

Is abnormal gallbladder ejection fraction hokum? Retrospective chart review of gallbladder ejection fraction and subsequent postoperative symptom relief, surgical pathology, and current literature review

ABSTRACT

The purpose of this report is to investigate the clinical importance of increased or decreased gallbladder ejection fraction (GBEF) and ultrasound findings for biliary dyskinesia by evaluating postsurgical symptom relief and surgical pathology. Single institution electronic medical record review was prepared for patients who underwent hepatobiliary iminodiacetic acid (HIDA) scan with GBEF and cholecystectomy between January 2013 and March 2020. Relevant data included patient demographics, ultrasound results, surgical pathology, HIDA with GBEF results, and postoperative symptom relief at the time of follow-up. Student's *t*-test was also utilized for additional statistical analysis. A total of 67 patients underwent cholecystectomy within a 1-month period of time after HIDA with GBEF. Of these patients, 97% had findings consistent with chronic cholecystitis and 3% of the patients demonstrated both acute and chronic cholecystitis surgical pathology. Fifty-seven percent of the patients demonstrated a GBEF <38%, 30% had a GBEF >80%, and 13% had a GBEF 38%–80% with a postoperative symptom resolution around 82%, 77%, and 100%, respectively. GBEF alone may not be determinative regarding gallbladder pathology or postoperative symptom relief in patients that present with typical symptoms. Regarding dyskinetic gallbladders, elevated and decreased GBEF groups were not significantly different in terms of surgical pathology or symptom relief. These patients may benefit from being treated as a single group rather than as separate entities. Elevated and decreased GBEF groups demonstrated mostly normal ultrasound results that raised concern for the utility of ultrasound as a rule out test for gallbladder inflammation.

Keywords: Biliary dyskinesia, chronic cholecystitis, elevated gallbladder ejection fraction

INTRODUCTION

Hepatobiliary iminodiacetic acid (HIDA) provides functional information that compliments anatomic imaging such as ultrasound or computed tomography. Technetium-99m labeled radiopharmaceutical is administered intravenously and secreted by hepatocytes in nonconjugated form into a biliary system, entering a gallbladder and subsequently into a second portion of the duodenum, all of which occur after an hour of the initial injection.^[1]

A normal HIDA scan demonstrates blood pool activity, followed by a rapid hepatic uptake, and subsequently, visualization of

radiopharmaceutical activity in the gallbladder and the small bowel, usually within an hour.^[2]

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In the setting of acute cholecystitis, the initial insult is thought to be cystic duct obstruction. Cystic duct obstruction is demonstrated by a lack of filling in the gallbladder. Additional steps, when the gallbladder is not seen in the initial images, include administration of morphine to induce sphincter of the Oddi constriction with imaging for an additional 20–30 min or 4 h delayed imaging.^[1]

HIDA imaging provides functional information to aid evaluation of biliary dyskinesia. Once gallbladder filling has been demonstrated, cholecystokinin (CCK) analog is administered to stimulate gallbladder contraction enabling investigators to quantify the ejection fraction of the gallbladder.

Despite HIDA being available since 1976, the standard of CCK cholescintigraphy for functional gallbladder disease was established more recently based on multidisciplinary meetings held in 2010.^[3] 0.02mcg/kg of CCK infused over 60 min was recommended as a standard protocol to obtain the gallbladder ejection fraction (GBEF). Normal GBEF was defined as being $\geq 38\%$.^[4]

Chronic cholecystitis can exhibit multiple HIDA findings including normal (38%–90%) gallbladder visualization after an hour in the setting of normal biliary and bowel transit, delayed gallbladder filling relative to small bowel but within the 1st hour, normal gallbladder filling with delayed biliary to bowel transit, slow/irregular/eccentric gallbladder filling, very small or septa across the gallbladder, nonvisualized gallbladder, low GBEF, or any combination of above.^[2]

Until recently, there had been limited literature regarding the significance of an elevated gallbladder ejection. In 2019, one study showed 90% of patients with elevated GBEF demonstrated chronic cholecystitis on surgical pathology.^[5] Lindholm *et al.* demonstrated GBEF $> 80\%$ in pediatric patients with chronic cholecystitis who underwent cholecystectomy.^[6] Another study in the pediatric/young adult population demonstrated no significant relation with elevated or low GBEF and cholecystitis pathology ($P > 0.05$).^[7]

Our hypothesis is that GBEF may not play a major role in patient outcomes in the setting of chronic cholecystitis.

