

REVIEW

Cholecystokinin-Cholescintigraphy in Adults: Consensus Recommendations of an Interdisciplinary Panel

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BACKGROUND & AIMS: Cholecystokinin-cholescintigraphy (CCK-CS) provides a physiologic, noninvasive, and quantitative method for assessing gallbladder contraction and calculation of a gallbladder ejection fraction (GBEF). At present, it is used most commonly to identify patients with suspected functional gallbladder disorder. However, the methodology of CCK infusion and normal values differ markedly among imaging centers. **METHODS:** This document represents the consensus opinion of an interdisciplinary panel that gathered to assess the current optimal method for performing CCK-CS in adults, potential uses and limitations of CCK-CS, and questions that require further investigation. **RESULTS:** The panel recommended the use of a single, standardized, recently described CCK-CS protocol that involves infusion of 0.02 $\mu\text{g}/\text{kg}$ of sincalide over 60 minutes with a normal gallbladder ejection fraction defined as $\geq 38\%$. The panel emphasized the need for a large, multicenter, prospective clinical trial to establish the utility of CCK-CS in the diagnosis of functional gallbladder disease. Although not without controversy regarding its clinical utility, the primary indication for CCK-CS at present is the well-selected patient with suspected functional gallbladder disorder. **CONCLUSIONS:** Agreement was reached that the adoption of this standardized protocol is critical to improve how CCK-CS is used to direct patient care and will represent an improvement over the diverse methods currently in use by eliminating the current lack of uniformity and adding both reliability and credibility to the results.

Keywords: Functional Gallbladder Disorder; Cholecystokinin-cholescintigraphy; Gallbladder Ejection Fraction.

Cholecystokinin-cholescintigraphy (CCK-CS) is commonly performed to evaluate patients with upper abdominal pain thought to be biliary in origin who have an ultrasonographically normal appearing gallbladder. The pathogenesis of this condition is poorly understood, thus explaining why many different names have been used to describe it, including functional gallbladder disorder, gallbladder dyskinesia, chronic acal-

culous gallbladder dysfunction, acalculous biliary disease, chronic acalculous cholecystitis, and biliary dyskinesia. Although there was not unanimous agreement among members of the panel, the term “functional gallbladder disorder” (FGBD) was chosen to be used throughout this report to describe this syndrome as this is currently the accepted Rome consensus nomenclature. Symptoms alone are generally considered unreliable in the diagnosis of FGBD, leading to a search for an objective test.

Imaging has been used in an attempt to confirm the clinical diagnosis of FGBD dating back to 1959.¹ In these early studies, use of an oral iodopanoic acid contrast agent to visualize the gallbladder and either a fatty meal or CCK to stimulate gallbladder contraction²⁻⁵ led to conflicting findings.⁵⁻⁷ Technetium (Tc)-99m labeled hepatobiliary iminodiacetic acid (HIDA) radiotracers became available for scintigraphic imaging in 1976. It was rapidly appreciated that HIDA radiotracers had the potential to accurately quantify gallbladder contraction.^{8,9}

Ultrasonography has been investigated as an alternative to the radionuclide method. Its principal advantage is that it does not expose the patient to ionizing radiation, but evidence to support its use in FGBD is limited. Furthermore, ultrasonography is operator-dependent, quantification is based on geometric assumptions, and it has an unacceptable frequency of suboptimal or nondiagnostic studies.¹⁰⁻¹² The use of fatty meals to stimulate gallbladder contraction has been advocated as more physiologic and less expensive than intravenous CCK infusion. Although a variety of fatty meals have been investigated, few have reliable normal values.¹³⁻¹⁶ Another limitation of the fatty meal methodology is that gastroparesis is not uncommon in patients with FGBD¹⁷ and may lead to delayed

Abbreviations used in this paper: CCK, cholecystokinin; CS, cholescintigraphy; FGBD, functional gallbladder disorder; GBEF, gallbladder ejection fraction; HIDA, hepatobiliary iminodiacetic acid; ROI, region of interest.

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endogenous CCK release and an underestimation of gallbladder contraction.

For the reasons stated above, and because it provides a physiologic, noninvasive, and accurate quantitative assessment of gallbladder contraction, CCK-CS with measurement of a gallbladder ejection fraction (GBEF) has become the standard in clinical practice. During CCK-CS, a Tc-99m-labeled HIDA radiopharmaceutical is taken up by the liver and excreted into the biliary system where it accumulates in the gallbladder. A GBEF is then calculated after stimulating gallbladder emptying with CCK. An abnormal (ie, low) GBEF has been reported to be indicative of gallbladder dysfunction and supportive of a diagnosis of FGBD. Therefore, CCK-CS has been advocated as a diagnostic test for the clinical evaluation of individuals presenting with suspected biliary pain and an anatomically normal appearing gallbladder, aiding in the decision on whether to proceed with cholecystectomy.¹⁸ Nevertheless, lack of standardization of this test between imaging centers, particularly in terms of the CCK dose, duration of CCK administration, normal values, and inappropriate patient referral for testing has raised questions about the clinical utility of this test. To determine the utility of this test in any clinical scenario, a consensus is needed for a standardized CCK-CS protocol. Hence, the goal of this panel was to propose a protocol for performing CCK-CS in adults for clinical practice that is reliable and feasible to perform using readily available technology and normative data, which will provide clinicians with standardized results.

