

# Cholecystokin Cholescintigraphy: Victim of Its Own Success?\*

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Numerous publications have reported that a low gallbladder ejection fraction (GBEF) determined by cholecystokin (CCK) cholescintigraphy has a high positive predictive value for the diagnosis of chronic acalculous cholecystitis (CAC). Clinicians and surgeons have found this test to be clinically useful as an objective method to confirm their clinical diagnosis. However, an abnormally low GBEF is not specific for CAC. For example, numerous other diseases have been associated with a low GBEF, and various therapeutic drugs can cause poor gallbladder contraction. Importantly, improper CCK infusion methodology can result in an erroneously low GBEF. More than one third of healthy subjects and patients who receive sincalide, 0.02 µg/kg infused over 1–3 min, will have an erroneously low GBEF but will have a normal GBEF with a slower infusion (30–60 min) of the same total dose. Because of enthusiastic acceptance of CCK cholescintigraphy by clinicians, the types of patients referred for this test have changed over time. Patients investigated in publications confirming the usefulness of CCK cholescintigraphy had a high pretest likelihood of disease. They underwent extensive workup to rule out other diseases and were followed up for months or years before CCK cholescintigraphy was performed, allowing other diseases to become manifest or symptoms to resolve. However, CCK cholescintigraphy is now being used by clinicians to shorten the workup and follow-up time based on the rationale that CCK cholescintigraphy can quickly confirm or exclude the diagnosis. This new group of referral patients has a lower likelihood of the disease. Many will ultimately be diagnosed with diseases other than CAC. The positive predictive value of this test will likely be lower and the false-positive rate will likely be higher. Nuclear medicine physicians must work to minimize false-positive studies to maintain the confidence of referring clinicians. First, we can educate referring physicians as to the proper use of this study. Next, we must perform CCK cholescintigraphy using optimal methodology that will result in the lowest possible false-positive rate. And finally, we must interpret CCK cholescintigraphy in light of the patient's history, prior workup and clinical setting.

**Key Words:** gallbladder; cholecystokin cholescintigraphy; acalculous cholecystitis; gallbladder ejection fraction

**J Nucl Med 1999; 40:2038–2042**

**C**holecystokin (CCK) cholescintigraphy has become accepted by clinicians and surgeons as an accurate test to preoperatively confirm the clinical diagnosis of chronic acalculous cholecystitis (CAC). Numerous investigations have reported this test to have a high positive predictive value for CAC (1–10). These studies found that a low gallbladder ejection fraction (GBEF) has a >90% positive predictive value for CAC, as proven by postoperative pathohistologic confirmation and by resolution of the patient's symptoms. Two particularly impressive published reports are those of Fink-Bennett et al. (1), the largest retrospective study, and Yap et al. (2), a scientifically rigorous randomized prospective study.

As the name implies, CAC is chronic cholecystitis without stones. Because of past controversy over its cause and diagnosis, the disease has been given various names in the medical literature, e.g., acalculous biliary disease, gallbladder dyskinesia, gallbladder spasm and cystic duct syndrome. The acalculous form of chronic cholecystitis occurs in 10% of patients with symptomatic chronic cholecystitis; however, the symptoms and natural history of the calculous and acalculous disease are identical. Before CCK cholescintigraphy, the clinical dilemma had been the lack of an objective test to preoperatively confirm the clinician's clinical impression. CCK cholescintigraphy has filled this important clinical diagnostic need.

Clinicians and surgeons have for the most part accepted CCK cholescintigraphy as a valuable test to confirm their clinical diagnosis of CAC. However, a change in the patient referral pattern for CCK cholescintigraphy has been noted. Published reports confirming the usefulness of CCK cholescintigraphy investigated a select group of patients. The patients had symptoms of recurrent biliary colic that were strongly suggestive of chronic cholecystitis; however, the patients did not have imaging evidence of chronic calculous cholecystitis (i.e., cholelithiasis). All patients had received extensive medical workups to rule out other diseases and had been followed up for many months and often years, allowing other diseases to become manifest or the symptoms to resolve. These patients had a high pretest likelihood of the disease (CAC).

The patients being referred for CCK cholescintigraphy more recently are not the same group of patients. Clinicians are

Received May 24, 1999; revision accepted Aug. 10, 1999.