MATERIALS AND METHODS

A retrospective medical record review was made for patients from a single institution that underwent HIDA with ejection fraction and cholecystectomy between January 2013 and March 2020 upon the institutional review board approval. Of

these, only patients who underwent cholecystectomy within a 1-month period from HIDA were included for the final analysis to exclude any possible new pathology development. The primary endpoint included surgical pathology findings.

The information collection included age, sex, calculated body mass index (BMI), ultrasound results, surgical pathology, HIDA with GBEF results, presenting symptoms including nausea, vomiting, and abdominal pain, and postoperative symptom relief at the time of follow-up. Presenting and postoperative symptoms were collected from history and physical and postoperative follow-up visit clinical notes, respectively.

HIDA with GBEF was performed at two different facilities utilizing the same protocol and patient preparation using mostly technetium-99m labeled mebrofenin (57 of 67) and less frequently with technetium-99m labeled disofenin (10 of 67). The patient was kept nothing by mouth (NPO) status at least 4 h before the study. If the patient had prolonged NPO status reaching over 24 h, the patient was given a onetime dose of sincalide, synthetic C-terminal octapeptide of CCK, 1 ug before HIDA to prevent false-positive study due to full gallbladder with bile secondary to prolonged starvation. Current medications were reviewed giving particular attention to recent opioid administration leading to delay in the study for 4 half-lives if given any opioids.

Technetium-99m mebrofenin (bromo-2, 4, 6-trimethylacetanilido iminodiacetic acid) was prepared using the Bracco Diagnostics kit and Tc-99m disofenin (2, 6-diisopropylacetanilido iminodiacetic acid) was prepared using the Hepatolite Diagnostic kit in standard fashion per manufacture protocol. The patient dose was averaging 7.5 mCi for the population who underwent cholecystectomy within 1 month of HIDA with GBEF.

For GBEF, gallbladder stimulation was induced by intravenous infusion of sincalide at 0.02ug/kg over 60 min. The images were acquired using Skylights (Philips), Forte (Philips), or Orbiter (Siemens) gamma cameras using a large field of view and low-energy high-resolution collimator. Dynamic images were obtained starting at intravenous radiopharmaceutical injection continuing for 60 min in 60 frames/s rate which was reformatted as 5-min images.

Following imaging acquisition, the regions of interest was drawn by technologists around the gallbladder and adjacent liver for the background using three different commercially available software. GBEF was then calculated from the gallbladder time activity curve using $GBEF (\%) = (\text{maximum gallbladder count} - \text{minimum gallbladder count}) \times 100 /$

maximum gallbladder count. Student's *t*-test was also utilized for statistical analysis.

RESULTS

A total of 132 patients underwent cholecystectomy following GBEF. Of these patients, only one patient demonstrated normal and another patient demonstrated cholesterolosis on surgical pathology. The remainder of 130 patients demonstrated acute, acute and chronic, mild chronic, and chronic cholecystitis on surgical pathology. Approximately half of these patients (67 of 130) underwent cholecystectomy within a 1-month period after HIDA with GBEF. The rest of the patients underwent cholecystectomy at various intervals ranging from just over 1 month to 4 years.

Sixty-seven patients underwent cholecystectomy within a 1-month period after HIDA with GBEF. Of these patients, 97% had chronic cholecystitis and 3% of the patients had findings consistent with both acute and chronic cholecystitis

on surgical pathology. (Interestingly, there were no normal surgical pathology results who met the criteria).

Thirty-eight patients with GBEF <38% underwent cholecystectomy within a 1-month period of time [Figure 1]. Of these patients, 3% demonstrated acute and chronic cholecystitis on surgical pathology and 97% demonstrated chronic cholecystitis. The surgical pathology result was not statistically, significantly different when compared to elevated GBEF ($P = 0.65$). The average age for this group was 39.9 years and ranged from 13 to 93 years. BMI ranged from 16.1 to 56.4 kg/m², averaging 30.9 kg/m². Eighty-four percent of the patients were female and 16% of the patients were male [Table 1]. Eighty-two percent of GBEF <38% patients underwent ultrasound shortly before HIDA, of which 61% demonstrated no evidence of acute cholecystitis, 35% were inconclusive for acute cholecystitis, and 3% had sonographic evidence of acute cholecystitis [Table 2]. The ultrasound results were not statistically, significantly different when compared to the elevated GBEF group ($P = 0.40$). Seventy-four percent of GBEF <38% patients had a documented follow-up

