Cholecystokinin Cholescintigraphy: Detection of Abnormal Gallbladder Motor Function in Patients with Chronic Acalculous Gallbladder Disease

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CCK cholescintigrams were performed in 374 patients with recurrent postprandial right upper quadrant pain, biliary colic, and a normal gallbladder sonogram and/or cholecystogram. The results of these examinations were correlated with the patients' final medical/surgical diagnoses. Twenty-seven patients recruited as control volunteers without objective clinical evidence of biliary disease also underwent CCK cholescintigraphy to determine if the degree of gallbladder contraction post-CCK differs in symptomatic versus asymptomatic subjects. Decreased gallbladder motor function was identified (maximal gallbladder ejection fraction response to CCK less than 35%) in 94% of patients with histopathologically confirmed chronic acalculous cholecystitis or the cystic duct syndrome and in 88% of patients clinically believed to have chronic acalculous biliary disease. Decreased gallbladder motor function does not distinguish symptomatic from asymptomatic gallbladder disease.

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The chronic acalculous disorders of the biliary tree include chronic acalculous cholecystitis, the cystic duct syndrome, and sphincter of Oddi and gallbladder dyskinesia. Clinically, all are manifested by recurrent postprandial right upper quadrant pain and biliary colic. Diagnosis is difficult because routine blood chemistries, oral cholecystograms and biliary sonograms are normal. Endoscopic retrograde cholangiopancreatography is also normal, except in some patients with sphincter of Oddi dyskinesia, who have either elevated basal and/or cholecystokinin-induced sphincter of Oddi pressures (*1,2*). Diagnosis is important, for without it, patients with chronic acalculous biliary disease may be improperly treated (if at all) and forced to endure continuous postprandial pain.

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To determine if cholecystokinin (CCK) cholescintigraphy could successfully identify patients with depressed gallbladder motor function secondary to a chronically inflamed, partially obstructed, or functionally impaired gallbladder, we retrospectively analyzed the maximal gallbladder ejection fraction response to CCK in 374 symptomatic (recurrent postprandial right upper quadrant pain and/or biliary colic) patients with normal oral cholecystograms and/or biliary sonograms and correlated them with their final medical/surgical diagnosis. In addition, CCK cholescintigrams were performed in 27 patients (recruited as "control" volunteers) without subjective/clinical evidence of biliary disease to determine if the degree of gallbladder contraction post-CCK differed in patients with and without recurrent postprandial right upper quadrant pain and biliary colic.

MATERIALS AND METHODS

Between November 1981 and December 1984, CCK cholescintigrams were performed in 374 patients (286 female, 88 male) with recurrent postprandial right upper quadrant pain, biliary colic, and a normal gallbladder sonogram and/or oral cholecystogram. In addition, the maximal gallbladder ejection fraction response to CCK was determined in 27 (19 female, 8 male; ages 15–53 yr) asymptomatic subjects recruited as control volunteers, each of whom had a biliary sonogram within 1-2 wk of their CCK cholescintigrams.

After an overnight fast, each patient and/or asymptomatic recruited control volunteer received 5 mCi of ^{99m}Tc-disofenin (Hepatolite™) intravenously. Utilizing a large field of view gamma camera and a low-energy medium-resolution all-purpose collimator, and a 20% window centered at 140 keV, anterior 500,000 count hepatobiliary images were obtained every 10 min × 6, or until the gallbladder maximally filled (little to no activity within the major hepatic radicals, most within the gallbladder itself). Image acquisition time was approximately 2–3 min and never exceeded 5 min. An infusion of 0.02 μg/kg of CCK (Sincalide) was then administered over 3 min. Following the CCK infusion, anterior post-CCK analog hepatobiliary images were obtained q.5 min × 4 for set times. The post-CCK analogue images were obtained for set times, not counts, and the time per

image was determined from the number of seconds required to obtain the pre-CCK anterior 500,000 count biliary scintiscan.

