

Utilization of Cholecystokin Cholescintigraphy in Clinical Practice

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Cholecystokin-cholescintigraphy (CCK-HIDA) is commonly performed to evaluate patients with upper abdominal pain thought to be biliary in origin and with a normal gallbladder on abdominal ultrasonography. The nomenclature of this disease entity, based on the finding of an abnormally low gallbladder ejection fraction (GBEF) on the CCK-HIDA examination, varies in the literature and has been known as biliary dyskinesia, gallbladder dyskinesia, functional gallbladder disorder, chronic acalculous cholecystitis, and chronic acalculous biliary dysfunction, just to name a few. For the purposes of this review, we will use the term *gallbladder dyskinesia* because this is the term most referenced in the surgical literature. Cholecystectomy is commonly recommended as the treatment of choice in these patients.¹

Although used commonly in today's clinical surgical practice, the CCK-HIDA testing methodology, test interpretation, patient selection, and controversies surrounding long-term treatment outcomes pertaining to surgical intervention for gallbladder dyskinesia are controversial and poorly understood by many practicing clinicians. This review details the controversies surrounding the testing methodology, the method of determining normal vs abnormal CCK-HIDA values, and the data both supporting and questioning its clinical use to select patients for cholecystectomy based on the current available literature. In addition, evidence-based recommendations for the use of CCK-HIDA in clinical practice are presented.

HISTORY

For years, surgeons have encountered patients who had symptoms compatible with biliary disease, but were found to have a sonographically normal gallbladder. Because of the inherent unreliability of a purely

symptom-based diagnosis, clinicians have searched for an objective test to define which patients would benefit from cholecystectomy as far back as 1959.² In these early studies, oral administration of iodopanoic acid was used to opacify the gallbladder, followed by the ingestion of a fatty meal (or CCK administration) to stimulate gallbladder contraction.³⁻⁶ These studies, however, led to conflicting findings and inconsistent results with respect to quantification of the GBEF, and therefore, the degree of "abnormal" gallbladder emptying.^{6,7}

Ultrasound has also been used as an alternative method of calculating abnormal gallbladder emptying. Proponents argue that it avoids radiation exposure, but it suffers from significant interobserver variability, and the calculations of GBEF are based on geometric gallbladder measurements before and after administration of a fatty meal or CCK, which may be inconsistently measured based on the degree of expertise of the sonographer. Because of these shortcomings, this method has not been widely used to diagnose gallbladder dyskinesia.⁸⁻¹⁰

The emergence of technetium (Tc-99)-labeled hepatobiliary iminodiacetic acid (HIDA) as a radiotracer in 1976 quickly replaced the previously mentioned methods due to its accuracy in measuring GBEF during scintigraphy.^{11,12} For the reasons stated previously, and because it provides a physiologic, noninvasive, and accurate quantitative assessment of gallbladder contraction, CCK-HIDA with measurement of a GBEF has become the standard in clinical practice. During CCK-HIDA, 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 abnormally low GBEF has been reported to be indicative of gallbladder dysfunction and supportive of a diagnosis of gallbladder dyskinesia. Therefore, CCK-HIDA 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.^{1,13} However, concerns about the utility of CCK-HIDA testing have arisen. These include lack of standardization of the test methodology (dose of CCK, duration of administration, what constitutes normal vs abnormal values), which patients are most appropriate for CCK-HIDA testing,

CME questions for this article available at
<http://jacscme.facs.org>

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Received December 31, 2012; Accepted February 27, 2013.

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Abbreviations and Acronyms

CCK	= cholecystokinin
CCK-HIDA	= cholecystokinin-cholescintigraphy
GBEF	= gallbladder ejection fraction
HIDA	= hepatobiliary iminodiacetic acid
SNM	= Society of Nuclear Medicine

and whether or not abnormal test results are truly predictive of success with surgical intervention, just to name a few.

The following sections will focus on the major areas of controversy surrounding the use of CCK-HIDA in clinical practice. The specific areas of discussion are:

1. Problems with standardization and administration of the CCK-HIDA testing itself.
2. Issues surrounding the interpretation of the CCK-HIDA test by clinicians.
3. Proper patient selection for CCK-HIDA testing and subsequent cholecystectomy.
4. Controversies surrounding the accuracy of the test in predicting a favorable and durable response to cholecystectomy.