The process leading to this report involved a meeting organized by the Gastrointestinal Council of the Society of Nuclear Medicine and held in Philadelphia, Pennsylvania on April 24, 2010. An interdisciplinary group including gastroenterologists, surgeons, primary care physicians, nuclear medicine technologists, and nuclear medicine physicians was invited to attend and participate in a series of prepared presentations and discussions of the potential uses and limitations of CCK-CS, focusing on the needs of patients and ordering clinicians, a review of published evidence on the clinical utility of CCK-CS, and evidence comparing different methods of performing CCK-CS.

The intent of this meeting was to allow a forum for multidisciplinary dialogue that would result in a consensus regarding a uniform CCK-CS protocol and discussion of the potential for a multicenter clinical trial to confirm the clinical utility of CCK-CS using this standardized protocol. After this meeting, a core writing group was selected and drafted a consensus statement that, after multiple revisions, was ratified by the entire group. The current document does not address all questions raised during the discussions but instead focuses on those areas felt to be most important in terms of standardization including the dose and duration of CCK infusion, the duration of image acquisition, and the validation of normative data. Furthermore, this report addresses concerns regarding the clinical utility of CCK-CS and identifies areas in need of further study.

Normal and Abnormal Gallbladder Function and Clinical Correlation

The gallbladder and biliary tract play an important role in the controlled delivery of bile into the duodenum. The gallbladder stores and concentrates bile during the fasting state, supported by the function of the sphincter of Oddi, which maintains the pressure in the common bile duct higher than that in the duodenum or the gallbladder. The gallbladder emp-

ties mainly postprandially due to the coordinated contraction of the gallbladder and simultaneous relaxation of the sphincter of Oddi. Both fasting and postprandial gallbladder motility are controlled by hormonal and neural mechanisms.¹⁹ Postprandially, CCK appears to be the principal hormone controlling gallbladder emptying. CCK is a 33 amino acid polypeptide hormone produced endogenously in the proximal small bowel and stimulated to be released into the blood after ingestion of a meal. CCK binds to receptors in the gallbladder causing contraction and receptors on the inhibitory neurons innervating the sphincter of Oddi causing relaxation leading to increased bile flow into the intestine. Other gastrointestinal effects of CCK include inhibition of gastric emptying, suppression of appetite, and increased intestinal peristalsis; the latter being responsible for abdominal cramping after rapid intravenous infusion.⁶ The c-terminal octapeptide of CCK, the physiologically active portion, was first isolated and then synthesized in 1970.²⁰⁻²² Its analogue, sincalide, is the only commercially available drug in clinical use for CCK-CS.

Biliary pain is thought to occur as the result of increased gallbladder pressure caused by an abnormal pattern of gallbladder contractions in the setting of either structural or functional outflow obstruction. Theories proposed include gallbladder hypomotility, partial structural or functional gallbladder outlet obstruction, discoordination between gallbladder contraction and sphincter of Oddi relaxation, and visceral hypersensitivity. It has been suggested that motility disturbances affecting the gallbladder and resulting in functional biliary pain can be divided into hypokinesia and dyskinesia.¹⁹ While both result in impaired gallbladder emptying, the mechanism is postulated to be different: hypokinesia causes impaired gallbladder contractility (ie, hypomotility) while dyskinesia results from partial obstruction, either structural or functional, distal to the gallbladder. Despite this theoretical basis, the pathogenesis of functional biliary pain remains poorly understood.

Factors to Consider in Measurement of Gallbladder Ejection Fraction

Despite the common use by clinicians and surgeons, the clinical usefulness of CCK-CS has been questioned.^{23,24} The reasons include factors related to patient selection for the test and factors related to the methodology of the test itself. In order to determine the usefulness of CCK-CS to direct patient management, it is necessary for the ordering clinician to be aware of its correct use and limitations, in particular, selecting the proper patients to refer for testing, and for the nuclear medicine physician or radiologist to perform the test using optimal methodology and to interpret the test in light of the patient's history, prior evaluation, and clinical setting.

