

Can gallbladder ejection fraction measured by fatty meal cholescintigraphy diagnose chronic cholecystitis?

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ABSTRACT

Introduction: Despite presence of a body of evidence in support of high accuracy of cholecystokinin cholescintigraphy (CCK-CS), for diagnosis of chronic cholecystitis(CC), some authors have claimed that gallbladder ejection fraction (GBEF) has poor predictive diagnostic values. The purpose of this study was to determine if there is any difference in GBEF between normal individuals and patients with CC.

Methods: In a prospective case-control study, we studied 36 subjects as control group who did not have any abdominal symptoms, or history of abdominal disease or gallstone. Patients group were 42 with established chronic calculous cholecystitis(CCC) who complaining of chronic biliary-like pain and had gallstone on ultrasonography. All subjects underwent gallbladder scintigraphy and GBEF was calculated at 30 and 60 minutes after fatty meal (FM) ingestion.

Results: In control group GBEF at 30-minute and at 60-minute after FM ingestion were 69.54%±21.04% and 84.26%±11.41% respectively while in patients group GBEF at 30-minute was 61.21%±16.01% and at 60-minute was 80.22%±12.57%. No significant difference was noticed between control and patient groups. GBEF didn't show significant difference between different groups based on the number of gallbladder stone, severity of chronic inflammatory (lymphoplasm) cell infiltration, wall thickness and evidence of fibrosis in the gallbladder wall.

Conclusion: Our data are against the diagnostic value of the GBEF as measured by FM-CS in the workup of patients with CC. Thus, interpretation of GBEF should take the proper clinical context into consideration.

Keywords: Gallbladder ejection fraction, Chronic acalculous cholecystitis, Fatty meal, Cholescintigraphy, Chronic calculous cholecystitis

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INTRODUCTION

Based on previous investigations, diminished gallbladder (GB) contractility is the main characteristic of both chronic calculus cholecystitis (CCC) and chronic acalculous cholecystitis (CAC)(1). Patients who demonstrate a low gallbladder ejection fraction (GBEF) in response to cholecystokinin(CCK)- or fatty meal-cholescintigraphy (FM-CS) have a higher probability of symptomatic relief after cholecystectomy (2). It is reported that except for presence of gallstones; symptoms and natural history of both CAC and CCC are identical, as well as the microscopic gallbladder histopathologic changes are similar in both CAC and CCC (1-3). Similar decreased GBEF indicating similar functional abnormalities as well as similar results in relief of symptoms after cholecystectomy have been reported for both CAC and CCC (1). With the current shortage and impending non availability of CCK-8 specially in our country, fatty meals, which release endogenous CCK, have been used as alternative methods for evaluating GB contraction (4,6-8).

Despite a body of evidence in support of high accuracy of CCK- or FM-CS (9), for the diagnosis of chronic cholecystitis(CC) and prediction of symptomatic relief after cholecystectomy (10) , some authors have claimed that GBEF has poor predictive and specificity values (11,12). Now the validity of GBEF for the prediction of outcome after cholecystectomy in CC is a matter of negotiation (13, 14). This may be due to a change in the patient referral pattern as well as CAC and CCC might reflect part of a spectrum of gallbladder chronic inflammation. Despite different published studies, FM-CS has not been utilized in a sufficient number of patients, suspected of having CC (13).

We tried to investigate this controversy by studying patients with CCC as compared to the normal subjects and determine whether

an abnormal FM-CS GBEF correlated with histopathologic evidence of chronic gallbladder inflammation as well as other parameters (the number of stones, gallbladder wall thickness, fibrosis, chronic inflammatory (lymphoplasma) cell infiltration.

METHODS

Two subjects group chosen for the study were control group (36 subjects) who were referred for ^{99m}Tc -sestamibi myocardial perfusion imaging (MPI) and 42 patients with CCC. All subjects gave their written consent to participate in the study after the purpose of the study had been explained to them. This study was approved by the local ethical committee. The result of study on control group was reported in our previous published paper (15, reproduced with permission).