PROBLEMS WITH THE STANDARDIZATION OF TESTING METHODOLOGY

Until recently, no consensus existed as to the dose of CCK administered, rate and duration of CCK administration, and time of GBEF calculation. The degree of gallbladder contraction (and subsequent GBEF) is affected by these specific factors: the total weight-based dose ($\mu\text{g/kg}$), infusion rate, infusion duration, and what is defined as a normal vs abnormal value for GBEF.^{11,12,14,15} For example, dosage has varied among published studies from 0.005 to 0.05 $\mu\text{g/kg}$, the infusion duration from a bolus to a 60-minute infusion in varying increments, and abnormal values ranging from <35% up to <65%.

The variation in test methodology is relevant for a number of reasons. First of all, variations in infusion duration can lead to wide variations in calculated GBEF. The first published investigation that directly compared 2 different infusion durations was reported by Sarva and colleagues in 1985.¹⁴ They compared a 1-minute and a 45-minute infusion of 0.02 $\mu\text{g/kg}$ 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% to 92%) compared with the 45-minute infusion (GBEF, 65% to 96%). Two subsequent studies by Ziessman and associates^{16,17} directly compared different sincalide infusion durations

in the same healthy subject groups, which included both sexes and determined normal values. In the first study of 23 subjects, 0.02 $\mu\text{g/kg}$ 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 $\mu\text{g/kg}$ 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% to 100% and 12% to 74%, respectively). However, for the 30- and 60-minute infusions, normal GBEF values could be determined; >30% (mean $\pm$ 2 SD) and >40% (5th percentile), respectively. These findings are indicative of the fact that variations in technique can and do affect the reproducibility and variability of the results.

Subsequently, and in an attempt to define the optimal protocol in terms of validity and reproducibility, the Gastrointestinal Council of the Society of Nuclear Medicine (SNM) initiated a multicenter trial that directly compared 15-minute, 30-minute, and 60-minute infusions of 0.02 $\mu\text{g/kg}$ sincalide in 60 healthy volunteers.¹⁸ For this study, "optimal" was defined as the method with the least variability in GBEF, based on the coefficient of variation. A second objective was to establish normal values for each infusion method. Thirty-two women and 28 men, aged 20 to 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. (The finding that a shorter duration of CCK infusion may result in symptoms is particularly relevant because some authors have suggested using symptoms produced by CCK infusion as a way in which to select patients for cholecystectomy. This controversial issue will be explored later in the manuscript.) 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% to 17%. The 60-minute infusion had lower limits of normal of 38% (first percentile) and 49% (fifth percentile). There was no statistically significant difference in GBEF when males were compared with females or when younger subjects were compared with older subjects.¹⁸

Based on these data, it was concluded that an infusion of 0.02 µg/kg of sincalide over 60 minutes should become the standard CCK-HIDA protocol, with an abnormal GBEF being defined as <38%.¹⁸ A multidisciplinary panel consisting of surgeons, gastroenterologists, nuclear medicine physicians, and primary care physicians was subsequently convened by the SNM. The panel recommended the use of the standardized CCK-HIDA protocol and cut off level for an abnormal study described above (<38%) to be used in appropriately selected patients.¹⁹ These recommendations have since been adopted by the SNM as the recommended testing protocol (Table 1).²⁰

Other factors also affect the validity and reproducibility of the CCK-HIDA scan, most notably, the conditions under which the test is ordered. The SNM and other thought leaders in the nuclear medicine field have specifically stated, for example, that CCK-HIDA should be performed solely on an outpatient basis—not while the patient is acutely ill—so that confounding factors and medications may be avoided. Opiates are known to falsely lower GBEF, and it is therefore recommended that they be withheld for a minimum of 4 half-lives of the opiate before CCK-HIDA scanning.²⁰