Patient related. Patient selection impacts the results of CCK-CS. Patients are sometimes referred for testing with atypical symptomatology and with less extensive evaluation and follow-up resulting in a lower pretest likelihood of FGBD.²⁵ This has the potential to increase the false positive rate. Based on the available data, current expert recommendation favors cholecystectomy for patients with biliary pain and an abnormal GBEF;^{26,27} however, a clear definition of biliary pain remains a source of controversy.²⁸ A standardized and reliable set of diagnostic criteria for functional biliary pain is important in selecting patients for CCK-CS.²³ The consensus panel favored the use of the Rome III criteria for FGBD (Table 1) as the

Table 1. Rome III Criteria for the Diagnosis of Functional Gallbladder Disorder²⁶

Episodes of pain in the right upper quadrant and/or epigastrium and all of the following:
1. Episodes last at least 30 minutes
2. Recurrent episodes occur at different intervals (not daily)
3. Pain builds to a steady level
4. Pain is severe enough to interrupt the individual's activities or lead to a visit to a clinician
5. Pain is not relieved by bowel movements, postural change, or antacids
6. Other structural diseases that may explain the symptoms have been excluded
7. Gallbladder is present
8. Normal liver tests and pancreatic enzymes
Supportive criteria
The pain may present with 1 or more of the following:
1. Pain is associated with nausea and vomiting
2. Pain radiates to the back and/or right infrascapular area
3. Pain awakens one from sleep

preferred symptom complex for the selection of patients to undergo CCK-CS for suspected FGBD.²⁶ It was recognized by the panel that because considerable overlap with other functional gastrointestinal disorders exists, further study is needed to determine whether these criteria can adequately distinguish functional biliary pain. Patients with suspected functional biliary pain and an intact gallbladder without evidence of gallstones on transabdominal ultrasonography should be carefully evaluated to exclude other causes for their symptoms. At a minimum, serologic testing of liver and pancreatic enzymes and upper endoscopy has been recommended.²⁶

The performance of CCK-CS in patients with atypical symptoms should be discouraged, as some of these patients may have an abnormal GBEF in the absence of gallbladder disease. The finding of an abnormal GBEF is not specific for FGBD and may occur in patients with a variety of medical conditions including diabetes, celiac disease, or irritable bowel syndrome,²⁵ as a result of a number of medications such as opioid analgesics, calcium channel blockers, oral contraceptive agents, histamine-2 receptor antagonists, and benzodiazepines,²⁹ and infrequently in asymptomatic healthy individuals.³⁰ Furthermore, it must be recognized that the gallbladder may not be responsible for a decreased GBEF and, occasionally, outflow obstruction from abnormalities of the cystic duct or sphincter of Oddi may be responsible.

Technique related. There has been no prior consensus on the dose, rate, and duration of CCK infusion. This represents a significant limitation when determining the validity of this test to direct clinical decision-making. The degree of gallbladder contraction and the calculated GBEF depend on several factors: the total administered weight-adjusted dose ($\mu\text{g}/\text{kg}$), the dose rate ($\mu\text{g}/\text{kg}/\text{minute}$), and the infusion duration (minutes).^{8,9,31,32} These factors have varied considerably in the many published reports leading to confusion and lack of comparability of the results regarding the clinical utility of CCK-CS.^{33,34} Indeed, many different methodologies for sincalide infusion have been used in investigations and are used clinically: the total dose administered has varied between 0.005 and 0.04 $\mu\text{g}/\text{kg}$; the infusion duration has varied from bolus, 1–3, 10–15, 30, 45, and 60 minutes; and abnormal cut-off

values have ranged from <30%, <35%, <40%, and <65%. Furthermore, few studies actually validated their stated normal values and the normal values that are available are generally based on a small number of subjects.

The first published investigation that directly compared 2 different infusion durations was reported by Sarva and colleagues in 1985.³¹ They compared a 1-minute and 45-minute infusion of 0.02 $\mu\text{g}/\text{kg}$ sincalide in men with abdominal pain but subsequently found not to have hepatobiliary disease. They found that the 1-minute infusion resulted in considerable variability of GBEF response (11%–92%) compared with the 45-minute infusion (GBEF, 65%–96%). However, this study was limited by the fact that the 1-minute and 45-minute infusions were not tested in the same subjects; only men were studied while FGBD affects predominantly women, and the study participants were not healthy, asymptomatic volunteers. Two studies by Ziessman et al directly compared different sincalide infusion durations in the same healthy subject groups that included both genders and determined normal values.^{35,36} In the first study of 23 subjects, 0.02 $\mu\text{g}/\text{kg}$ infused over 3 minutes was compared with a 30-minute infusion of the same total dose. In the second study of 20 subjects, a 0.01 $\mu\text{g}/\text{kg}$ infusion dose over 3 minutes was compared with a 60-minute infusion. In neither study could normal values be established for the 3-minute infusion (using either the mean \pm 2 standard deviations or the 5th/95th percentile) because of the wide variability of response in these healthy subjects (GBEF, 0–100% and 12%–74%, respectively). However, for the 30- and 60-minute infusions, normal GBEF values could be determined; >30% (mean \pm 2 standard deviation [SD]) and >40% (5th percentile), respectively. The latter methodology and normal values were similar to that determined by Yap et al.³⁷ This study included 40 healthy subjects using a protocol consisting of CCK infusion of 0.02 $\mu\text{g}/\text{kg}$ infused for 45 minutes with the GBEF calculated 15 minutes later (ie, 60 minutes after the start of the CCK infusion).