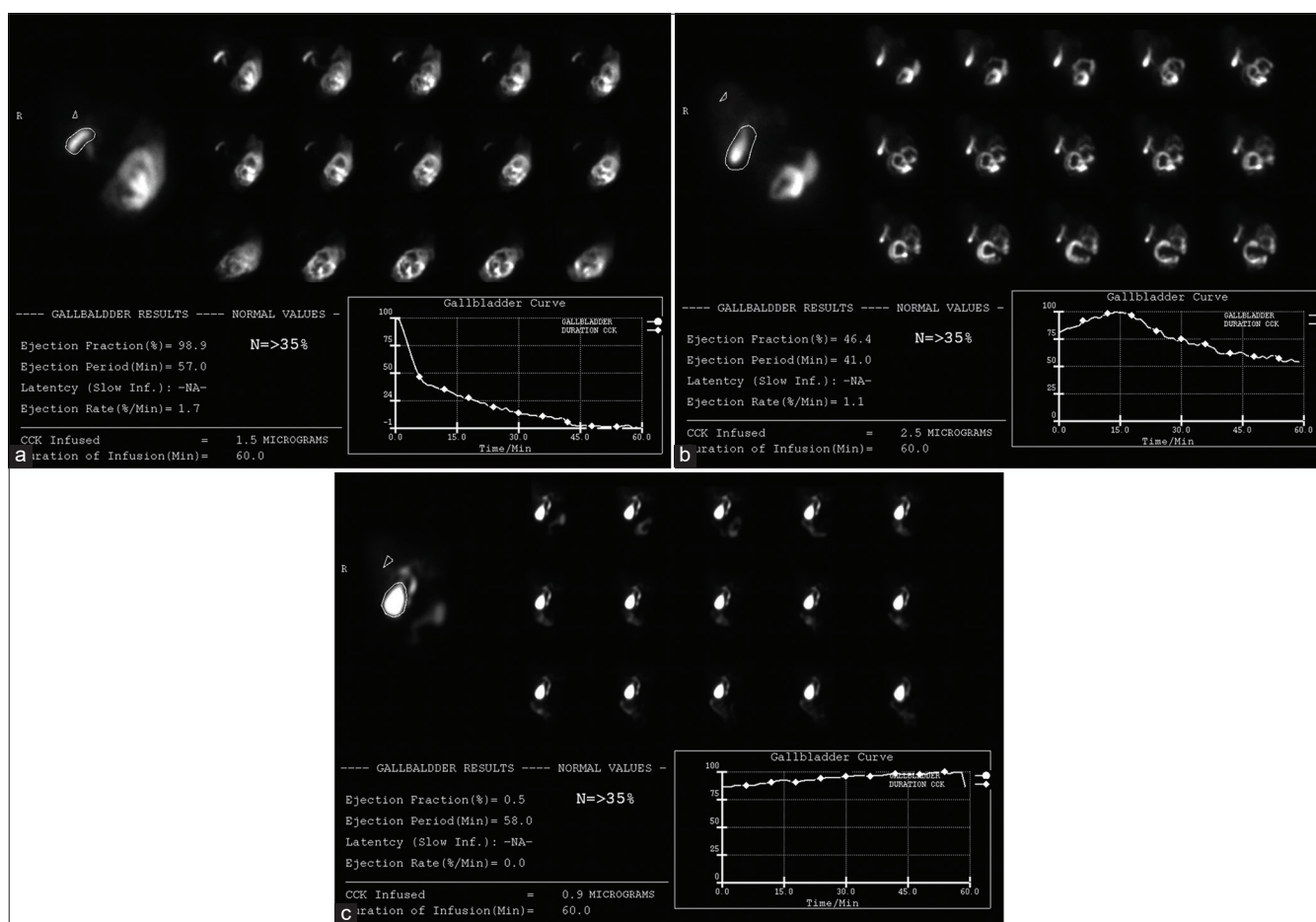


Figure 1: Examples of elevated, normal, and decreased gallbladder ejection fraction. All three patients demonstrated chronic cholecystitis on surgical pathology. (a): Elevated gallbladder ejection fraction as 98.9%, (b): Normal gallbladder ejection fraction as 46.4%, (c): Decreased gallbladder ejection fraction as 0.5%

with a symptom resolution around 82% and 18% were without symptom resolution [Table 2]. The postoperative symptom resolution was not statistically significantly different from the elevated GBEF group ($P = 0.70$).