We studied 36 patients (18 men and 18 women) as control group aged 33-87 years (mean: 51.7 ± 10.9 years) who were referred for MPI. All subjects did not have any abdominal symptoms, history of hepatobiliary and gallbladder disease, diabetes mellitus, abdominal surgery, or family history of hepatobiliary disease and were not taking any medication known to affect biliary system. Other medications were discontinued at least 2 days before the study. In the day of performing MPI, all were prescreened with a GB and liver ultrasonography to exclude any abnormality (15). All 36 subjects underwent stress/rest myocardial perfusion imaging using a 2-day protocol started with a MPI examination after stress and continued next day with rest MPI. In the rest phase, after 6 hour fasting 740-925 MBq of ^{99m}Tc -sestamibi was injected intravenously and 90min later the subjects ingested the 120 CC of formula (Humana :containing 10 g fat) (15). In this group; we used ^{99m}Tc -sestamibi instead of

^{99m}Tc -mebrofenin to determine the amount of radioactivity in the gallbladder before and after FM ingestion for calculation of GBEF. ^{99m}Tc -methoxy-methylpropyl isonitrile (sestamibi) has been in use for myocardial perfusion imaging. Normally about 20% of injected dose of ^{99m}Tc -sestamibi is taken up by the liver and secreted into bile. Thus gallbladder is well visualized after injection of ^{99m}Tc -sestamibi (15, 16). The 42 patients (patients group: 19 males and 23 females) aged 24-76 years (mean: 52.99 ± 14.76) with established CCC were referred from the general surgery clinic for FM-CS. The patients complained of chronic biliary-like pain. They had normal liver function but had gallstone on ultrasonography. They were candidate for cholecystectomy, not taking any medication known to affect biliary system before the scintigraphy. After 6–8 h of fasting, each subject underwent cholescintigraphy, receiving 185 MBq of ^{99m}Tc -mebrofenin (^{99m}Tc -BrIDA) intravenously. 60min after tracer injection the subjects ingested the 120 CC of formula (Humana; containing 10 g fat).

Fatty meal

We used 120ml of a commercially available formula (Humana; containing 10g fat) as a cholecystagogue to stimulate GB contraction.

Imaging

Imaging technique was similar in both groups. Anterior images from the abdomen were acquired before the FM ingestion, as

well as at 30- and 60-min after ingestion of FM. The images were obtained in the supine position using a large-field-of-view gamma-camera (E.CAM; Siemens) equipped with high-resolution, low-energy, parallel hole collimator. The images were stored in a 128×128 matrix in the computer.

GBEF Calculation

On the computer display, all regions of interest were drawn for the gallbladder and adjacent liver (Figure 1). After background and decay correction, GBEF was calculated at 30- and 60-min after FM ingestion using formula below (15):

$$\text{GBEF (\%)} = \frac{(\text{net GB counts before FM}) - (\text{net GB counts at 30- or 60-min})}{(\text{net GB counts before FM})}$$

Histopathology examination

The histology of the post cholecystectomy gallbladders in patient group was assessed by an independent expert pathologist for confirmation of chronic cholecystitis. Each specimen was evaluated for changes associated with CC. Number of gallbladder stone, normal or increased gallbladder wall thickness, severity of lymphoplasmic cell infiltration [no infiltration <5, Mild: 5-to-10, Moderate: 10-to-20 and severe lymphoplasmic cell infiltration: >20 lymphoplasmic cells in each high power field on microscopic examination), and existence of fibrosis were recorded.

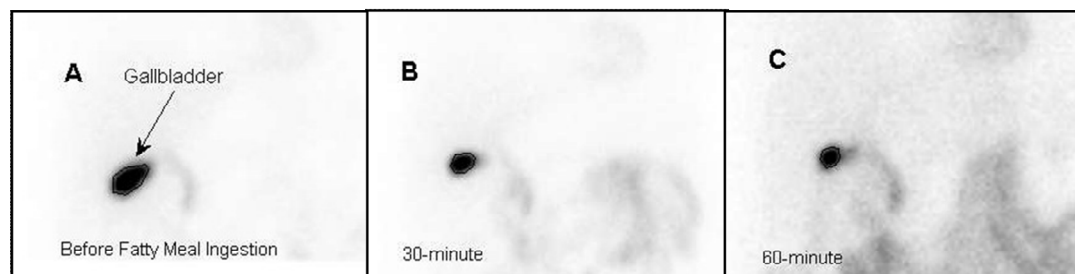


Fig 1. Anterior images from the liver and gallbladder before fatty meal ingestion(A), 30-min after fatty meal ingestion(B) and 60-min after fatty meal ingestion(C) in a subject without chronic cholecystitis underwent ^{99m}Tc -Sestamibi scintigraphy. (15, reproduced with permission).

Table 1. Fatty meal cholescintigraphy gallbladder ejection fraction (GBEF) at 30-min and 60- min in control group and patients with chronic calculous cholecystitis (CCC).