Because of the wide variation in prior methodologies, there has been no consensus on the definition of an abnormal GBEF. The Rome group considers an abnormal GBEF <40% based on the results from a single study in which 40 healthy volunteers were studied using a slow infusion technique,³⁷ yet most of the other published studies and most clinicians consider a value of <35% as abnormal.^{23,34} The clinical significance of this degree of difference in the GBEF is likely negligible.

Validation of Proposed CCK-Cholescintigraphy Protocol

Previously published investigations have reported that longer infusions of sincalide result in less variable GBEF in healthy individuals; however, many different methods are in common use. Furthermore, sufficient published data have shown that a 3-minute infusion, a method that appears to be commonly used in clinical practice, exhibits considerable variability and unpredictability in normal subjects and commonly produces side effects of abdominal cramping and nausea. The Gastrointestinal Council of the Society of Nuclear Medicine, therefore, initiated a large multicenter trial that directly compared a 15-minute, 30-minute, and 60-minute infusion of 0.02 $\mu\text{g}/\text{kg}$ sincalide in 60 healthy volunteers.³⁰ The purpose of the investigation was to determine the optimal method for sincalide infusion. For this study, optimum was defined as the

method with the least variability in GBEF, based on the coefficient of variation (CV). A second objective was to establish normal values for each infusion method. Thirty-two women and 28 men, aged 20–62 years participated. All subjects were without gastrointestinal or other health problems, and had normal laboratory studies and gallbladder ultrasonography. They were randomized to undergo cholescintigraphy with 1 of the 3 sincalide infusions on separate days; the order of which was randomized. All had gallbladder filling at 60 minutes. Only 2 subjects, both with the 15-minute infusion, reported nausea or abdominal cramping with the infusions. Both the 15- and 30-minute infusions had wide variation in GBEF values, while the 60-minute infusion showed significantly less variation: 52%, 35%, and 19% coefficient of variation for the 15-, 30-, and 60-minute groups, respectively. The lower range of normal for GBEF for the 15- and 30-minute infusions was 13%–17%. The 60-minute infusion had a lower limit of normal of 38% (first percentile) and 49% (fifth percentile) (Figure 1). There was no statistically significant difference in GBEF when males were compared with females or when younger subjects were compared with older subjects. It was concluded that an infusion of 0.02 $\mu\text{g}/\text{kg}$ over 60 minutes should become the standard CCK-CS method, with an abnormal GBEF being defined as <38%.

Recommended Protocol

The recommended protocol described below reflects an adaptation from the recent Society of Nuclear Medicine guideline on hepatobiliary scintigraphy, specific for the indication considered.³⁸

Patient preparation. Patient preparation is important to avoid false positive results. The patient should optimally

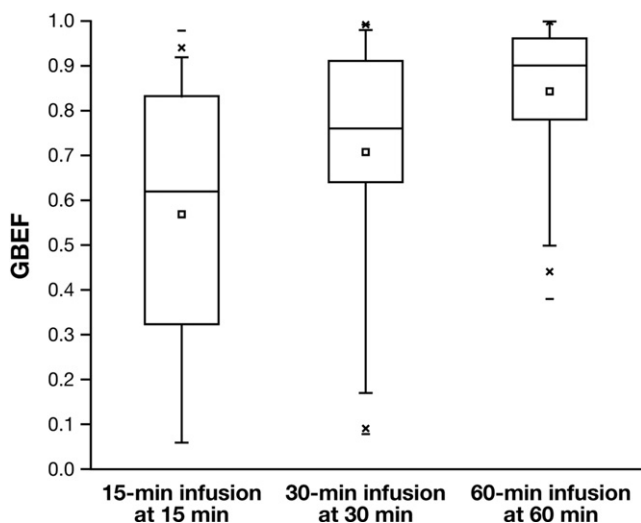


Figure 1. Box-whisker plots showing distribution of GBEF values for infusion groups at times of 15, 30, and 60 minutes. Boxes represent interquartile range (25th–75th percentiles, median line in center, mean is a square). Bars represent 5th and 95th percentiles, X's represent 1st and 95th percentiles, and dash is minimum and maximum. Reprinted by permission of the Society of Nuclear Medicine from Ziessman HA, Tulchinsky M, Lavelly WC, et al. Sincalide-stimulated cholescintigraphy: a multicenter investigation to determine optimal infusion methodology and gallbladder ejection fraction normal. *J Nucl Med.* 2010;51(2):277–281 (Figure 1).

fast the evening before the study or at least 4–6 hours prior to the study. CCK-CS with calculation of a GBEF to confirm the suspected diagnosis of FGBD should be performed on an outpatient basis, and not while the patient is hospitalized or acutely ill, as there are many confounding factors in acutely ill hospitalized patients who can spuriously decrease GBEF, eg, the illness itself and therapeutic medications.^{28,39} The only contraindications to CCK-CS are a known allergic reaction to the sincalide and intestinal obstruction. Although the radiopharmaceutical, Tc-99m HIDA radiotracer, at the dose typically used is generally considered safe for the mother and fetus during pregnancy, sincalide use is contraindicated in pregnancy as it may stimulate preterm labor.

