Reproducibility of Gallbladder Ejection Fraction Measured by Fatty Meal Cholescintigraphy

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Abstract

Purpose There are conflicting data in the literature regarding the reproducibility of the gallbladder ejection fraction (GBEF) measured by fatty meal cholescintigraphy (CS). We aimed to test the reproducibility of GBEF measured by fatty meal CS.

Methods Thirty-five subjects (25 healthy volunteers and 10 patients with chronic abdominal pain) underwent fatty meal CS twice in order to measure GBEF1 and GBEF2. The healthy volunteers underwent a repeat scan within 1–13 months from the first scan. The patients underwent a repeat scan within 1–4 years from the first scan and were not found to have chronic acalculous cholecystitis (CAC). Our standard fatty meal was composed of a 60-g Snickers chocolate bar and 200 ml full-fat yogurt.

Results The mean $\pm$ SD values for GBEF1 and GBEF2 were $52 \pm 17\%$ and $52 \pm 16\%$, respectively. There was a direct linear correlation between the values of GBEF1 and GBEF2 for the subjects, with a correlation coefficient of 0.509 ($p=0.002$). Subgroup data analysis of the volunteer group showed that there was significant linear correlation between volunteer values of GBEF1 and GBEF2, with a correlation coefficient of 0.473 ($p=0.017$). Subgroup data analysis of the non-CAC patient group showed no

significant correlation between patient values of GBEF1 and GBEF2, likely due to limited sample size.

Conclusions This study showed that fatty meal CS is a reliable test in gallbladder motility evaluation and that GBEF measured by fatty meal CS is reproducible.

Keywords Gallbladder ejection fraction · Reproducibility · Cholescintigraphy · Fatty meal · CCK

Introduction

Measurement of gallbladder ejection fraction (GBEF) by cholescintigraphy (CS) is considered the test of choice for confirming the diagnosis of chronic acalculous cholecystitis (CAC) [1–4]. Gallbladder emptying has several variables, including latent period, GBEF, and patterns of gallbladder emptying [5]. However, GBEF is the single most important gallbladder emptying variable in the diagnosis of CAC [5]. Low GBEF is the main abnormal finding upon which the diagnosis of CAC is usually confirmed [1–5]. Cholecystokinin (CCK) is widely used choleragogue stimulant to induce gallbladder contraction in CS [1–4]. Several investigators have found a fatty meal to be a physiologic, easy to handle and cheap alternative to CCK to induce gallbladder contraction in CS [4–8]. There are limited and conflicting data in the literature regarding the reproducibility of GBEF measured by fatty meal CS. Thus, GBEF measured by fatty meal CS was reported in three studies to be reproducible [9–11], whilst another study reported that it was not reproducible [12]. We aimed to study the reproducibility of GBEF measured by fatty meal CS prospectively on a group of healthy volunteers and retrospectively on a group of non-CAC patients who suffered from chronic abdominal pain.

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Materials and Methods

Ethics

This study was approved on July 23, 2008 by the Committee for Human Studies at Jordan University of Science and Technology. Written consent was obtained from all volunteers after explaining the purpose of the study.

Subjects

The study was performed at King Abdullah University Hospital (Irbid, Jordan) from November 16, 2008 to January 10, 2010. Thirty-five subjects (25 volunteers

prospectively and 10 patients retrospectively) underwent fatty meal CS in order to measure GBEF1. On another occasion, fatty meal CS was repeated in all subjects in order to measure GBEF2 (Table 1). The volunteers were recruited from the hospital staff and the records of the patients were retrieved from the hospital records. The mean age was 34.3 years, with a range of 21–70 years. There were 13 females and 22 males. All subjects had normal biliary ultrasonography. Women were neither pregnant nor lactating.

