrhosis included: hepatitis B, 20/62 patients, hepatitis C, 17/62 patients, alcoholic cirrhosis 15/62 patients and primary bile cirrhosis in 10/62 patients. The diagnosis of liver cirrhosis was made by clinical symptoms and signs, laboratory tests, imaging and histopathological studies. The cirrhotic patients were

divided into two groups, those with gallstones 15/62 and those without gallstones, 47/62 as diagnosed by ultrasonography (USG). According to the severity of liver cirrhosis, using the modified Child-Pugh classification criteria, patients were divided into three groups. The Child-Pugh criteria included: hepatic encephalopathy, ascites, bilirubin serum levels, serum albumin, prothrombin index, and prothrombin time. Child-Pugh A group included 28/62 patients, Child-Pugh B group 21/62 patients and Child-Pugh C group included 13/62 patients. Subjects who had undergone cholecystectomy or had a history of gallbladder disease were excluded from the study. None of the patients had undergone prior gastric or ileac surgery. Informed consent was obtained from each subject before examination. This study was approved by the Institutional Review Board of Beijing Friendship Hospital, Capital Medical University.

### Fatty meal

We prepared 200mL of liquid fatty meal, including 18g fat, 13g protein and 19g sugar using a commercially available formula as an analogy to CCK, in order to stimulate GB contraction. The fatty meal was equivalent to 18g fat and 500kcal and was ingested within 4-5min.

### Cholescintigraphy and gallbladder ejection

The study began at 8 a.m., after 4-6h of fasting, the subjects being for 24h without any medication that might have influenced gallbladder motility. Each subject was given i.v. 185MBq, of technetium-99m-ethylhydroiminodiacetic acid ( $^{99m}\text{Tc}$ -EHIDA). Serial hepatobiliary dynamic images started at 60min post injection. The patients lied supine under a large-field gamma camera, fitted with a low-energy, all-purpose, parallel-hole collimator. We used a 20% window centered at 140keV. Images were obtained anteriorly. After the scan started, the patient ingested the fatty meal in 4-5min. Dynamic acquisitions were performed over a 60min period at a rate of one image per 60sec.

On the computer display, all regions of interest were drawn around the gallbladder and the adjacent liver (Figure 1). After processing, time-activity-curves (TAC) were acquired. From these curves, we acquired the ejection period (EP: the time from maximum to minimum radioactivity in gallbladder corrected for background (bg) and for decay). Finally, GBEF was calculated using the following formula:

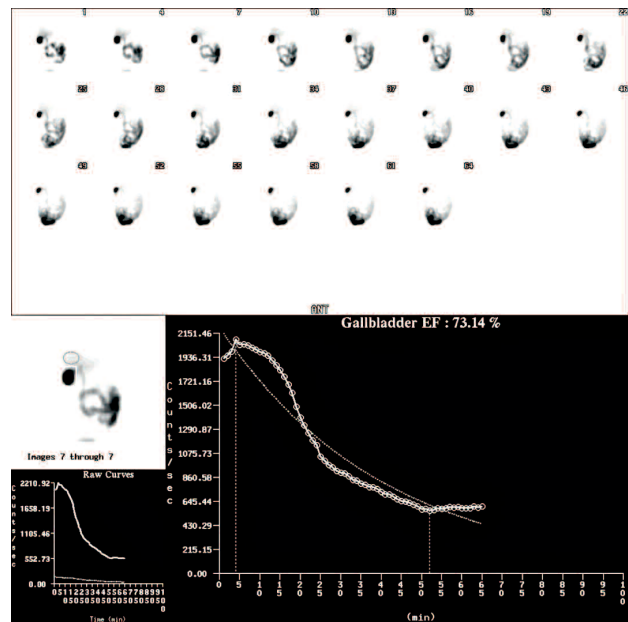
$$\text{GBEF (\%)} = \frac{\text{net GBmax counts} - \text{GBmin counts}}{\text{net GBmax counts}}$$

$$\text{Net GBmax counts} = \text{Total GBmax counts} - \text{GB bg counts}$$

$$\text{Net GBmin counts} = \text{Total GBmin counts} - \text{GB bg counts}$$

### Statistical analysis

Statistical analysis was made by using SPSS software (version 15.0). Univariate statistics are expressed as mean±standard deviation (SD). To evaluate the gallbladder contractility of cirrhotic patients, the mean of GBEF and of EP in the cirrhotic patients and in normal subjects were compared using an independent sample t test. One way ANOVA was used for comparison between multiple groups with Tukey Honestly Significant Difference, also called Tukey method test as post-hoc analysis. We considered as statistically significant, P value of less than 0.05.