Medications. Opiate and anticholinergic drugs should be withheld for at least 48 hours before testing. Other drugs that may affect gallbladder contraction and that should not be taken within 24 hours prior to the study include nifedipine, indomethacin, octreotide, theophylline, benzodiazepines, phentolamine, isoproterenol, and progesterone.²⁹ Nicotine and alcohol may also affect gallbladder contraction and should be avoided prior to testing.

Radiopharmaceutical. Three to 5 mCi of Tc-99m mebrofenin or disofenin is administered intravenously. Both are Food and Drug Administration (FDA) approved HIDA radiotracers.

Camera. A large field of view gamma camera equipped with a low-energy collimator is used for imaging. Images are acquired with a 140 keV photopeak and 20% window.

Presincalide procedure.

1. After starting an intravenous line, inject an HIDA radiotracer intravenously with the patient supine on the imaging table.
2. Imaging should be obtained up to 1 hour to ensure visualization of the gallbladder prior to sincalide infusion.
3. If the gallbladder has not filled by 60 minutes in a properly prepared patient, the finding is reported as abnormal, potentially consistent with either acute or chronic cholecystitis depending upon the clinical presentation.⁴⁰
4. If the gallbladder has filled, place the camera in the left anterior oblique projection (35–40 degrees) for imaging to ensure minimal overlap of the gallbladder with duodenum and small bowel. Visualization of the small bowel is not necessary prior to sincalide infusion.

Sincalide infusion procedure.

5. A 0.02 $\mu\text{g}/\text{kg}$ dose of sincalide should be drawn into a 30–50 mL syringe and diluted with normal saline to the volume of the syringe. The syringe should be placed in an infusion pump. The tubing between the syringe and the patient should be filled with the sincalide infusate prior to starting the infusion. The infusion pump should be set so that the sincalide is infused continuously with the infusion completed at 60 minutes.
6. Dynamic imaging (1 image per minute) should be started simultaneously with sincalide infusion and stopped at the end of the 60-minute infusion.

Computer processing and quantification. The region of interest (ROI) should be drawn around the gallbladder

and a background liver ROI drawn about 1–2 cm superior lateral to the gallbladder. The GBEF (percent gallbladder emptying is defined as maximum minus minimum and divided by maximum counts [all corrected for background]) should be calculated at 60 minutes. Examples of a normal and abnormal CCK-CS scan are shown in Figure 2.

Interpretation

Using this protocol, a GBEF <38% is considered abnormal.³⁰ Given that the GBEF upper limit of normal approaches 100%,³⁰ there is no convincing evidence that a high normal GBEF is of clinical significance.

Reporting of Results

The CCK-CS report should contain several key components including patient history, reason for referral, and imaging protocol. The image findings and results of the GBEF calculation and final impression should be reported. Although the interpretation should be based on the patient's prior history and evaluation and not only on the GBEF, this information is often not available to the radiologist performing the study. Therefore, the report generally should conclude with a statement regarding a normal or abnormal GBEF response with a statement such as "In the appropriate clinical setting, this is consistent with functional gallbladder disorder" leaving the final interpretation to the ordering clinician who is most familiar with the patient involved (see example report in Appendix 1).

It has been suggested in the literature that provocation of typical biliary symptoms after CCK administration is diagnostic of functional biliary pain syndromes.⁴¹ CCK administration, particularly when infused in less than 30 minutes, is known to stimulate not only the gallbladder but also the duodenum and colon. It was appreciated as early as the 1960s that rapid bolus infusion of CCK could cause spasm of the neck of the gallbladder and cystic duct resulting in poor fundal contraction and abdominal cramping.^{6,42,43} CCK infusions over 1–3 minutes are not physiologic and result in a very rapid rise and high peak serum CCK levels,³¹ which is very different from slower infusions and, with the use of fatty meals, show a gradual rise and much lower peak CCK serum level. Indeed, in the 2 Ziessman et al studies, 48% and 53% of the subjects developed abdominal cramping and or nausea in the 3-minute CCK infusion groups; however, no subjects developed symptoms with the 30-minute or 60-minute infusions.^{35,36} Therefore, the panel recommends that CCK-induced provocation of abdominal pain or other gastrointestinal symptoms should not be considered a reliable test of gallbladder dysfunction/disease, especially with rapid infusion.⁴⁴ Although it was recommended that symptoms experienced by the patient during testing be mentioned in the report, it was also felt that the report should note that the development of symptoms does not have diagnostic value and, therefore, does not necessarily reflect the presence of gallbladder disease.