Although the effects of opiates on GBEF are known to most clinicians, a number of other drugs commonly used

in practice may also falsely lower GBEF and should be avoided before CCK-HIDA testing. These include benzodiazepines, atropine, calcium channel blockers, indomethacin, octreotide, theophylline, phentolamine, and progesterone. Knowledge of these drugs' effect on GBEF is less prevalent among clinicians, and failure to consider their effect on CCK-HIDA results and adhere to the SNM recommendations may result in lower values for GBEF than would be obtained under optimal test conditions in the same patient.²⁰

ISSUES SURROUNDING THE INTERPRETATION OF THE CCK-HIDA TEST BY CLINICIANS

Besides the above factors pertaining to the variability and consistency of results, a number of misconceptions exist about the CCK-HIDA scan. A key aspect of the CCK-HIDA scan is the manner in which normal vs abnormal GBEF results are determined, and how this differs from other diagnostic tests.

As with the majority of diagnostic tests, an abnormal test value is predictive of pathology. Examples include, for example, the finding of a pancreatic head mass on CT, a spiculated density on mammography, or a mass or infiltrate on chest x-ray. The CCK-HIDA values are distinctly different, however, in that the normal vs abnormal values for GBEF are calculated from values obtained from normal subjects, with the cutoff of normal vs abnormal typically designated at 2 standard deviations from the mean. In other words, the values are calculated from what is “normal” in the general population, and “abnormal” values, by definition, are therefore not necessarily predictive of a disease state. Rather, these are simply values that fall outside the normal distribution. For this reason, it is expected that some healthy volunteers will have an abnormal GBEF. Conversely, some patients with biliary pain may have GBEF values within the normal range.²¹ A significant number of patients are referred for evaluation for cholecystectomy based purely on their CCK-HIDA results and are often told in advance that their gallbladder is “diseased” or “needs to come out.” Clearly, the manner in which the normal values are calculated makes this an incorrect assumption without the appropriate supportive clinical information.

PROPER PATIENT SELECTION FOR CCK-HIDA TESTING AND SUBSEQUENT CHOLECYSTECTOMY

Proper patient selection affects the results of CCK-HIDA. Patients are sometimes referred for testing with atypical symptomatology and with less extensive evaluation and follow-up, resulting in a lower pre-test likelihood of

Table 1. Society of Nuclear Medicine Practice Guidelines for Hepatobiliary Scintigraphy: Determination of Gallbladder Ejection Fraction²⁰

- Study should be performed as outpatient
 - Nothing by mouth for 4-6 hours prior to the study
 - No opiates for 4 half-lives of the drug or 6 hours prior to the study
 - Other drugs that may inhibit gallbladder contraction that should be withheld include:
 - atropine
 - calcium channel blockers
 - octreotide
 - progesterone
 - indomethacin
 - theophylline
 - benzodiazepines
 - histamine-2 receptor antagonists
 - Tc-99m mebrofenin or disofenin, 3-5 mCi, is injected intravenously while the patient lies under the gamma camera
 - Imaging acquisition over 60 minutes
 - If the gallbladder fills, sincalide (Kinevac, CCK) 0.02 µg/kg is infused at a slow constant rate over an additional 60 minutes with images acquired over same time period
- GBEF calculation: Region of interest is drawn on computer around gallbladder.

$$\text{GBEF}\% = \frac{\text{GB counts (maximum)} - \text{GB counts (minimum)}}{\text{GB counts maximum}}$$

- Abnormal GBEF is less than 38%

CCK, cholecystokinin; GEF, gallbladder ejection fraction.

gallbladder dyskinesia as the cause.²² 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;^{1,23} however, a clear definition of biliary pain remains a source of controversy.²⁴ A standardized and reliable set of diagnostic criteria for functional biliary pain is important in selecting patients for CCK-HIDA.²⁵

Given the presumed functional nature of gallbladder dyskinesia, the Rome III criteria for functional gallbladder disorder (Table 2) have been recommended as the preferred symptom complex to be used for selecting patients to undergo CCK-HIDA for suspected gallbladder dyskinesia.²³ Nevertheless, because considerable overlap of these symptom-based criteria 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. Although this remains an area of controversy, serologic testing of liver and pancreatic enzymes and upper endoscopy has been recommended by some authors to exclude other disease processes.²³