Gallbladder ejection fractions were determined from data simultaneously acquired on the computer at 1 frame/min for 20 min stored on a 64 × 64 × 16 computer matrix. Acquisition was begun 1 min prior to and continued for 20 min following the intravenous administration of CCK. Ejection fractions were determined by manually assigning areas of interest around the gallbladder and an adjacent background area on the pre-CCK, 5-, 10-, 15-, 20-min post-CCK digital images. The background area [region of interest (ROI)] was selected adjacent and to the right of the gallbladder, with a width measuring approximately 5 pixels and a length equal to the anterior maximal height of the gallbladder itself. Background activity was subtracted from both pre- and post-CCK images. Total counts and the number of pixels within each ROI were determined and the ejection fraction was calculated according to the following formula:

$$GBEF(i) = \frac{\text{Net pre-CCK GB ct} - \text{Net post-CCK GB cts (at t i min),}}{\text{Net pre-CCK GB cts}}$$

where i = the time post-CCK administration, and for each observation Net GB cts = Total GB cts − BK where BK = (background cts/pixel) × (the number of pixels in the GB ROI).

A normal gallbladder ejection fraction response to CCK was defined as one in which the gallbladder ejected at least 35% of its contents.

Pathologic criteria of chronic cholecystitis and/or the cystic duct syndrome included hypertrophy of the gallbladder wall (>1.5-2 mm), diffuse hypertrophy of the muscularis propria with or without a concomitant monocellular infiltrate, the presence of Aschoff-Rokitansky sinuses and/or foamy macrophages filling the tips of mucosal folds and yellow papillary nodules. Cystic duct syndrome was deemed present if fibrosis of the cystic duct producing at least a 60% luminal narrowing was demonstrated histologically and/or kinking or adhesions of the cystic duct was seen at surgery (*3*).

Histopathologic diagnoses were obtained in 124 patients, the other 221 patients had their final diagnoses gleaned from their medical records and/or were obtained from their primary care physicians. Current clinical status was obtained from the patients themselves or their primary care physicians. The duration of follow-up ranged from 3-48 mo in both post-cholecystectomy and medically treated patients.

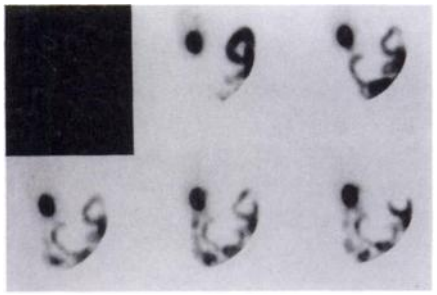

FIGURE 1. Abnormal CCK cholescintigram. Pre-CCK and q.5 min post-CCK (set time, not counts) anterior hepatobiliary images × 4. Qualitatively, there is no evidence to suggest that the gallbladder has ejected greater than or equal to 35% of its contents.

RESULTS

Of the 374 symptomatic patients who had a CCK cholescintigram, 124 have had a cholecystectomy, 2 had exploratory laparotomy, and 248 have been medically followed/managed. Twenty-seven of the 248 medically managed patients have been lost to follow-up and therefore have been excluded from this analysis.

Of the 124 symptomatic patients who had a cholecystectomy, 115 had histopathologically confirmed chronic acalculous biliary disease (8 cystic duct syndrome, 11 cystic duct syndrome in conjunction with chronic acalculous cholecystitis, and 96 chronic acalculous cholecystitis) and 9 had normal gallbladders. The maximal gallbladder ejection fraction response to CCK in these patients and their clinical outcome are depicted in Table 1 (Figs. 1 and 2). Two patients who underwent an exploratory laparotomy, but did not have their gallbladders removed have been deleted from analysis. One had inoperable pancreatic carcinoma, the other had a lymphoma.

Of the 221 patients with adequate medical follow-up, 78 are believed to have chronic acalculous biliary disease because they have persistent biliary colic. Their symptoms have not been alleviated and/or stones have been demonstrated on a follow-up biliary sonogram. The remaining 143 medically followed patients are believed not to have

TABLE 1
MGBEF/Outcome of 124 Post-CCK Treated Patients Clinically Suspected of Chronic Acalculous Biliary Disease (CABD)

Patients	Histopath. Dx	MGBEF-to-CCK	Clinical status
108	CABD	<35%	105—Improved to asymptomatic
			1—No change
			2—Lost to follow-up
7	CABD	>35%	7—Improved to asymptomatic
5	Normal gallbladder	<35%	5—Improved to asymptomatic
4	Normal gallbladder	>35%	3—Improved*
			1—Lost to follow-up

* Lysis of adhesions, treatment of irritable bowel, s/p sphincterotomy.