**Figure 1.** This was a figure of a normal subject. On the computer display, one region of interest (ROI) was drawn around the gallbladder, the other ROI was drawn around the adjacent liver. After this process, a time-activity-curve was acquired. From this curve, we acquired the ejection period. After background and decay corrections, gallbladder ejection fraction was calculated by using the formula mentioned in the text.

## Results

a) The mean postprandial GBEF and EP of cirrhotic patients were significantly lower than those of normal subjects (Table 1).

**Table 1.** Comparison of mean postprandial GBEF and EP between normal and cirrhotic patients

Group	Case	GBEF(%)	EP(min)
Normal	14	81.25±13.94	2.36±0.81
Cirrhotic	58	67.04±26.94*	6.10±0.72**

Compared with normal control, \*P 0.01, \*\* P>0.05

b) The mean GBEF of cirrhotic patients with gallstones was lower than that of patients without gallstones. There was significant difference of GBEF between the two groups. The EP of cirrhotic patients with gallstones was similar with that of patients without gallstones. There was no significant difference of mean EP between the two groups (Table 2).

**Table 2.** Comparison of mean GBEF and EP between cirrhotic patients with and without gallstones

Group	Case	GBEF(%)	EP(min)
Without stones	47	69.30±26.75	5.89±0.63
With stones	14	61.12±28.69*	6.15±1.01**

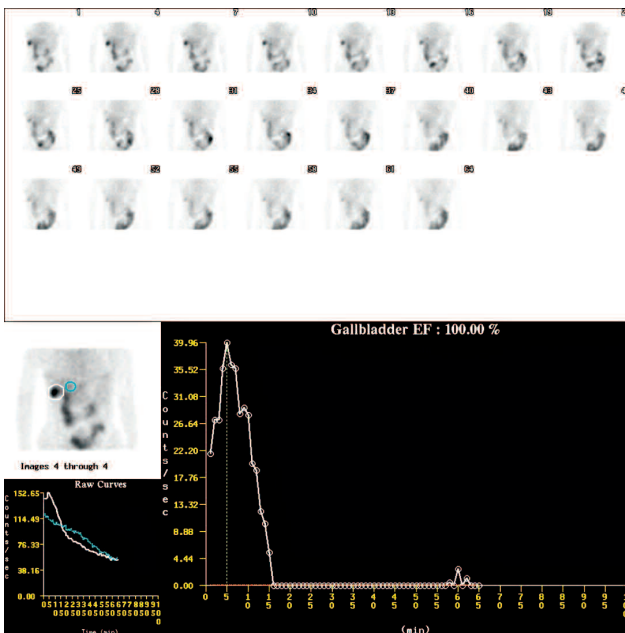
Compared with cirrhosis patients without stones, \* P 0.05, \*\* P>0.05.

c) The mean of GBEF and of EP of cirrhotic patients were compared among different Child-Pugh grade groups and showed significant difference with a tendency of GBEF to decrease and EP to increase (Figures 2 and 3, Table 3).