Clinical Role of CCK-Cholescintigraphy

At present, CCK-CS with measurement of the GBEF is the most commonly ordered test in the United States for determining gallbladder contraction. The following potential indications were discussed by the members of the interdisciplinary panel, although high quality clinical trials using this

proposed standardized method are needed to assess the clinical utility of CCK-CS in these settings.

Potential Indications for CCK-Cholescintigraphy

1. Functional Gallbladder Disorder

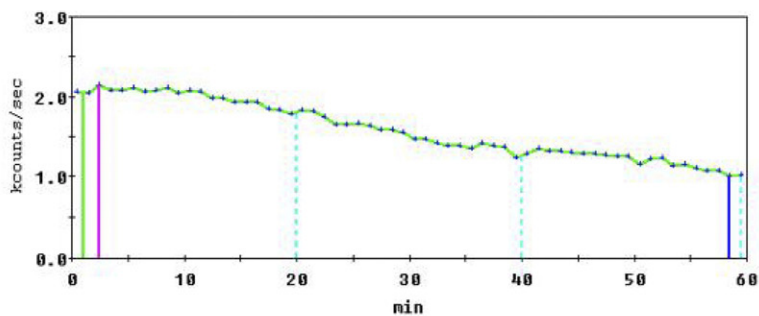
To date, Yap and colleagues have published the only randomized controlled study of cholecystectomy based on GBEF in FGBD.³⁷ They studied 21 patients with suspected functional biliary pain and a GBEF <40% based on a 45-minute infusion of CCK. Eleven patients were randomized to cholecystectomy and 10 to no surgery. Over a 3-year period, 10 patients became asymptomatic after cholecystectomy and 1 reported improved symptoms after surgery. In contrast, the majority of the patients in the no surgery group reported their symptoms to be unchanged, 2 of whom requested cholecystectomy and subsequently improved. Based on these findings, the authors concluded that CCK-CS is useful in identifying a group of patients with acalculous gallbladder disease and biliary-like pain who respond to cholecystectomy. While encouraging, application of these results to the general population with suspected FGBD is limited by the small study size and lack of concealed allocation to the treatment group.

Despite the findings of Yap et al and similar findings from a number of retrospective case series,^{23,34,45} the appropriateness of this approach in patients with presumed functional biliary pain remains controversial. A recent systematic review specifically questioned the utility of CCK-CS with the calculation of the GBEF in predicting symptomatic outcome following cholecystectomy in patients with suspected functional biliary pain. Of the 23 studies reviewed, 19 concluded that calculation of a GBEF was useful.²³ Nevertheless, quality evidence was shown to be lacking because of multiple limitations of these studies including that most were retrospective and uncontrolled, only 1 was randomized,³⁷ and most had small samples sizes and short duration of follow-up. Additionally, variable definitions of biliary pain, different means of determining symptom outcome, and differences in CCK-CS technique were employed. A meta-analysis incorporating 9 of the studies noted in the systematic review arrived at the same conclusion and also determined that publication bias may have played a role in the benefits demonstrated previously.²⁴ Importantly, they found that 94% of patients with abnormal GBEF had a positive outcome compared with 85% among those with normal GBEF. The odds ratio for positive outcome was 1.37 (95% confidence interval [CI], 0.56–3.34; $P = .56$). Thus, based on their pooled analysis, they found no difference in outcomes after cholecystectomy between patients with abnormal GBEF and normal GBEF. Finally, a recent Cochrane review⁴⁶ of the evidence for cholecystectomy in suspected FGBD concluded that there is a high risk of bias in previous studies in this area and lack of sufficient data to assess the role of cholecystectomy in FGBD leading to a recommendation that randomized clinical trials are necessary.

2. Cholelithiasis With Atypical Symptoms

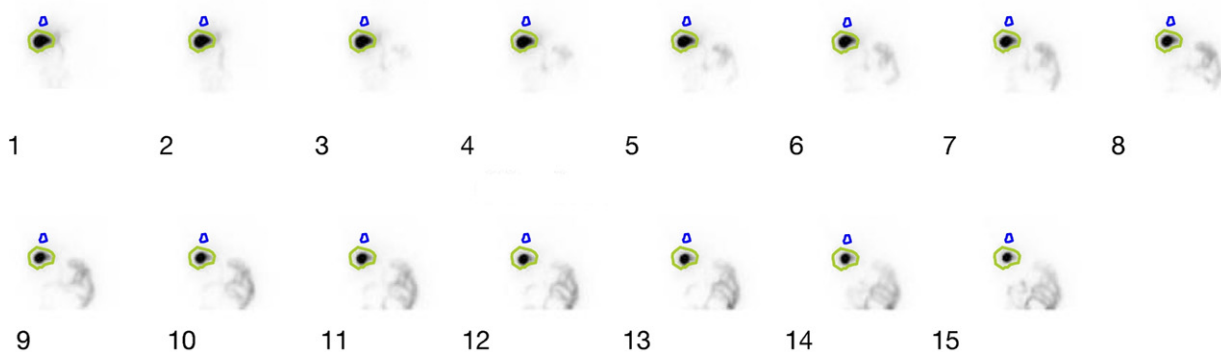
Gallstone disease is common. Estimates of the lifetime risk of gallstone formation are as high as 10% to 20% of the general population.^{47,48} Gallstones, regardless of type, are typically classified into symptomatic or asymptomatic. It has been previously demonstrated that GBEF is frequently reduced in