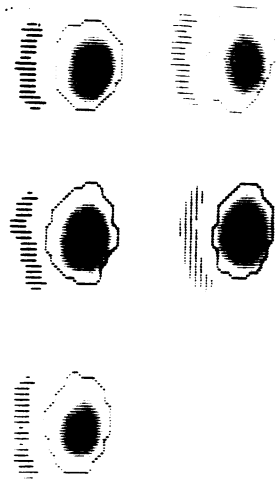

FIGURE 2. Quantitative CCK cholescintigram demonstrating an abnormal ejection fractional response to a 3-min infusion of CCK since the gallbladder has failed to eject greater than or equal to 35% of its contents. (5, 10, 15, 20 min. GBEFs = 0%, 0%, 13%, 13%).

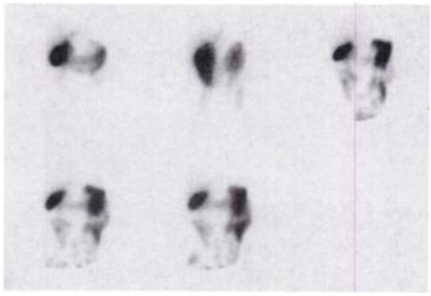

FIGURE 3. Normal CCK cholescintiscan. Pre-CCK and q.5 min post-CCK (set time, not counts) anterior hepatobiliary images × 4. Note obvious decrease in amount of disofenin within the gallbladder post-CCK.

gallbladder disease because their abdominal pain and biliary colic have been relieved following treatment for gastritis, irritable bowel disease, hiatal hernia, esophagitis, peptic ulcer disease, Chrohn's disease and esophageal reflux. Their maximal gallbladder ejection fraction responses to CCK and their outcomes are depicted in Table 2 (Figs. 3 and 4).

Of the 27 individuals without a history of recurrent postprandial right upper quadrant pain and/or biliary colic who were recruited as control volunteers, 9 had an ejection fraction response greater than 35%, 16 less than 35%, and 2 were incalculable (bowel overlap). Of the 16 subjects whose ejection fraction was less than 35%, 2 had cholelithiasis demonstrated sonographically, 4 had a delay (greater than 60 min) in biliary-to-bowel transit (none of whom were pretreated with CCK), and 1 had a delay (greater than 60 min) in gallbladder filling. In addition, one of these subjects subsequently had a cholecystectomy that revealed microscopic changes of chronic cholecystitis. A delay in biliary-to-bowel transit and cholelithiasis were present in each of those subjects whose ejection fractions could not be calculated due to overlying bowel activity neither of which were pretreated with CCK (Table 3).

DISCUSSION

Determining the maximum gallbladder ejection fraction response to CCK can be employed to confirm the presence of reduced gallbladder motor function resulting from chronic acalculous cholecystitis and/or the cystic duct syndrome. Ninety-four percent (108/115) of the patients with histopathologic confirmation of one or both of these disorders demonstrated an abnormal (less than 35% maximal gallbladder ejection fraction) response to CCK. Five patients whose maximal gallbladder ejection fraction response to CCK was less than 35% did not demonstrate microscopic changes of chronic acalculous biliary disease, but all improved postoperatively; findings that suggest that their decreased gallbladder motor function was a manifestation of gallbladder dyskinesia. Only seven (6%) of the patients with confirmed chronic acalculous cholecystitis and/or cystic duct syndrome demonstrated normal gallbladder motor function and were false-negative. In addition, 69/78 (88%) of our medically managed patients with reduced gallbladder motor function are clinically deemed to have chronic acalculous biliary disease. All have persistent recurrent right upper quadrant pain and biliary colic and though their diagnoses are not based on an unequivocal gold standard (surgery), their symptoms are believed to be a manifestation of abnormal gallbladder contraction and/or evacuation.