Performance of CCK-HIDA in patients with atypical symptoms should be discouraged because some of these

patients may have an abnormal GBEF in the absence of gallbladder disease. As mentioned above, the finding of an abnormal GBEF is not specific for gallbladder dyskinesia and may occur in patients with a variety of medical conditions including diabetes, celiac disease, or irritable bowel syndrome,²² as a result of a number of medications,²⁰ and infrequently, in asymptomatic healthy individuals.^{18,20} Furthermore, it must be recognized that the gallbladder may not be responsible for a decrease in measured GBEF and, occasionally, outflow obstruction from abnormalities of the cystic duct, biliary tree, or sphincter of Oddi may be responsible and must be considered.¹⁹

Finally, it has been suggested that the reproduction of pain with CCK injection might be useful in predicting a successful response to cholecystectomy.^{26,27} These studies, however, are small, nonrandomized, retrospective, and poorly defined in terms of outcomes measures. Administration of CCK, particularly when infused in less than 30 minutes, is known to stimulate not only the gallbladder but also the duodenum and colon.^{7,28,29} 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. Infusions of CCK over 1 to 3 minutes are not physiologic and result in a very rapid rise and high peak serum CCK levels.¹⁴ This is very different from slower infusions and the use of fatty meals, both of which show a gradual rise and much lower peak CCK serum level. Indeed, in 2 previously published studies by Ziessman and colleagues,^{16,18} 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. Therefore, based on current available literature, CCK-induced provocation of abdominal pain or other gastrointestinal symptoms should not be considered a reliable test of gallbladder dysfunction or disease, especially with rapid infusion.^{23,30} Although it is recommended by the SNM that symptoms experienced by the patient during testing be mentioned in the report, it was also thought that the report should note that development of symptoms does not have diagnostic value and, therefore, does not necessarily reflect the presence of gallbladder disease.^{19,21}

CONTROVERSIES SURROUNDING THE ACCURACY OF THE TEST IN PREDICTING A FAVORABLE AND DURABLE RESPONSE TO CHOLECYSTECTOMY

In 1991, results of a randomized, prospective study were published by Yap and associates³¹ in which a population

Table 2. The Rome III Criteria for Functional Gallbladder and Sphincter of Oddi Disorders²³

I. Functional gallbladder and sphincter of Oddi disorders: Must include episodes of pain located in the epigastrium and right upper quadrant and all of the following:
1. Episodes lasting 30 minutes or longer.
2. Recurrent symptoms occurring at different intervals.
3. The pain builds up to a steady level.
4. The pain is severe enough to interrupt the patient's daily activities or lead to an emergency room visit.
5. The pain is not relieved by bowel movements.
6. The pain is not relieved by postural change.
7. The pain is not relieved by antacids.
8. Exclusion of other structural diseases that would explain the symptoms
Supportive criteria: The pain may present with one or more of the following:
1. Associated with nausea and vomiting.
2. Radiates to the back and/or right infrascapular area.
3. Awakens patient from sleep in the middle of the night.
II. Functional gallbladder disorder Must include all of the following:
1. Criteria for functional gallbladder and sphincter of Oddi disorder.
2. Gallbladder is present.
3. Normal liver enzymes, conjugated bilirubin, and amylase/lipase.

of patients with suspected pain of biliary origin (and a negative gallbladder ultrasound) underwent CCK-HIDA scan with calculation of the GBEF. Those with an abnormal GBEF (<40%) comprised the primary study group and were randomized to either cholecystectomy or no cholecystectomy (observation) groups. Patients who underwent cholecystectomy did dramatically better than those who were observed. The remainder of the patients — those with pain but a with a normal ejection fraction — were treated at the discretion of their primary clinician. Those who had a normal ejection fraction and underwent surgery did no better than those who were observed. The conclusion of the Yap study was that a low GBEF was predictive of success in patients undergoing cholecystectomy for chronic acalculous biliary pain.³¹