A

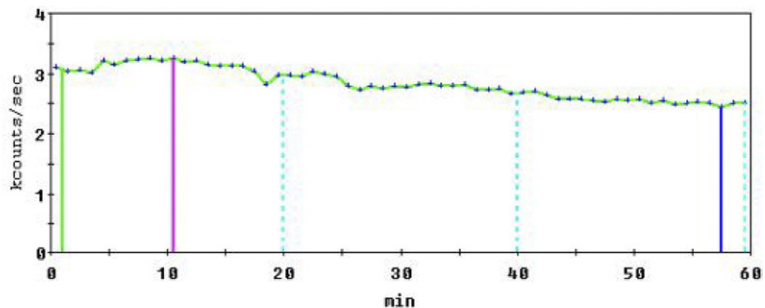


GBEF = 53%

Images formatted at 4 min./frame



B



GBEF = 19%

Images formatted at 4 min./frame

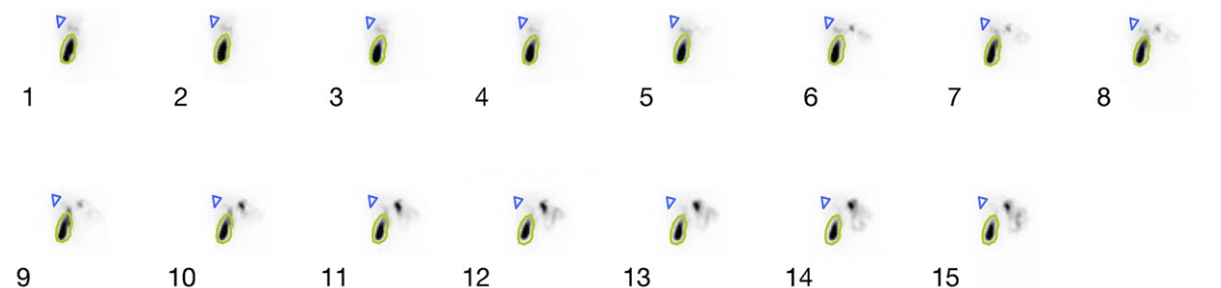


Figure 2. Examples of (A) normal and (B) abnormal CCK-cholescintigraphy scans. After gallbladder filling with HIDA radiotracer, 0.02 $\mu\text{g}/\text{kg}$ of sincalide was infused intravenously over 60 minutes. Images (below) were acquired in the left anterior oblique projection by the gamma camera at 1-minute frames for 60 minutes (4-minute summed images are shown). An ROI was drawn around the gallbladder (green outline) and liver (blue outline), gallbladder counts were corrected for the liver background, and the resulting time-activity curve was processed and displayed. The 4 minutes per frame summed images with overlaid ROIs confirm accurate processing. The GBEF was calculated as peak counts-minimum counts/peak counts, all corrected for background. In panel A, the images show normal gallbladder contraction (GBEF 53%) while in panel B, the images show abnormal gallbladder contraction (GBEF 19%).

patients with gallstones,^{49,50} although the role this plays in the pathogenesis of gallstone disease remains unclear as does its association with symptoms. Two major questions have emerged regarding the possible use of CCK-CS in patients with cholelithiasis: (1) can CCK-CS predict which asymptomatic patient will progress to symptoms; and, (2) can CCK-CS determine whether atypical symptoms are of gallbladder origin?

It is estimated that as many as 80% of patients with gallstones remain asymptomatic throughout their lives.⁵¹ Given the benign course, the recommended management for asymptomatic cholelithiasis is expectant, with surgery reserved only for those who become symptomatic or in those with certain high risk conditions (eg, those at risk for gallbladder cancer, or incidentally at the time of another abdominal operation).⁵² There is little evidence supporting the use of CCK-CS to identify individuals with asymptomatic cholelithiasis who would benefit from cholecystectomy and, in the opinion of the panel, further investigational testing would not likely be useful given the benign and well-established clinical course of this entity, the low rate of progression to symptoms (and subsequent complications), and the well-established treatment strategy.