GBEF	Control group	Patients with CCC	<i>p</i> value
GBEF 30-min	69.54%±21.04% (15.1%-100%)	61.21%±16.01% (12.70%-91.65%)	0.051
GBEF 60-min	84.26%±11.41% (40.44% -100%)	80.22%±12.57% (41.41% -98.56%)	0.14

Statistical analysis

Statistical analysis was done using SPSS software (version 11.5). Univariate statistics are expressed as mean± standard deviation (SD). The statistical difference between the two groups was tested by Student's independent sample t-test. One way ANOVA was used for the comparison between multiple groups with Tukey HSD test as post Hoc analysis. A P value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 shows GBEF in control and patient groups. No significant difference was

noticed between control and patient groups in GBEF 30-min ($P=0.051$) as well as in GBEF 60-min ($P=0.14$). GBEF in our control group showed a gaussian distribution. Therefore the 95% confidence interval using mean-2 SD would show lower limit of normal values: 27.46% and 61.44% for FM-CSEF 30min and 60min respectively (15, reproduced with permission).

Figure 2 shows the percentile rank versus the GBEF in control group. In our previous study, we estimated the percentile rank in this group using linear regression (15).

All subjects in patient group had evidence of chronic cholecystitis on histopathology examination.

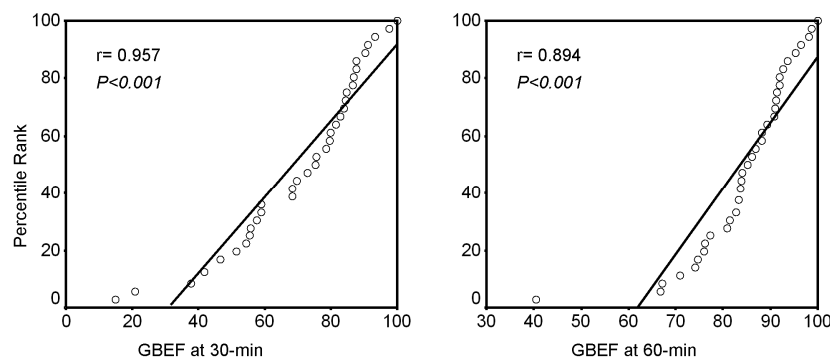
**Fig 2.** Percentile rank for gallbladder ejection fraction at 30-min and at 60-min after fatty meal ingestion in control group (15, reproduced with permission).

Table 2. Fatty meal cholescintigraphy gallbladder ejection fraction (GBEF) at 30-min and 60-min in patient group based on number stones.

GBEF	Number of Gallbladder Stones			<i>p</i>
	One Stone N=10	Two Stones N=3	Stones>2 N=29	
GBEF 30-min	60.46±21.53	53.31±27.12	62.29±12.88	0.65
GBEF 60-min	78.36±18.23	85.21±8.82	80.35±10.72	0.71

Table 3. Fatty meal cholescintigraphy gallbladder ejection fraction (GBEF) at 30-min and 60- min in patient group based on lymphoplasma cell infiltration.

GBEF	Lymphoplasma Cell Infiltration			<i>p</i>
	Mild (13)	Moderate (16)	Severe (13)	
GBEF 30-min	61.92±19.80	64.21±16.84	56.81±9.78	0.46
GBEF 60-min	80.64±15.68	84.51±10.11	74.53±10.30	0.10

All patients had at least one gallbladder stone (1-3) and all of them had evidence of lymphoplasma cell infiltration (mild: 13, moderate: 16 and severe infiltration: 13) (Table 2 and 3). Thirty seven patients from 42 patients had normal wall thickness while 5 patients had increased wall thickness. From 42 patients, 37 patients had evidence of fibrosis in the gallbladder wall (Table 4).

GBEF 30-min and 60-min didn't show significant difference between different groups based on the number of gallbladder stone, severity of lymphoplasma cell infiltration, wall thickness and evidence of fibrosis in the gallbladder wall. When all tests were repeated with inclusion of control group, no significant differences were noticed again.

Table 4. Fatty meal cholescintigraphy gallbladder ejection fraction (GBEF) at 30-min and 60-min in patient group based on existence of increased gallbladder wall thickness and fibrosis.