There were a total of 20 patients who met the criteria for GBEF >80% who underwent cholecystectomy within 1 month [Figure 1]. Of these patients, 5% demonstrated acute and chronic cholecystitis on surgical pathology and 95% demonstrated chronic cholecystitis [Table 2]. The average age for this group was 43.9 years, ranging between 14 and 60 years [Table 1]. BMI ranged from 20.9 to 39.2 kg/m², averaging 30.6 kg/m² [Table 1]. Ninety-five percent of the patients were female and 5% of the patients were male [Table 1]. Seventy-five percent of GBEF >80% patients underwent ultrasound shortly before HIDA, of which 80% demonstrated no evidence of acute cholecystitis, 13% were inconclusive for acute cholecystitis, and 7% included sonographic evidence of acute cholecystitis. Sixty-five percent of GBEF >80% patients had a documented follow-up with a symptom resolution of 77% and 23% were without symptom resolution [Table 2].

A total of nine patients who met the criteria for normal GBEF, ranging between 38% and 80%, underwent cholecystectomy within a 1-month period of time [Figure 1]. Of these patients, 0% of the patients demonstrated acute cholecystitis on surgical pathology and 100% of the patients demonstrated chronic cholecystitis [Table 2]. The average age for this group was 39.3 years, ranging between 21 and 60 years [Table 1]. BMI ranged from 23.7 to 47.5 kg/m², averaging 39.3 kg/m² [Table 1]. Eighty-nine percent were female and 11% were male [Table 1]. Seventy-eight percent of normal GBEF patients underwent

ultrasound before HIDA, of which 28% demonstrated no evidence of acute cholecystitis, 44% were inconclusive for acute cholecystitis, and 28% included sonographic evidence of acute cholecystitis. Twenty-two percent of these patients had a documented follow-up, all of which reported symptom resolution [Table 2].

DISCUSSION

Chronic cholecystitis is typically evaluated with ultrasound and HIDA which is later confirmed by surgical pathology. Despite ultrasonography being widely used for cholecystitis evaluation, most patients who demonstrated normal ultrasound later revealed chronic cholecystitis surgical pathology. Our result raised concern for using ultrasounds as a rule out test for gallbladder inflammation, although much greater number of patients are needed for further evaluation.

HIDA findings for chronic cholecystitis vary but may be more sensitive than ultrasound. Findings include delayed gallbladder filling with normal biliary to bowel transit, delayed/disparate gallbladder filling relative to small bowel within the 1st hour, delayed biliary to bowel transit with normal gallbladder filling, unusually slow filling of the gallbladder, irregular or eccentric gallbladder filling, faint or very small contracted gallbladder, band or septa across gallbladder, photopenic defects in the gallbladder, nonvisualization of gallbladder-likely representing advanced chronic cholecystitis, abnormal response to CCK analog with low or high GBEF, combinations of the above findings, and less commonly, normal HIDA result.^[2]

Postoperatively, confirmation of chronic cholecystitis was indicated when collections of lymphocytes in the wall, submucosal, and subserosal thickening from fibrosis, mucosal ulcerations, gallstone without acute inflammation, or mere presence of a gallbladder stone.^[8]

Biliary dyskinesia has been postulated as one of the main causes of chronic cholecystitis. Unfortunately, the pathophysiology of biliary dyskinesia is poorly understood. Speculated mechanisms include increased CCK receptors

Table 1: Patient demographics based on the gallbladder ejection fraction subgroups

	Average age (years)	Average BMI (kg/m ²)	Male (%)	Female (%)
Low GBEF	39.9	30.9	16	84
High GBEF	43.9	30.6	5	95
Normal GBEF	39.3	39.3	11	89

There is no significant demographic difference among the subgroups. GBEF: Gallbladder ejection fraction; BMI: Body mass index

Table 2: Patient distribution in surgical pathology, postoperative symptom resolution, and ultrasound results before hepatobiliary iminodiacetic acid scan among low, high, and normal gallbladder ejection fraction