**Table 3.** Comparison of the means of GBEF and EP among different Child-Pugh grade cirrhotic patients

Groups	Case	GBEF(%)	EP(min)
Child-Pugh A	13	72.37±22.23	5.78±0.72
Child-Pugh B	21	66.30±29.81	6.54±0.81
Child-Pugh C	28	61.0±29.73*	7.22±0.61*

Comparison among different Child-Pugh grade patients, \* P<0.05

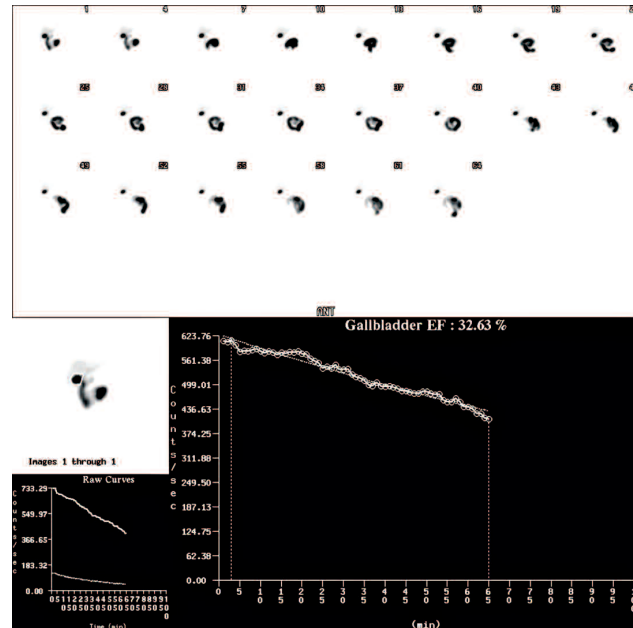


**Figure 2.** This was a figure of a Child-Pugh grade A cirrhotic patient. The time-activity curve showed that the mean gallbladder ejection fraction was 100% when the ejection period was 11min.

## Discussion

Gallbladder function can be measured by cholecystography, cineradiography and manometry [8]. Almost all these methods give essentially morphological information and have some limitations: a) the tests are invasive in nature; b) the contrast agents used in the test may cause side effects, sometimes severe; and c) the tests interpretation is usually subjective [9].

Ultrasonography is also often used for gallbladder diseases. The main advantages of USG are its low cost, its availability, and lack of radiation exposure. However, like other structural imaging techniques, USG is highly operator-dependent, and the gallbladder emptying study is based on a geometric formula. Cholescintigraphy is a well tolerated method, can rather easily be performed and is more efficient when compared with USG [10, 11].



**Figure 3.** This was the figure of a Child-Pugh grade C cirrhotic patient. The time-activity curve showed that the mean of gallbladder ejection fraction was 32.63% while the ejection period was 62min.

The pathogenesis of gallbladder dyskinesia is not fully understood and functional assessment of gallbladder emptying using cholescintigraphy is widely considered as diagnostic. Gallbladder dysfunction, also known as bile dyskinesia, is characterized by functional changes without structural abnormalities. Although GBEF scintigraphy using cholecystokinin (CCK) can often provide diagnosis, the dose of CCK, its dose rate and duration of infusion have not been standardized up to now. Recently, oral fatty meal including (equal parts) of milk, yolk and chocolate, to release endogenous CCK is used as a more physiologic cholagogue stimulant than exogenous CCK [2, 12]. In countries where CCK is not available, gallbladder scintigraphy with fatty meal has become common practice. In our study, we used fatty meal as a stimulant of CCK, with sufficient fat (18g) to stimulate gallbladder contraction. Stone et al. (1992) suggested that 4g of fat does not result in gallbladder contraction motility and that at least 10g of fat are required to produce good gallbladder emptying [13]. Normal values for fatty-meal cholescintigraphy also depend on the other contents of the meal, on the other contents of the meal and on the methodology of meal intake. In the present study, we prepared 200mL of liquid fatty meal (including 18g fat, 13g protein and 19g sugar) according to a previous study [14]. The fatty meal was equivalent to 18g fat and 500kcal and was ingested within 4-5min.

Gallstones in liver cirrhosis are mainly of the pigment type. Metabolic alterations have been found in liver cirrhosis to account for gallstone formation, such as increased unconjugated bilirubin excretion into bile, secondary to hemolysis and or hypersplenism, decreased cholesterol secretion and adequate in bile acid pool in the liver and also decreased apoAI and apoAII secretions in the fibrotic liver [15]. Gallstones formation increases with progression of the disease, being increased in the advanced stages of cirrhosis [5, 16].