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now referring patients with less prior workup and often after only a short history of pain. Clinicians seem to be using CCK cholescintigraphy to speed up the diagnostic workup. Convinced that this is an accurate study, why not use CCK cholescintigraphy to rapidly confirm or exclude the diagnosis? Patients are sometimes referred even during their acute illness or while they are hospitalized. It also seems that nuclear medicine physicians are sometimes interpreting CCK cholescintigraphy without taking into consideration the patient's clinical history, prior workup and present clinical setting.

The patients now being referred to us likely have a lower pretest likelihood of CAC as the cause of their pain. Many of these patients will ultimately be diagnosed with various other diseases. The accuracy of CCK cholescintigraphy in this new patient referral group is uncertain. However, one would surmise that the positive predictive value is likely lower and the false-positive rate is likely higher.

It is important to remember that an abnormal GBEF is not per se diagnostic of chronic cholecystitis. Numerous chronic diseases have been associated with a low GBEF, including sprue, achalasia, diabetes, irritable bowel syndrome, sickle cell disease and pregnancy (11–16). Few data are published regarding gallbladder function during nonhepatobiliary acute illnesses. Acute viral syndromes and metabolic derangement can cause gastric paresis (17). Thus, it would not be surprising if some acute illnesses result in gallbladder dysfunction. In addition, numerous commonly used therapeutic drugs cause gallbladder dysfunction and a low GBEF, e.g., morphine, atropine, octreotide, nifedipine, progesterone and phentolamine (18–23). This list is likely to be incomplete. All are potential causes of false-positive CCK cholescintigraphy.

Another important potential source of false-positive studies is associated with the use of improper methodology for the infusion of CCK. CCK injected as a bolus can cause spasm of the neck of the gallbladder and result in ineffective contraction, i.e., a low GBEF. With this in mind, the Food and Drug Administration–approved package insert for sincalide (Kinevac; Bristol Meyers Squibb, Princeton, NJ) recommends infusing 0.02 µg/kg over 30–60 s. Sincalide is the only commercially available form of CCK in the United States. The 0.02 µg/kg recommended dose came from limited experience in its use with cholecystography.

Early investigators of the use of CCK cholescintigraphy in the diagnosis of CAC took this recommendation into consideration. As a result, most infused 0.02 µg/kg sincalide over 1–3 min. It was generally believed that a GBEF of <35% was abnormal using this method (24). In retrospect, the basis for this belief is uncertain, and the belief is thought to have been based on the available medical literature and the experience of those using CCK. However, at that time, few published data were available to substantiate that this was the optimal CCK dose or infusion methodology. Also, substantial data relating to what was normal or abnormal gallbladder contraction were not available.

The studies cited by early investigators regarding optimal dose rates and normal values for GBEF using sincalide often included few subjects, included data derived from ingestion of fatty meals rather than CCK (25), used nonsincalide CCK preparations (26), used variable dose rates (27), used intramuscular rather than intravenous administration of CCK (28), included patients with gastrointestinal symptoms (29) and often included male subjects (29–31) even though CAC is predominantly a disease that affects females.

In fact, before 1985, when many of these investigations were initiated, a small number of healthy subjects had been studied with the sincalide dose rate of 0.02 µg/kg over 1–3 min. After an extensive search, only two small studies using sincalide 0.02 µg/kg infused over 1–3 min were found, in which truly healthy volunteers (albeit males) were studied (29,30). Of a total of 12 patients, 6 had GBEFs that were <35%. In another study using a nonsincalide preparation of CCK infused at a comparable dose rate, the data were nearly identical, i.e., 3 of 7 patients had GBEFs that were <35% (26). Interestingly, in the 1991 study of Fink-Bennett et al. (1), 27 healthy volunteers were also studied, and 16 of these had GBEFs that were <35%, the value used in the same report to diagnose CAC in symptomatic patients.

In 1985, Sarva et al. (29) compared the sincalide dose of 0.02 µg/kg infused over 1 min with a 0.02 µg/kg/h dose rate infused over 45 min in male patients who did not have hepatobiliary disease. With the 1-min infusion, a wide range of GBEFs (12%–92%) was found in these patients. Those who received the longer 45-min infusion had considerably higher GBEFs (65%–96%) with a much narrower range. The limitations of this study were that these patients had gastrointestinal symptoms, although proven to the authors' satisfaction not to be gallbladder related; all were males and the two different dose rates were given to separate patient groups.