The volunteers were asymptomatic for any hepatobiliary disease. All volunteers were healthy and did not take any medication that potentially might affect gallbladder motility. The patients had chronic biliary-like pain

Table 1 Subject characteristics with paired values of GBEF from duplicate studies

No.	Subject	Age	Gender	Interval (months)	GBEF1	GBEF2
1	Volunteer	40	M	3	0.43	0.36
2	Volunteer	30	M	2	0.25	0.26
3	Volunteer	37	F	13	0.45	0.53
4	Volunteer	38	M	3	0.4	0.4
5	Volunteer	25	F	12	0.54	0.61
6	Volunteer	26	M	2	0.57	0.35
7	Volunteer	32	M	12	0.5	0.66
8	Volunteer	28	M	10	0.53	0.36
9	Volunteer	35	M	1	0.2	0.48
10	Volunteer	31	F	4	0.69	0.64
11	Volunteer	24	M	2	0.61	0.96
12	Volunteer	27	M	13	0.67	0.7
13	Volunteer	24	M	3	0.65	0.76
14	Volunteer	40	F	12	0.51	0.35
15	Volunteer	36	M	1	0.55	0.35
16	Volunteer	27	M	11	0.61	0.54
17	Volunteer	27	M	12	0.14	0.27
18	Volunteer	25	M	11	0.78	0.46
19	Volunteer	24	M	2	0.56	0.47
20	Volunteer	23	M	12	0.57	0.48
21	Volunteer	38	F	9	0.26	0.4
22	Volunteer	32	M	11	0.33	0.59
23	Volunteer	29	F	2	0.55	0.7
24	Volunteer	43	M	3	0.67	0.46
25	Volunteer	21	M	12	0.74	0.6
26	Patient	62	F	8	0.31	0.24
27	Patient	37	M	6	0.7	0.44
28	Patient	28	F	44	0.3	0.45
29	Patient	46	F	3	0.52	0.5
30	Patient	28	M	24	0.3	0.58
31	Patient	28	M	12	0.6	0.6
32	Patient	70	F	18	0.7	0.6
33	Patient	38	F	5	0.67	0.67
34	Patient	47	F	12	0.57	0.75
35	Patient	55	F	24	0.77	0.75

M male, *F* female

suspicious for CAC. However, the final diagnosis was not CAC since the first and second fatty meal CS tests were normal. In addition, they improved on medical management, which was either empirical treatment for gastritis/irritable bowel syndrome or clinical observation. Of note, none of the medications taken by the patients was known to affect gallbladder motility.

Technique

The subjects fasted for 4–8 h before receiving an intravenous injection of Tc99m-hepatic iminodiacetic acid (92.5 MBq for volunteers and 185 MBq for patients) while lying supine underneath a large-field-of-view gamma camera (Siemens E.CAM or Toshiba GCA) fitted with a low-energy, all-purpose, parallel-hole collimator. The volunteers underwent repeat scan within 1–13 months from the first scan. Six patients, three patients and one patient underwent repeat scan within 1 year, 2 years and 4 years from the first scan respectively.

Image Acquisition

Gallbladder filling-phase images were obtained at one frame per minute for 60 min. Gallbladder emptying-phase image data were collected separately at one frame per minute for another 30 min. Both studies were recorded on a 64×64×16 computer matrix. The standard fatty meal (60 g Snickers chocolate bar with 16.4 g fat and 200 ml full-fat yogurt with 6 g fat) was ingested in the sitting position, immediately after the gallbladder filling-phase and 15 min before the gallbladder emptying-phase data collection in the supine position. Each fatty meal included on average 20 g fat, 16 g carbohydrate, 16 g protein, and 320 calories.

Image Processing

Computer processing was performed. On the computer display, regions of interest were drawn for the gallbladder and adjacent liver. Background- and decay-corrected time-activity curves were generated. GBEF was calculated using the maximum counts minus the minimum counts divided by the maximum counts (Fig. 1). Minimum counts were taken at the end of gallbladder emptying-phase (105 min from the beginning of the gallbladder filling-phase).

Statistical Analysis

A paired-samples *t*-test was used to analyze the difference in repeated GBEF values taken from the same subjects. Means and standard deviations were used to describe data. A *p* value of <0.05 was considered significant. Pearson's correlation coefficient was used to assess the correlation

Fig. 1a–c Fatty meal cholescintigraphy time-activity curves. **a** Time-activity curve of gallbladder filling phase. **b** Time-activity curve of gallbladder emptying phase. **c** Calculation of GBEF

between values of GBEF1 and GBEF2. Statistical analyses were performed using the Statistical Package for Social Sciences, version 15 (SPSS, Chicago, IL, USA).