Besides metabolic alterations, the gallbladder motility may account for gallstones formation. The present study demonstrated that the GBEF of cirrhotic patients is lower than that of normal subjects, which means that gallbladder motility of cirrhotic patients is impaired. Buzas C et al. (2011) compared gallbladder emptying in patients with chronic hepatitis C virus and in those with hepatitis C virus cirrhosis. They found a decreased in gallbladder motility in both these groups of patients. This might be a risk factor for the formation of gallstones [17].

There are some possible reasons of why cirrhotic patients have impaired gallbladder contractility, which are as follows: a) Delayed gastric emptying of cirrhotic patients has been noted, with subsequently delayed CCK release and impaired gallbladder motility [18]. Furthermore, increased gastric emptying might also account for diminished gallbladder motility, as the meal rapidly passes through the duodenum, while CCK release is decreased [19]. b) In the presence of increased plasma concentrations of intestinal peptides such as VIP, somatostatin, glucagon, which normally undergo hepatic degradation, there is a weaker response of the gallbladder to the action of CCK in cirrhotic patients. These intestinal peptides act as relaxing factors on gallbladder in patients with poor liver function [20]. These peptides have a relaxant effect on gallbladder smooth muscles [21].

Our study also demonstrated that the GBEF of cirrhotic patients with gallstones was lower than that of patients without gallstones. Results of the present study were similar with some previous studies, which also demonstrated the impaired gallbladder motility in cirrhotic patients [22]. In contrast with our data, Li et al. (2000) reported that gallbladder emptying was not impaired compared with healthy individuals using postprandial gallbladder emptying evaluation tested by USG [14]. The different fatty meal used in their study contained a high-fat liquid meal and their patients were different from our patients as for the severity of liver cirrhosis. These differences could account for the above discrepancies. Our study showed that the GBEF of patients with different Child-Pugh grade differed significantly. Other researchers also showed that GBEF decreased in patients with Child-Pugh C cirrhotic patients [23], but this difference was not related to the worsening of liver function. In cirrhotic patients, the level of CCK was higher than in controls [24], presumably due to impaired hepatic function, as CCK-8 is normally metabolized on its first passage through the liver [21]. Gallbladder hypomotility could also be due to the increased nitric oxide production in cirrhotic patients, leading to relaxation of gallbladder smooth muscle or to autonomic neuropathy [25].

A main difference of the present study from previous studies was that we compared the EP of cirrhotic patients with and without gallstones and with different Child-Pugh grades with the EP of normal subjects. Our study showed that the EP of cirrhotic patients was longer than that of normal subjects which means that not only GBEF was lower, but also contraction time or EP was longer than in normal subjects. Our study also showed that the EP of different Child-Pugh grade patients was different. The EP of Child-Pugh A patients was the shortest among three Child-Pugh groups (Figure 2). The cause of EP increasing in Child-Pugh

C cirrhotic patients has not been established.

Limitations of this study included that: a) there are no normal values of GBEF of fatty meal cholescintigraphy in the literature for comparison to our results and b) we did not further follow-up the GBEF and EP of these patients, especially in different Child-Pugh A and B group patients, using cholescintigraphy.

Previous studies reported that the GBEF after CCK stimulation was lower than 35% and the gallbladder motility function was abnormal in cirrhotic patients [26]. However, up to now there are no normal values of GBEF after a fatty meal cholescintigraphy. Based on the present study, we suggested that the study of the indices of gallbladder motility function in post prandial cholescintigraphy should include not only the GBEF, but also EP. We will further follow-up the GBEF and EP of these patients, especially in Child-Pugh A and B patients, using fatty meal cholescintigraphy.

*In conclusion*, the gallbladder ejection fraction (GBEF) of cirrhotic patients was lower and the ejection period (EP) was longer than that of normal subjects. Cirrhotic patients with higher Child-Pugh grade and also with gallstones had lower GBEF and longer EP. It is the opinion of the authors of this paper that the study of the indices of abnormal gallbladder motility should include not only the GBEF, but also the EP.

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*The authors declare that they have no conflicts of interest.*

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Asclepius and his daughter Hygea, Vatican Museum, Rome. Notice the apathetic face of Asclepius, showing power of mind.