GBEF	Wall thickness			Existence of Fibrosis		
	Normal (37)	Increased (5)	<i>p</i>	No (N=5)	Yes (N=37)	<i>p</i>
GBEF 30-min	61.59±16.65	58.39±11.03	0.68	70.67±13.12	59.93±16.09	0.16
GBEF 60-min	80.59±13.13	77.50±7.48	0.61	86.12±6.83	79.42±13.01	0.26

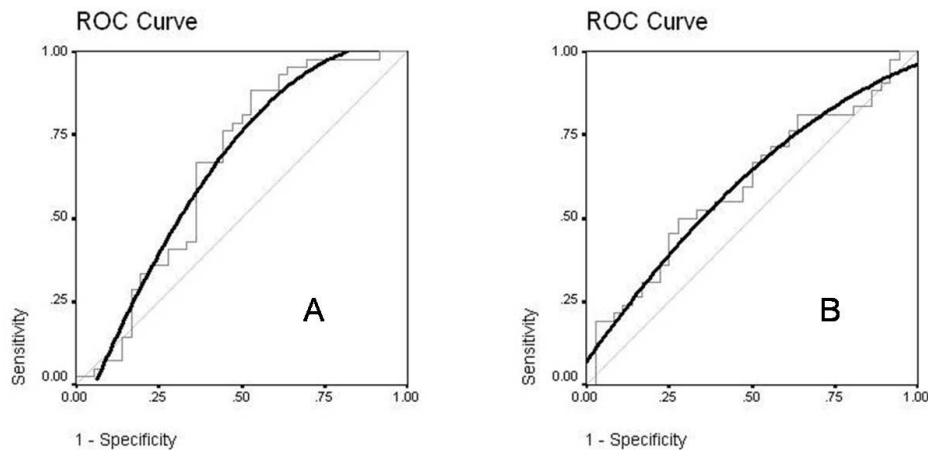
**Fig 3.** Receiver operating characteristic (ROC) curve analysis of fatty meal cholescintigraphy gallbladder ejection fraction (GBEF) at 30-min (A) and 60-min (B). (area under the curves were 0.655 and 0.601 respectively).

Figure 3 shows ROC curve analysis for diagnosis of chronic cholecystitis based on GBEF.

DISCUSSION

In routine practice, calculation of GBEF aids surgeons in their clinical decision making to

determine who have CC and may benefit from cholecystectomy (15, 17, 18). Numerous previous published investigations have reported that a low GBEF has a high accuracy for the diagnosis of CC (3).

For stimulation of GB contraction during cholescintigraphy, we used a common formula which is easily available and

contains sufficient fat (10 g) to produce gallbladder contraction (15). In our previous work which is used as control group in the study, we demonstrated that the gender or body mass index didn't affect the GBEF value. There was no significant difference between women and men or between normal weight, overweight and obese subjects (15, reproduced with permission). Also control group data in our 36 subjects showed a gaussian distribution. Therefore the 95% confidence interval using mean-2 SD would show lower limit of normal GBEF values (15). However observed values in the lower tail of the distribution especially at 30-min may be quite unstable as well as a wide range of GBEF was noticed in these 36 subjects (15). So problems sometimes are seen in clinical situations due to overlap between healthy subjects and patients. So it may be more appropriate to use percentile rank methodology to convey the clinical import of a GBEF (4, 15).

Information about sensitivity and specificity of the GBEF is a matter a debate now (6). Although previous studies have suggested that a GBEF of less than 35% is abnormal and predicts success of cholecystectomy in relieving symptoms (6), nowadays, despite the common use by clinicians and surgeons, the clinical usefulness of CCK-CS has been questioned (19). Raymond et al (20) studied 101 patients (98% with gallbladder stone) and reported that 76% of patients with CC had normal GBEF values (20, 21). Davis et al (22) studied normal volunteers and symptomatic patients and reported that individual variations were so high that no GBEF value could be considered typical either of normal or abnormal (21, 22). There has been some controversy regarding the normal cutoff for the GBEF in response to CCK or FM (23). So an arbitrary cutoff level may be chosen and tested to see how this affects sensitivity and specificity results in healthy and patients subjects (7).

Except for the presence of cholelithiasis, the microscopic gallbladder histopathologic

changes are similar in both CAC and CCC. Reduction in the GBEF indicating similar functional changes is common factor for both CAC and CCC (1).