Other investigators have had an equally sanguine experiences in detecting patients with reduced gallbladder motor function resulting from chronic acalculous biliary disease. Jaros et al. (*17*), Swayne et al. (*18*), Bruger et al. (*19*) and Pickleman et al. (*20*) have performed CCK cholescintigrams on over 150 patients suspected of having impaired gallbladder contraction and/or evacuation, 52 of whom have had a cholecystectomy. The sensitivity and positive predictive value of an abnormal gallbladder ejection fraction response to CCK being a manifestation of decreased

TABLE 2
MGBEF/Outcome of 221 Medically Treated Patients Clinically Suspected of Chronic Acalculous Biliary Disease (CABD)

Patients	Medical diagnosis	MGBEF-to-CCK	Clinical status
130	Normal gallbladder	>35%	Improved status post-treatment for nongallbladder disease
13	Normal gallbladder	<35%	Improved status post-treatment for nongallbladder disease
69	CABD	<35%	Continued symptoms
9	CABD	>35%	Continued symptoms

FIGURE 4. Normal quantitative CCK cholescintigram demonstrating a normal maximal gallbladder ejection fractional response to a 3-min infusion of CCK. (5, 10, 15, 20 min. GBEFs = 53%, 72%, 69%, 68%).

gallbladder motor function secondary to chronic acalculous cholecystitis and/or the cystic duct syndrome ranged from 82% to 100% and 90% to 100%, respectively. Recently, however, Westlake et al. (*21*) reported that a low gallbladder ejection fraction did not correlate with abnormal gallbladder pathology, did not predict a good clinical outcome, nor did histologic findings predict clinical outcome. Why their experience differs from ours and the other advocates of CCK cholescintigraphy is not totally clear, but probably is related to technical differences (i.e., their use of a 30-min infusion of Sincalide and a gallbladder ejection fraction response to CCK of less than 65%, indicating reduced gallbladder motor function). In addition, they did not section the cystic duct. Possibly, had they employed our technique and microscopically evaluated the cystic duct, their results would have been different.

The negative predictive value of CCK cholescintigraphy is 91% since 130/140 patients with normal gallbladder motor function who were originally thought to have chronic acalculous biliary disease have ultimately been found to have another etiology for their recurrent postprandial right upper quadrant pain and/or biliary colic.

TABLE 3
Maximal Gallbladder Ejection Fraction of 27 Asymptomatic "Control Volunteer" Recruits

>35%	Non-calculable	<35%
9	2 Gallstones delayed biliary-to-bowel transit	16 Gallstones (2) Delayed biliary-to-bowel transit (4) Delayed gallbladder filling (1) Symptoms + (Surgery → chronic acalculous cholecystitis) (1)

All have responded to treatment for those conditions and are free of their "biliary symptomatology."

The results of CCK cholescintigrams performed on our 27 asymptomatic control voluntary recruits indicate that reduced gallbladder motor function occurs in symptomatic and asymptomatic gallbladder disease. Four patients who stated that they did not experience postprandial right upper quadrant pain and/or biliary colic with reduced gallbladder motor function had cholelithiasis, while one had cholelithiasis and histologically confirmed chronic cholecystitis. An additional five patients had scintigraphic findings indicative of underlying gallbladder disease; four had delayed biliary-to-bowel transit and one had delayed gallbladder filling (*15*). None were pre-treated with CCK nor had they ingested opiates, thereby excluding delay in biliary-to-bowel transit as a manifestation of preferential gallbladder filling following pretreatment with CCK or from increased resistance to bile flow secondary to opiate-induced increased Sphincter of Oddi pressure (*22,23*).

We did not monitor total gallbladder dynamics or onset of pain post-CCK administration. We only evaluated the maximal gallbladder ejection fraction to CCK to determine if this parameter could identify depressed gallbladder motor function in symptomatic subjects with chronic acalculous cholecystitis or cystic duct syndrome. In retrospect, we could and probably should have done this, but we did not. Our data, however, indicate that determining the maximal gallbladder ejection fraction response to CCK can identify decreased gallbladder motor function resulting from a chronically inflamed gallbladder and/or a partially obstructed cystic duct. Thus, when interpreted in an appropriate clinical setting, CCK cholescintigraphy can be employed to confirm the gastroenterologist's and/or surgeon's clinical impression of symptomatic acalculous biliary disease. Its high negative predictive value should alert the physician that in the absence of abnormal gallbladder motor function, recurrent postprandial right upper quadrant pain and biliary colic is probably not the result of chronic acalculous biliary disease and another etiology for their patient's symptomatology should be sought.

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