The Yap study, although widely quoted, has a number of criticisms that are worth noting. First, the study population of patients with low GBEF was very small (11 had surgery, 10 observation). Of the 11 undergoing surgery, 10 experienced total relief and 1 experienced improvement. Of the 10 in the observation group, all remained symptomatic, and 2 of these crossed over to the surgery arm and subsequently did well.³¹ This remains the only randomized prospective trial to date examining the role of surgery in treating this condition, and it was criticized in a 2008 Cochrane review for not only being severely underpowered in terms of sample size, but also at significant risk of bias.³²

Despite the findings of Yap and colleagues³¹ and similar findings from a number of retrospective case series,^{23,33} the appropriateness of this approach in patients with presumed gallbladder dyskinesia remains controversial. A systematic review specifically addressed the utility of CCK-HIDA with the calculation of the GBEF in predicting symptomatic outcomes after cholecystectomy in patients with suspected gallbladder dyskinesia. Of the 23 studies reviewed, 19 concluded that calculation of a GBEF was useful.²⁵ 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 (Yap and colleagues³¹), and most had small samples sizes and short duration of follow-up. Additionally, variable definitions of biliary pain, different means of determining symptom outcomes, and differences in CCK-HIDA technique were used. 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.³⁴ Importantly, in patients undergoing cholecystectomy, 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 a positive

outcome was 1.37 (95% confidence interval [CI] 0.56 to 3.34; $p = 0.56$). Therefore, based on their pooled analysis, they found no difference in outcomes after cholecystectomy between patients with abnormal GBEF and normal GBEF.³⁴ Randomized clinical trials are necessary to further investigate the use of CCK-HIDA in clinical surgical practice to determine its role in selecting patients for cholecystectomy.

SUMMARY

Based on review of the current literature on this topic, it seems appropriate to conclude the following:

1. The use of CCK-HIDA scan (and GBEF) to select which patients with pain of biliary origin should undergo cholecystectomy is an acceptable practice under current Society of Gastrointestinal and Laparoendoscopic Surgeons (SAGES) clinical guidelines.
2. The use of the CCK-HIDA should be restricted to those patients meeting criteria for gallbladder dyskinesia/functional biliary pain according to established criteria, such as those proposed by the Rome III committee. The use of CCK-HIDA in the investigation of atypical symptoms should be avoided.
3. No substantial large scale data exist to suggest that symptom reproduction with CCK injection (or degree of GBEF decrease) is predictive of relief of symptoms by cholecystectomy, and although they may be considered in the overall clinical picture, they should not be used to select patients for surgery.
4. Clinicians should adhere to the recommendations of the SNM guidelines with respect to the conduct of the CCK-HIDA scan, (including which medications should be held before testing), to minimize the risk of a false positive scan.
5. Surgeons should take an active role in ensuring that their hospital's nuclear medicine and radiology staff are in compliance with current SNM guidelines for CCK-HIDA administration protocols pertaining to CCK dosing, infusion timing, rate and duration, and calculation of normal values. Attention should be given to the conduct of the test as specified in the report when patients are referred from outside institutions, which may not be current and compliant with updated SNM guidelines.
6. Clinicians should be reminded that normal vs abnormal CCK-HIDA values are based on results obtained in normal subjects. By definition then, the test itself is not predictive of a disease state and represents only 1 piece of the clinical information used to select surgical candidates for the treatment of gallbladder dyskinesia.

7. An adequately powered, randomized, prospective, controlled trial is needed to definitively investigate the role of CCK-HIDA scan in the diagnosis of gallbladder dyskinesia and in patient selection for cholecystectomy. The fact that the National Institutes of Health is currently sponsoring a large, multicenter trial evaluating predictors and interventions in sphincter of Oddi dysfunction (EPISOD trial)³⁵ suggests that such a trial can be performed in patients with functional biliary pain and an intact gallbladder. This would be a welcome addition to the current literature, and would contribute greatly to resolving many of the dilemmas surrounding the evidence-based treatment of this challenging patient population.

Author Contributions

Study conception and design: Richmond, DiBaise, Ziessman

Acquisition of data: Richmond, DiBaise, Ziessman

Analysis and interpretation of data: Richmond, DiBaise

Drafting of manuscript: Richmond, DiBaise, Ziessman

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