	GBEF (%)	Pathology (%)		Symptom (%) (recorded)		US (%) (performed)		
		Acute and chronic	Chronic	Resolved	Unresolved	Acute	Inconclusive	Normal
Low GBEF	<38	3	97	82 (23/38)	18 (5/38)	3 (1/38)	35 (11/38)	61 (19/38)
High GBEF	>80	5	95	77 (10/20)	23 (3/20)	7 (1/20)	13 (2/20)	80 (12/20)
Normal GBEF	38-80	0	100	100 (2/9)	0 (0/9)	28 (2/9)	44 (3/9)	28 (2/9)

Postoperative symptom relief and US results were partly available on each group. The number of patients was listed in parenthesis. No statistically significant difference was present between low and high GBEF groups in pathology, symptom relief, and US findings ($P>0.05$). GBEF: Gallbladder Ejection Fraction, US: Ultrasound

or increased CCK secretion, an increasing gallbladder contraction with fatty meals causing abdominal pain, and increased intraluminal pressure that may cause chronic inflammation.^[9]

Traditionally, biliary dyskinesia was defined as biliary colic in the absence of gallstones. The most commonly used imaging finding for biliary dyskinesia is decreased GBEF (<35%). For example, Constantinou *et al.* performed prospective data collection on 100 children with biliary dyskinesia on ultrasound and GBEF of <35%. Resultant symptom relief postlaparoscopic cholecystectomy was seen in 77%.^[10]

Hyperkinetic gallbladder, on the other hand, was not initially postulated as a potential pathologic state. However, recent studies have shown an elevated GBEF may also represent biliary dyskinesia, especially in the pediatric population. A retrospective chart review of 31 patients who had biliary colic associated with GBEF >80% demonstrated symptomatic relief postcholecystectomy in 78% and chronic cholecystitis surgical pathology result in 90%.^[5] Another study investigated 12 pediatric patients who had normal ultrasounds and > 80% of GBEF. All 12 patients demonstrated cholecystitis on surgical pathology with 11 patients reporting symptom relief.^[6]

These studies suggest that clinicians should be cautious about ruling out acute or chronic cholecystitis when GBEF is normal or above normal. Normal GBEF patients with postsurgical symptom relief have been postulated in multiple studies, defining normal GBEF as >35%.^[11] However, this definition of normal GBEF encompasses a hyperkinetic gallbladder, which may explain the result.

Our study is one of the few studies that investigated elevated, decreased, and normal GBEF with surgical pathology and evaluated symptom relief postcholecystectomy.^[12] There was no statistically significant difference between elevated, decreased, and normal GBEF and diagnosis of chronic cholecystitis.^[13]

Reproduction of symptoms upon CCK injection has been reported as a helpful clue to biliary dyskinesia when GBEF is not concordant in conventional ways.^[14]

In addition, typical biliary colic symptoms have also been found to be an indicator of postoperative resolution of symptoms. Eckenrode *et al.* retrospectively reviewed 438 patients who underwent laparoscopic cholecystectomy with symptom resolution in two groups: one with typical biliary colic symptoms of upper abdominal pain and/or nausea, including vomiting after large or fatty meals and another group with

atypical biliary colic symptoms of upper abdominal pain and/or nausea, including vomiting without correlation to meals or other abdominal complaints. For patients with typical biliary colic symptoms, the postoperative resolution of symptoms was not significantly different in GBEF of <35% vs. ≥35% GBEF. These results suggest that patients who present typical symptoms may not benefit from an evaluation of the GBEF.^[15]

CONCLUSION

In conjunction with our results and literature review, GBEF alone may not add any further information regarding gallbladder pathology or postoperative symptom relief, especially for patients that present typical symptoms. Regarding gallbladder dyskinesia, elevated and decreased GBEF groups were not significantly different from each other in surgical pathology or symptom relief, which suggests that they may be treated as a group rather than separate entities. Finally, elevated and decreased GBEF demonstrated predominantly normal ultrasound findings, which raised concern for using ultrasound as a rule out test for gallbladder inflammation. As to the normal GBEF group, a larger sample study will be necessary to be able to further explain chronic surgical pathologic changes and postoperative symptom relief.

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Conflicts of interest

There are no conflicts of interest.

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