Results

Table 1 shows the actual paired values of GBEF from duplicate studies on 35 subjects. GBEF1 values ranged

Fig. 2 Scatter plot showing the paired values of GBEF from duplicate studies on 35 subjects

between 14% and 78% with a mean $\pm$ SD of $52 \pm 17\%$. GBEF2 values ranged between 24% and 96% with a mean $\pm$ SD of $52 \pm 16\%$. There was no significant difference between the mean values of GBEF1 and GBEF2 ($p > 0.90$). Data analysis also showed that there was a direct linear correlation between the values of GBEF1 and GBEF2 of the subjects, with a correlation coefficient of 0.509 ($p = 0.002$) (Fig. 2). Subgroup data analysis of the volunteer group ($n = 25$) showed no significant difference between mean $\pm$ SD values of GBEF1 and GBEF2, which were $51 \pm 17\%$ and $51 \pm 17\%$ ($p = 0.98$). In addition, there was significant linear correlation

between volunteer values of GBEF1 and GBEF2, with a correlation coefficient of 0.473 ($p = 0.017$). Subgroup data analysis of the non-CAC patient group ($n = 10$) showed no significant difference between the mean $\pm$ SD values of GBEF1 and GBEF2, which were $54 \pm 18\%$ and $56 \pm 15\%$ ($p = 0.78$). However, there was no significant correlation between the patient values of GBEF1 and GBEF2, with a correlation coefficient of 0.59 ($p = 0.073$). The limited sample size for the non-CAC patient group ($n = 10$) seems to be responsible for the non-significant correlation between GBEF1 and GBEF2 values.

Discussion

The main utility of cholescintigraphy is in the confirmation or exclusion of CAC in patients who have a high clinical suspicion of CAC [1–4, 13–15]. Gallbladder emptying has several variables, including latent period, GBEF, and patterns of gallbladder emptying [5]. However, GBEF is the single most important gallbladder emptying variable in the diagnosis of CAC [5]. Although CCK is widely and routinely used in CS, a fatty meal was found by several investigators to be a cheap, easy to handle, physiologic alternative to CCK [4–7]. The literature has limited and conflicting data regarding the reproducibility of GBEF measured by fatty meal CS.

In the present study, the reproducibility of GBEF measured by fatty meal CS was studied prospectively on a group of healthy volunteers and retrospectively on a group of non-CAC patients who suffered from chronic abdominal pain. For this purpose, fatty meal CS was performed 70 times on 35 subjects (two scans for each

Table 2 Published reports on the reproducibility of GBEF measured by fatty meal CS, CCK CS and fatty meal sonography

Study and year	Method	Cholagogue stimulant	No. of subjects	Healthy subjects	Patients	GBEF reproducibility
Xynos et al., 1994 [9]	Cholescintigraphy	Fatty meal	30	6	4 (duodenal ulcer) 20 (gastric surgery)	Yes
Mackie et al., 1987 [10]	Cholescintigraphy	Fatty meal	9	9	0	Yes
Fullarton et al., 1990 [12]	Cholescintigraphy	Fatty meal	19	19	0	No
Buchpiguel et al., 1996 [11]	Cholescintigraphy	Fatty meal	10	10	0	Yes
Buchpiguel et al., 1996 [11]	Ultrasonography	Fatty meal	10	10	0	Yes
Donald et al., 1991 [16]	Ultrasonography	Fatty meal	30	30	0	No
Yap et al., 1991 [17]	Cholescintigraphy	CCK	20	20	0	Yes
Pons et al., 2003 [18]	Cholescintigraphy	CCK	44	0	44 (CAC)	Yes
Krishnamurthy et al., 2004 [19]	Cholescintigraphy	CCK	52	13	27 (CAC) 6 (CCC) 6 (opioid)	Yes
Fullarton et al., 1990 [12]	Cholescintigraphy	CCK	19	19	0	No

CAC chronic acalculous cholecystitis, CCC chronic calculous cholecystitis

subject). Our results showed that GBEF measured by fatty meal CS was reproducible. However, further investigation is needed to test the reproducibility of fatty meal CS on a large sample of CAC patients with low GBEF values and non-CAC patients with normal GBEF values.