In the present study, we compared patients with CCC and control group. In this case-control study, we found that there is no statistically significant difference in GBEF at 30-min and 60-min after FM between normal and CCC groups. Our findings question the clinical usefulness of FM-CS in patients with suspected chronic cholecystitis. Figure 3 showed ROC Curve analysis of our findings using control and patients groups. Area under the curve for GBEF 30-min and 60-min was 0.65 and 0.61 respectively which is relatively low. Bartel et al. (24) studied 30 patients with abdominal pain and reported that the area under the ROC curve was 0.963 for 60min. Based on our data, if we use 28% and 61% as cutoff values for GBEF 30-min and 60-min after FM respectively, the sensitivity of the test will be 4.76% and 9.52% respectively for diagnosis of chronic cholecystitis while the specificity test will be 94.44% and 97.22% respectively. If we use higher values such as; 45% cutoff value for GBEF 30-min, sensitivity and specificity will be 9.52% and 86.11% respectively or 70% cutoff value for GBEF 60-min they will be 21.43% and 91.67% respectively. More than 20 published studies are in favor of the utility of CS for the diagnosis of chronic cholecystitis. However, similar to our results, about 6 studies have not found CS helpful for predicting response to cholecystectomy (25). However, in our study we used histopatologic confirmation of chronic cholecystitis with no evaluation of patient's symptoms before the cholecystectomy and postoperative resolution of the symptoms. Ozden et al in a case-control study reported a high rate of symptom resolution in patients with a normal GBEF regardless of whether they underwent cholecystectomy or not (26). Numerous previous studies showed

complete symptomatic relief after cholecystectomy in 85% to 100% of patients who had a low GBEF. But, others question the sensitivity and specificity of cholescintigraphy and its ability for prediction of successful outcome (9). It was suggested that a significant number of patients with CAC would have normal gallbladder emptying (27). In another study, replication of symptoms following intravenous injection of CCK as part of a CCK-CS appeared to be superior to GBEF in predicting symptomatic relief following cholecystectomy (28). The data would suggest that normal GBEF is not reliable to rule out chronic inflammation (28). Possible explanations for these discrepancies between studies are referral biases, the retrospective researches and the limited samples in many studies. It is to mention that few of studies have a high rank on evidence-based medicine analysis (25). On the other hand, another explanation for our results is that physicians are comfortable in recommending cholecystectomy soon after detection of gallstones (CCC) with ultrasonography (15), but they seem to hesitate to recommend it for CAC patients (10). It should be noted that FM GBEF likely depends on the content of the meal, amount of fat in meal, and the methodology used. The gastric-emptying rate may also affect FM GBEF (15).

In early published studies, patients with CAC had a relatively high pretest probability. They had been worked up extensively to exclude other causes for their symptoms and had been followed for months or years (25).

On the other hand, a change in the patient referral pattern for CS has been noticed (3). Interestingly, as the popularity of this test has increased, many patients are being referred with less-extensive workups than those in early published investigations and often referred sooner than before, so utility of the GBEF seems to have decreased (25,26). The accuracy of CS in this new

patient referral group is uncertain (3). A meta-analysis which is done by Delgado-Aros et al (14) failed to show an increased likelihood of a positive outcome after cholecystectomy in patients with suspected chronic cholecystitis and reduced GBEF compared to those with normal GBEF. They concluded that there are no valid data to support the use of the GBEF in the workup of patients with recurrent abdominal pain suggestive of biliary disease (14).

It was postulated that CAC and CCC might reflect part of a spectrum of gallbladder chronic inflammation (26). Presumably, biliary pain may occur at any point in this spectrum (26). Thus, interpretation of FM CS should take into consideration the proper clinical context, with knowledge of the patient's clinical history, symptoms duration, medications, diagnostic evaluation, the clinical setting and otherwise negative medical workups that have excluded other diseases (3, 25). This test should not be used as a shortcut in workup of the patient (3).

So further studies, with careful design of randomized, controlled clinical trials are needed to answer definitively these important clinical questions in functional biliary pain (14). These studies require assessment of outcome and long-term follow-up of the patients. Further studies are also needed to evaluate the role of CCK- or FM CS in the patients with cholelithiasis, with or with no typical or atypical symptoms (19).

Study limitations

To avoid the radiation exposure to normal volunteers, we studied a group of patients suspected with coronary artery disease who referred for myocardial perfusion imaging. As these patients had normal GB ultrasonography and had no biliary disease, they can be considered as normal subjects. We used Tc99m-Sestamibi in control group (15). In our study we used histopatologic confirmation of chronic cholecystitis in patients with cholelithiasis with no evaluation of patient's symptoms before the

cholecystectomy and postoperative resolution of the symptoms.

CONCLUSION

Our data are against the use of the FM GBEP in the workup of patients with chronic cholecystitis. Thus, interpretation of FM GBEP should take into consideration the proper clinical context.

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