Similar results were reported in 1992 in a study of 23 healthy individuals (32). However, the study subjects were truly asymptomatic and included more females than males, and each individual received both dose rates for direct comparison. Using a dose rate of 0.02 µg/kg infused over 3 min, the GBEFs ranged from 0% to 100%! The mean GBEF ± SD was 55% ± 26% (Table 1). Because of the unusually wide range of values and the large SD, no clinically useful normal range could be determined. Importantly, 8 of 23 healthy individuals had GBEFs that were <35% with the 3-min infusion. Only 2 subjects had GBEFs that were <35% with a 30-min infusion of the same total dose.

Investigators have reported the use of a slow infusion rate of 0.02 µg/kg sincalide: Raymond et al. (33) (0.02 µg/kg infused over 15 min and calculated at 30 min), Sarva et al. (29) (0.02 µg/kg/h infused over 45 min), Ziessman et al. (32) (0.02 µg/kg infused over 30 min) (Table 1) and Yap et al. (2) (0.02 µg/kg/h infused over 45 min and calculated at 60 min). All found clearly definable normal ranges, between 30% and 40%, depending on the specific methodology used. Few healthy individuals had GBEFs below this normal range.

**TABLE 1**  
Gallbladder Ejection Fractions for Healthy Subjects Using  
Different Rates of Sincalide Infusion

Subject no.	Sex	Gallbladder ejection fraction (%)		
		3-min infusion 0.02 µg/kg	30-min infusion	
			0.02 µg/kg	0.01 µg/kg
1	F	0	17	
2	F	18	25	52
3	M	19	65	75
4	F	25	55	
5	F	30	36	
6	F	34	85	
7	M	35	61	62
8	F	35	81	43
9	F	37	55	51
10	F	38	54	26
11	F	52	79	80
12	M	54	85	73
13	M	55	74	75
14	F	61	69	43
15	F	67	87	87
16	M	68	84	
17	F	68	89	
18	M	75	97	95
19	F	78	86	
20	M	80	95	
21	F	80	91	
22	M	89	57	57
23	M	100	81	78
Mean ± SD		52 ± 26	70 ± 22	64 ± 20

Data from Ziessman et al. (32).

Thus, a clinically useful normal range for a sincalide dose rate of 0.02 µg/kg infused over 1–3 min cannot be established. Too much intersubject variability exists. At least one third of healthy subjects and patients will have ineffective contraction (low GBEP) with this dose rate, similar to that seen with a bolus infusion. In contrast, the slower infusion rate of the same total dose usually results in good gallbladder contraction. False-positive studies can be avoided by the slower infusion.

The reason for the high false-positive rate with the shorter infusion rates (0.02 µg/kg over 1–3 min) is that the dose rate is suprathysiologic. With a 1- to 3-min infusion, the serum CCK level rises very rapidly to a suprathysiologic peak and then falls rapidly back to baseline (34). This high peak dose causes spasm of the neck of the gallbladder in a significant number of persons similar to that described with bolus injections. With slower infusion rates (30–60 min), the rise and fall of the serum CCK level are more gradual and the peak serum CCK level is considerably lower, a pattern similar to that seen after oral ingestion of a fatty meal (26,34).

The degree of gallbladder contraction is determined by three factors: the total dose administered, the dose rate and the infusion length. The evidence is clear. The lower dose rate produced by the slow infusion of 0.02 µg/kg sincalide in

contrast with the 1- to 3-min infusion results in greater gallbladder contraction, less variability in response, clearly defined normal range and far fewer false-positive results. Interestingly, the <35% (30%–40%) threshold for abnormal contraction that has been used in most studies holds true for the slow infusion but not for the more rapid infusion.

There has been some resistance to change to the longer infusion method for reasons of logistics in a busy clinic. The question frequently raised is whether an infusion of <30 min, e.g., 10 min, would be adequate. Unfortunately, published data do not support the use of shorter infusions. However, a 30-min infusion study takes only 10 min longer than does a 3-min infusion, i.e., with a 3-min infusion, a 20-min acquisition is still required. However, the slower infusion method does require a constant rate of infusion.