Table 2 summarizes the published reports on GBEF reproducibility measured by fatty meal CS, by fatty meal sonography and by CCK CS. Xynos et al. [9] and Mackie et al. [10] studied the reproducibility of GBEF by fatty meal CS on 30 and 9 subjects respectively. They showed that GBEF values were reproducible, with a correlation coefficient of 0.84 and 0.95 respectively. Buchpiguel et al. [11] studied the reproducibility of GBEF by fatty meal CS and by fatty meal ultrasonography on ten healthy volunteers and reported that both techniques were reproducible, with correlation coefficients of 0.41 and 0.48 respectively.

Yap et al. [17] studied the reproducibility of GBEF by CCK CS on 20 healthy volunteers and found it reproducible with 11.7% mean variability between repeated tests. Pons et al. [18] and Krishnamurthy et al. [19] studied the reproducibility of GBEF by CCK CS on 44 subjects and 52 subjects respectively and found it reproducible with correlation coefficients of 0.439 and 0.73 respectively. On the other hand, Donald et al. [16] studied gallbladder contractility in 30 healthy subjects by fatty meal ultrasonography and reported wide GBEF variability within each subject. However, their study focused on variability of GB volumes and GBEF values between and within the subjects. Although they reported the percentage of GBEF variation in the same subjects, they did not calculate the statistical correlation between the repeated GBEF values obtained from the same subjects. Also, Fullarton et al. [12] studied the reproducibility of GBEF by fatty meal CS and by CCK CS in 19 healthy subjects. They demonstrated poor reproducibility of GBEF by CCK CS and improved but still variable fatty meal-induced gallbladder contraction. However, their study had a limited number of subjects for both CCK CS and fatty meal CS, which might justify their conclusion of the non-reproducibility of this technique.

Our standard meal contained more than 10 g fat, since a minimum of 10 g fat is needed to induce gallbladder contraction [20]. It is argued that the test meal could have a variable effect on gallbladder contraction as a result of fat content and liquid or solid meal [6, 7, 14]. However, our laboratory standard meal was used in both the first scan and the repeat scan in all individuals. Accordingly, the fat content of our test meal likely did not affect the results of our study. In this context, GBEF measured by CCK CS is also variable—depending on the dose, dose rate, and duration of infusion of CCK. Hence, it is important to establish a local normal value using standard CCK protocol [18, 21, 22]. The CCK protocol was the same in the first

and repeat scans in those studies that tested the reproducibility of GBEF measured by CCK CS [12, 17–19].

The mean interval between the first scan and repeat scan in our study was 10 months. In reproducibility studies it is better to repeat the test in few weeks to avoid a “time factor” effect on the results. However, Krishnamurthy et al. [19] showed that in CCK CS scans repeated after many months or years, GBEF was reproducible in normal subjects as well as in CAC patients and chronic calculous cholecystitis (CCC) patients. They showed that a normal GBEF takes many years to become abnormal as five of 17 (29%) subjects had a mean duration 52.6 months before the normal GBEF values became low. They also showed that low GBEF in CAC/CCC patients will not recover with time. Rather, GBEF in CAC/CCC patients continues to deteriorate as the mean reduction in GBEF in CAC/CCC patients was 7.18% during the first 12 months, 16.12% between 13 and 47 months, and 23.5% between 48 and 168 months. The mean interval between the first and repeat scans in our subjects was not long enough for a healthy subject to develop CAC with low GBEF. In addition, this applies to our ten patients who almost had normal GBEF.

Conclusion

This study showed that fatty meal CS is a reliable test in gallbladder motility evaluation and that GBEF measured by fatty meal CS is reproducible. However, further investigation is needed to test the reproducibility of fatty meal CS on a large sample of patients with normal and low GBEF values.

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References

1. Misra Jr DC, Blossom GB, Fink-Bennett D, Glover JL. Results of surgical therapy for biliary dyskinesia. *Arch Surg.* 1991;126:957–60.
2. Sorenson MK, Fancher S, Lang NP, Eidt JF, Broadwater JR. Abnormal gallbladder nuclear ejection fraction predicts success of cholecystectomy in patients with biliary dyskinesia. *Am J Surg.* 1993;166:672–4.
3. Mishkind MT, Pruitt RF, Bambini DA, Hakenewerth AM, Thomason MH, Zuger JH, et al. Effectiveness of cholecystokinin-stimulated cholescintigraphy in the diagnosis and treatment of acalculous gallbladder disease. *Am Surg.* 1997;63:769–74.
4. Al-Muqbel K, Bani Hani M, Daradkeh M, Rashdan A. Usefulness of fatty meal-stimulated cholescintigraphy in the diagnosis and treatment of chronic acalculous cholecystitis. *Ann Nucl Med.* 2009;23:137–42.
5. Al-Muqbel KM. Diagnostic value of gallbladder emptying variables in chronic acalculous cholecystitis as assessed by fatty meal cholescintigraphy. *Nucl Med Commun.* 2009;30:669–74.