Symptomatic cholelithiasis is classically suggested by the presence of biliary pain in the setting of known gallstones. Unfortunately, classical biliary pain occurs in the minority of individuals and, more commonly, the symptomatology is ambiguous.⁵³ These ambiguous or atypical symptoms, including indigestion, flatulence, heartburn, bloating, belching, and nausea (ie, dyspeptic symptoms) are less likely to resolve following cholecystectomy,^{54,55} leading some to propose that additional testing may be useful to discriminate those whose symptoms are attributable to the gallstones. However, there is no evidence that GBEF measurement adds to clinical judgment alone in predicting the surgical outcome.⁵⁶ Although there is a theoretical concern that CCK-CS in the setting of gallstones may precipitate acute cholecystitis or choledocholithiasis due to migration of a stone, to our knowledge, there are no published data that support this fear and, in the experience of the Nuclear Medicine panelists, this complication has never been encountered. Furthermore, at least with the more physiologic, slow CCK infusion methodology, the risk would theoretically be similar to risk associated with eating.

Summary of Recommendations

The panel recommends use of a single, standardized CCK-CS protocol in adults that uses infusion of 0.02 $\mu\text{g}/\text{kg}$ of sincalide over 60 minutes, with a normal GBEF being defined as $\geq 38\%$.³⁰ The consensus panel did consider how the longer imaging time might affect the workflow of camera use in imaging centers and the potential reluctance to adopt this protocol due to concerns that reimbursement may not be commensurate with the time and effort needed, and possible methods to shorten the methodology. Despite these concerns, agreement was reached that the adoption of the standardized 60-minute CCK infusion protocol described in this report is critical to improve how CCK-CS is used to direct patient care and will represent an improvement over the diverse methods currently in use. The panel recognized that further study using this standardized protocol is needed to determine its reproducibility and other test performance characteristics (ie, sensitivity, specificity, predictive values) in healthy individuals and in those with suspected biliary pain.

Despite ongoing debate about the clinical utility of CCK-CS in selecting patients for cholecystectomy, it was uniformly agreed that a standardized testing protocol based on currently available evidence as described in this report together with proper patient selection is a critical step in determining the optimal approach to patients with suspected FGBD. When considering whether to perform CCK-CS, it is preferable that it be performed in patients meeting the Rome III criteria for functional biliary pain and who are not having pain and who are not hospitalized at the time of the study. The use of CCK provocation of pain to determine patient care decisions was discouraged by the panel.

It is apparent that more data are required before CCK-CS can be unconditionally recommended as a diagnostic test in patients with suspected FGBD. The interdisciplinary panel unanimously agreed that a large, prospective controlled study with patients meeting a standardized definition of functional biliary pain (ie, Rome III criteria) and a normal gallbladder ultrasound, randomized to either surgery or no surgery using the standardized CCK-CS methodology proposed herein, is necessary. Such a study should require defined outcome measures and long-term follow-up in order to assess the clinical utility of CCK-CS in selecting patients with FGBD for cholecystectomy. That the National Institutes of Health is currently sponsoring a large, multicenter trial evaluating predictors and interventions in sphincter of Oddi dysfunction (EPISOD trial),⁵⁷ suggests that such a trial will eventually be performed in patients with functional biliary pain and an intact gallbladder. Further studies are also needed to evaluate the role of CCK-CS in the setting of known gallstones, particularly when atypical symptoms predominate.

Appendix 1. Sample Report (Companion Images Depicted in Figure 2B)

Reason for referral: Suspected functional gallbladder disease.

Clinical history: 45-year-old female with symptoms of recurrent upper abdominal pain for 10 months. The patient is taking no interfering medications and properly prepared for this test.

Comparison studies: Hepatobiliary ultrasonography (date) was negative for obstruction or gallstone disease.

Radiopharmaceutical: Tc-99m mebrofenin (or disofenin), 5 mCi intravenous.

Patient weight: 70 kg.

Interventional drug: sincalide 1.4 $\mu\text{g}/\text{kg}$ (0.02 $\mu\text{g}/\text{kg}$).

Technique and Findings

After injection of the radiopharmaceutical, imaging was performed for 60 minutes with the patient supine. After gallbladder filling, the camera was placed in the left anterior oblique projection for imaging during sincalide infusion. The sincalide dose was placed in a 30-mL syringe and the syringe filled with saline to 30 mL. The syringe was placed in a constant infusion pump set to be infused over 60 minutes.

Findings

There was prompt uptake by the liver and filling of the gallbladder with normal biliary-to-bowel transit. With sincalide infusion, the gallbladder contracted poorly. Following the ad-

ministration of intravenous sincalide, the patient reported transient periumbilical discomfort. The calculated gallbladder ejection fraction (GBEF) was 19% (normal range >38%).

Impression

Abnormal GBEF of 19% is consistent with functional gallbladder disorder in the proper clinical setting. It should be recognized that the development of symptoms following sincalide infusion does not have proven diagnostic value and may not reflect the presence of gallbladder disease.

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Conflicts of interest

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