The question that is unanswered is whether the false-positive results are attributed solely to high dose rate (milligrams per minute) or whether, in addition, the length of infusion itself allows more time for adequate contraction. If the false-positive results are attributed solely to the dose rate, it is possible that 0.01 µg/kg over 3–10 min might be effective. Studies have shown that the lower total dose (0.01 µg/kg) is effective when given over 30–45 min (29,32) (Table 1). Whether this results in good gallbladder contraction for shorter infusion times is only anecdotal (31). No adequate data substantiate the usefulness of this dose rate for general clinical practice and, importantly, normal values have not been established. This question needs further investigation. For the present, a 30-min infusion of 0.02 µg/kg is recommended. The protocol at this institution is described in the Appendix.

Another issue is often misunderstood. Nearly half of subjects who receive the shorter infusion rate of 0.02 µg/kg dose over 1–3 min complain of adverse symptoms, including abdominal cramping, nausea and occasionally vomiting. It has been stated repeatedly in the literature that precipitation of the patient's symptoms by CCK administration is diagnostic of chronic cholecystitis. However, published data do not support this assertion. Patients with proven CAC do not show reproduction of their symptoms with the slower infusion rates of CCK (2,28,32). On the other hand, CCK has been reported to aggravate the symptoms of irritable bowel syndrome (35). This aggravation is associated with another physiologic effect of CCK: It increases intestinal peristalsis. Symptoms associated with CCK infusion are related to dose rate and are not associated with specific pathology.

CCK cholescintigraphy is a valuable diagnostic test that clinicians have now generally accepted. The surgeon and patient get prompt pathologic and clinical feedback after cholecystectomy on the accuracy of CCK cholescintigraphy. An increase in the number of false-positive studies could quickly lead to disenchantment with the study. Disenchantment would be unfortunate because CCK cholescintigraphy is quite accurate when performed using the proper methodology, in the appropriate patient population and in the proper

clinical setting. This test should not be used as a shortcut or alternative to thorough workup of the patient.

As nuclear medicine physicians, we do not control which patients are referred to us. However, we can try to educate referring physicians regarding proper use of CCK cholescintigraphy. The procedure must be performed using optimal methodology that will result in a highly accurate diagnostic test with few false-positive findings. The study should be interpreted in the proper clinical context, with a knowledge of the patient's clinical history, medications, diagnostic up-to-date evaluation and the clinical setting during which the study is being performed. For example, a low GBEF in an acutely ill, hospitalized patient who is receiving multiple drugs should be viewed cautiously, and its diagnostic limitations should be understood and conveyed to the clinician. CCK cholescintigraphy for the diagnosis of CAC should be performed as an outpatient procedure on a patient who has a high likelihood of disease and is not having pain at that time.

## CONCLUSION

Compared with short 1- to 3-min infusions, the slow infusion method of sincalide (0.02 µg/kg dose over 30–60 min) is more physiologic, has no side effects, results in better emptying, more clearly separates normal from abnormal findings and has a lower false-positive rate. The use of proper methodology and interpretation in light of the clinical setting make this a valuable test that will continue to be requested by our referring clinical colleagues.

## APPENDIX

### Protocol for Cholecystokinin Cholescintigraphy for Gallbladder Ejection Fraction

#### Routine Cholescintigraphy

1. The patient should have nothing by mouth for 4 h before the study. Patients fasting >24 h should receive CCK before initiating the study. CCK should be infused as described. After CCK infusion, wait 30 min before radiopharmaceutical injection to allow time for the gallbladder to relax.
2. Camera: Large-field-of-view gamma camera; anterior projection.
3. Computer setup: 60 one-min frames.
4. Patient setup: Supine.
5. Inject <sup>99m</sup>Tc-mebrofenin or <sup>99m</sup>Tc-disofenin, 185 MBq (5 mCi) intravenously.
6. After the gallbladder has filled, usually at 60 min, commence setup for CCK cholescintigraphy.

#### CCK Cholescintigraphy

1. Computer setup: 30 one-min frames.
2. Place the camera in the left anterior oblique projection to minimize overlap of gallbladder, small bowel and common duct activity.
3. Infuse 0.02 µg/kg sincalide diluted in a 30-mL volume continuously over 30 min using a constant infusion pump or volutrol for intravenous rate control.

4. On the computer, draw a region of interest around the gallbladder and adjacent liver background.
5. Generate a gallbladder background-corrected time-activity curve.
6. Calculate the percentage of gallbladder emptying (GBEF): (maximum counts – minimum counts)/maximum counts.

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