6. Krishnamurthy GT, Brown PH. Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction. *J Nucl Med.* 2002;43:1603–10.
7. Ziessman HA, Jones DA, Muenz LR, Agarwal AK. Cholecystokinin cholescintigraphy: methodology and normal values using a lactose-free fatty-meal food supplement. *J Nucl Med.* 2003;44:1263–6.
8. Bartel TB, Juweid ME, Ponto JA, Graham MM. Corn oil emulsion: a simple cholecystagogue for diagnosis of chronic acalculous cholecystitis. *J Nucl Med.* 2005;46:67–74.
9. Xynos E, Pechlivanides G, Zoras OJ, Chrysos E, Tzovaras G, Fountos A, et al. Reproducibility of gallbladder emptying scintigraphic studies. *J Nucl Med.* 1994;35:835–9.
10. Mackie CR, Baxter JN, Grime JS, Hulks G, Cuschieri A. Gallbladder emptying in normal subjects—a data base for clinical cholescintigraphy. *Gut.* 1987;28:137–41.
11. Buchpiguel CA, Sapienza MT, Vezzozzo DP, Rockman R, Cerri GG, Magalhães AE. Gallbladder emptying in normal volunteers. Comparative study between cholescintigraphy and ultrasonography. *Clin Nucl Med.* 1996;21:208–12.
12. Fullarton GM, Meek AC, Gray HW, Bessent RG. Gallbladder emptying following cholecystokinin and fatty meal in normal subjects. *Hepatogastroenterology.* 1990;37 Suppl 2:45–8.
13. Ziessman HA. Cholecystokinin cholescintigraphy: victim of its own success? *J Nucl Med.* 1999;40:2038–42.
14. Kloiber R, Molnar CP, Shaffer EA. Chronic biliary-type pain in the absence of gallstones: the value of cholecystokinin cholescintigraphy. *AJR Am J Roentgenol.* 1992;159:509–13.
15. Fink-Bennett D, DeRidder P, Kolozsi WZ, Gordon R, Jaros R. Cholecystokinin cholescintigraphy: detection of abnormal gallbladder motor function in patients with chronic acalculous gallbladder disease. *J Nucl Med.* 1991;32:1695–9.
16. Donald JJ, Fache JS, Buckley AR, Burhenne HJ. Gallbladder contractility: variation in normal subjects. *AJR Am J Roentgenol.* 1991;157:753–6.
17. Yap L, Wycherley AG, Morphet AD, Tooouli J. Acalculous biliary pain: cholecystectomy alleviates symptoms in patients with abnormal cholescintigraphy. *Gastroenterology.* 1991;101:786–93.
18. Pons V, Sopena R, Hoyos M, Garrigues V, Cano C, Nos P, et al. Quantitative cholescintigraphy: selection of random dose for CCK-33 and reproducibility of abnormal results. *J Nucl Med.* 2003;44:446–50.
19. Krishnamurthy GT, Krishnamurthy S, Brown PH. Constancy and variability of gallbladder ejection fraction: impact on diagnosis and therapy. *J Nucl Med.* 2004;45:1872–7.
20. Stone BG, Ansel HJ, Peterson FJ, Gebhard RL. Gallbladder emptying stimuli in obese and normal-weight subjects. *Hepatology.* 1992;15:795–8.
21. Ziessman HA. Cholecystokinin cholescintigraphy: clinical indications and proper methodology. *Radiol Clin North Am.* 2001;39:997–1006.
22. Ziessman HA, Fahey FH, Hixson DJ. Calculation of a gallbladder ejection fraction: advantage of continuous sincalide infusion over the three-minute infusion method. *J Nucl Med.* 1992;33:537–41.